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Ovarian cancer

Overview

Ovarian cancer is diagnosed in nearly a quarter of a million women globally each year. It is the eighth most common cancer in women and the seventh leading cause of cancer death among women, responsible for approximately 140,000 deaths each year. It has the highest mortality rate of all gynaecological cancers.ⁱ

The prognosis for ovarian cancer patients is poor, particularly when the disease is diagnosed in its later stages.ⁱⁱ Symptoms are ambiguous and often misdiagnosed^{iii,iv}, so the majority of patients are only identified in the advanced stages of the disease.ⁱⁱ Ovarian cancer is therefore often referred to as “The Silent Killer”.

The current standard of care for ovarian cancer - surgery and chemotherapy - has remained unchanged for many years and the 5-year US survival rate has improved by only 9% since 1975.^v Statistics show that just 45% of women with ovarian cancer are likely to survive for five years compared to up to 89% of women with breast cancer.^{vi,vii}

In most cases front-line treatment (with surgery and chemotherapy) does not stop the disease returning. Most women with advanced ovarian cancer will have a relapse following initial treatment, usually within 15 months of initial diagnosis.^{viii} There is a real need for new, more effective treatment options for women with ovarian cancer.

This guide provides an overview of ovarian cancer, including its incidence, risk factors, symptoms, diagnosis and treatment options.

Section 1: Ovarian Cancer

Types of ovarian cancer

The vast majority (over 90%) of ovarian tumours arise from the uncontrolled growth and replication of epithelial cells which form the surface of the ovary. Cancer involving this type of cell is known as *epithelial ovarian cancer*.^{ix} Other types of ovarian cancer develop from the egg-producing germ cells or the connective tissue around the ovary known as stromal cells.^x If detected at a very early stage, ovarian cancers can usually be removed surgically and this can be potentially curative. However, there are often no clearly identifiable initial symptoms and in the majority of cases the cancer has spread to other parts of the body (metastasised) before the patient is diagnosed.

Figure 1: Anatomy of ovaries

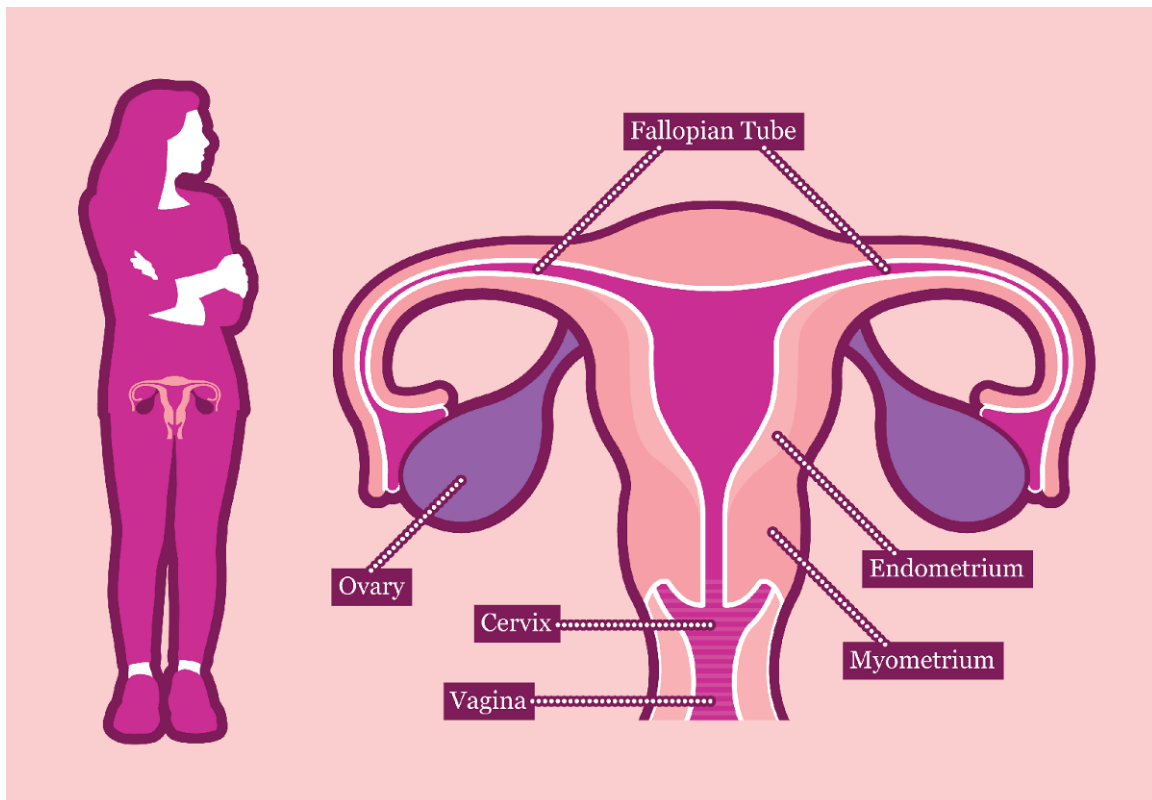
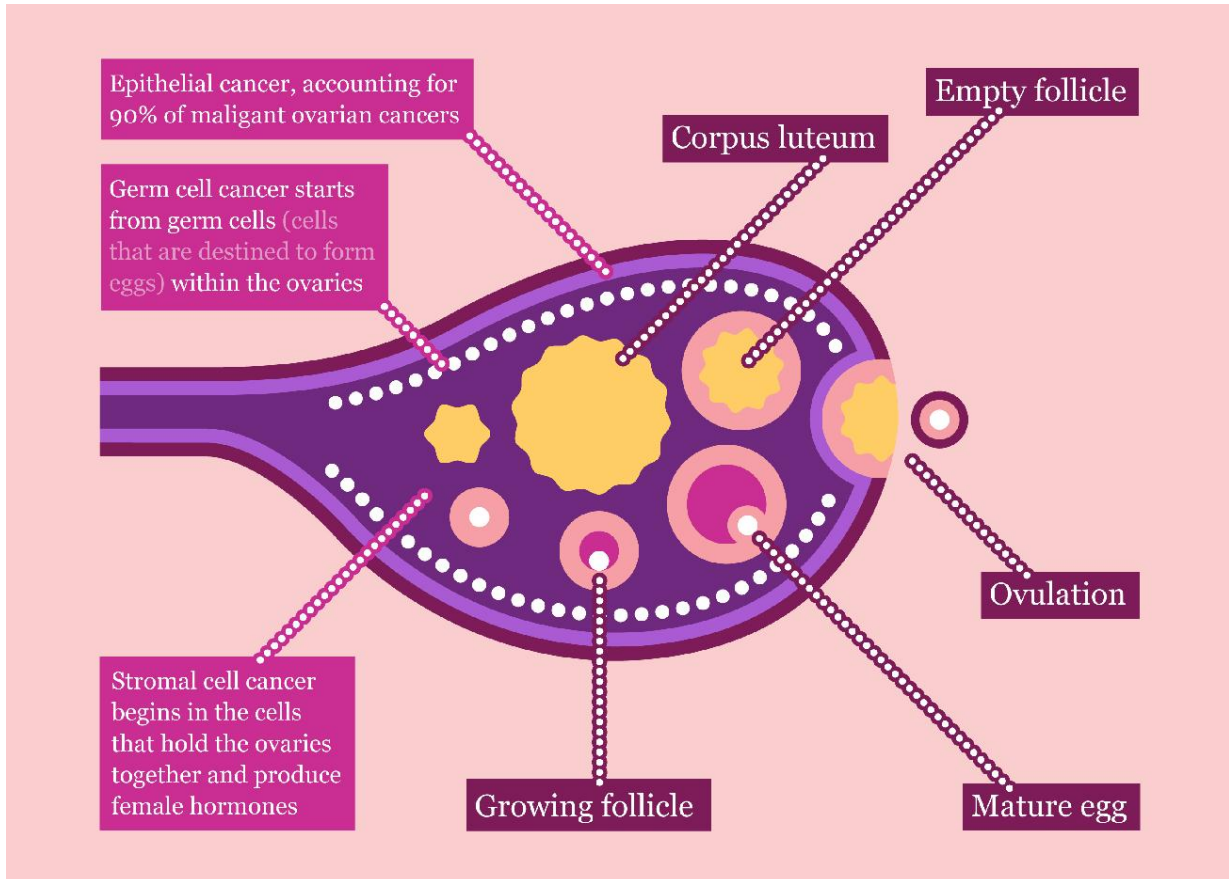


Figure 2: Types of ovarian cancer



Causes and risk factors

The underlying mechanism that leads to ovarian cancer is not well understood, but it is thought to be linked to reproduction and ovulation. A number of factors may increase a woman's risk of developing ovarian cancer:

- **Family history:** If a woman's mother or sister has had ovarian, breast, or uterine cancer she is at greater risk of developing ovarian cancer.^{xi}
- **Age:** The risk of ovarian cancer increases with age. Women over 50 have the highest risk of developing ovarian cancer.^{xii}
- **Childbirth and menopause:** Women who have not had children, never taken the contraceptive pill, who started menstruating at an early age or whose menopause started later than average have a higher risk of developing ovarian cancer. Most ovarian cancers are diagnosed after the menopause.^{xi}

- **Genetics:** Certain genetic traits can also increase the risk of developing ovarian cancer. For example women with mutations in the BRCA1 or BRCA2 genes (1 in every 500 women) have a 23-54% risk of developing ovarian cancer.^{xii}
- **Previous gynaecological problems:** Women who have previously had ovarian cysts or endometriosis are also more likely to develop ovarian cancer.^{xii}
- **Lifestyle:** Obesity, smoking and a sedentary lifestyle are linked to an increased risk of ovarian cancer.^{xii}

Symptoms and diagnosis

Early diagnosis has the potential to improve survival rates but symptoms of ovarian cancer, particularly in the early stages may be ambiguous and non-specific making early diagnosis difficult.ⁱⁱⁱ They can be confused with symptoms of other less severe diseases, particularly gastrointestinal complaints. In addition, there is no routine, simple test to accurately and reliably detect ovarian cancer in the general population so reliable screening for the disease is not yet feasible.^{xiii}

This means the majority of women are not diagnosed until the disease has reached an advanced stage when the tumour may be large and could have spread (metastasised) to other parts of the body. Approximately 70% of women with ovarian cancer are diagnosed at stage III or IV (see staging) of the disease.^{xii}

Cancerous cells can greatly increase the volume of peritoneal fluid (the natural fluid that coats and lubricates the lining of the abdomen and covers internal organs) in ovarian cancer. This can cause the build up of fluid in the abdomen called **ascites** which is a common complication of ovarian cancer that can cause swelling, fatigue and shortness of breath.

Being aware of the frequency and combination of certain symptoms can help with early diagnosis. Symptoms to watch out for include:^{iv,xiv}

- Persistent bloating
- Abdominal pain
- Irregular periods
- Loss of appetite
- Fatigue
- Change in bowel movements - constipation, excess wind
- Abnormal vaginal bleeding

Methods of diagnosis vary from country to country but typically when a woman goes to her doctor with symptoms, she will be given a physical examination. If this raises any concerns, a number of additional tests may be performed:

- A blood test to check for raised levels of a protein in the blood called CA-125
- An MRI (Magnetic Resonance Imaging) or CT (Computerised (Axial) Tomography) scan
- Ultrasound^{xv}

Exploratory surgery of the abdomen known as a laparotomy, or less invasive keyhole surgery known as a laparoscopy, is required to confirm diagnosis and determine how advanced the ovarian cancer is.^{viii,xvi}

Staging

Staging determines how advanced the cancer is and whether it has spread to other parts of the body. It helps to identify the most appropriate treatment options for the patient. Staging of ovarian cancer is confirmed along with surgery using:

- biopsies
- CT scans
- chest X-rays
- colonoscopies^{xvii}

Staging is defined by the FIGO (International Federation of Gynaecology and Obstetrics) system.

Table 1: The stages of ovarian cancer (FIGO)

Stage I	Tumour confined to ovaries
Stage II	Tumour involving one or both ovaries and extending into tissues in the pelvic region
Stage III	Tumour involving one or both ovaries and evidence of spread to the abdominal lining outside of the pelvic region
Stage IV	Most advanced stage when cancer has spread to more distant organs e.g. lungs, liver

Early stage disease (stage I and II) describes a tumour that is localised to its original site, with no spread either to lymph nodes or other areas in the body. With early stage disease there is the chance of a cure if the tumour can be successfully surgically removed.

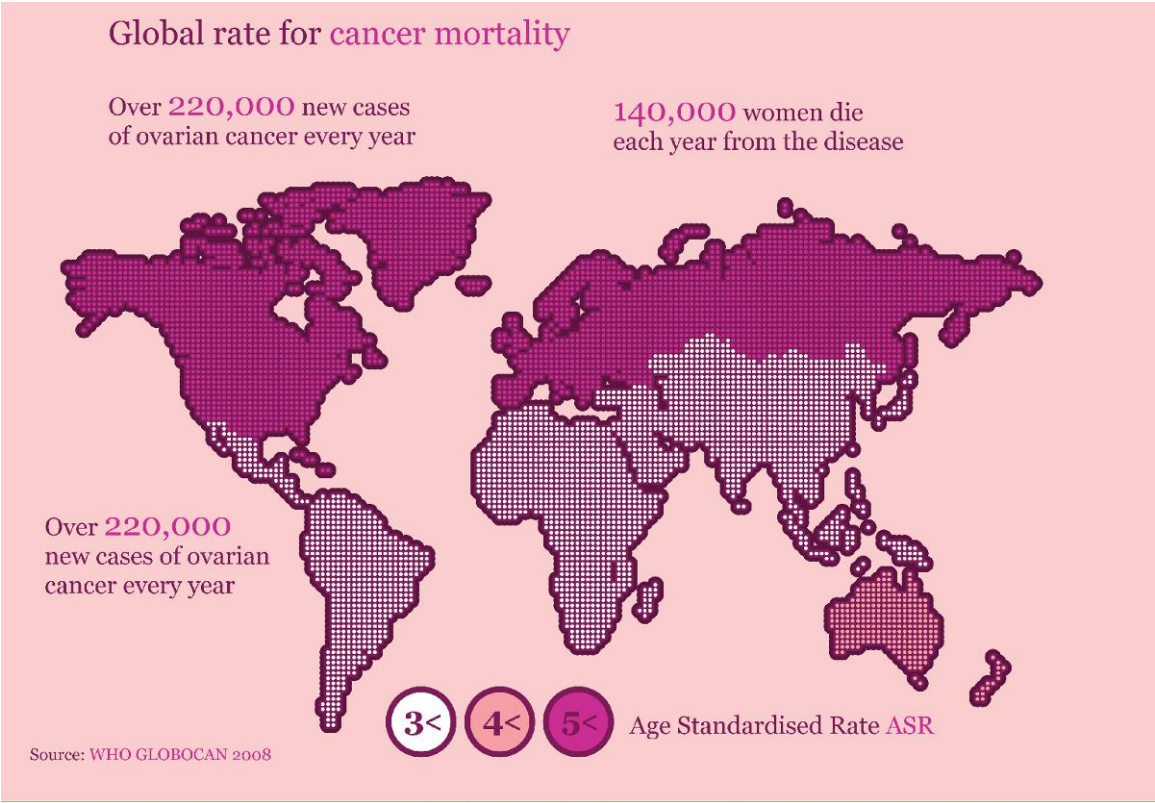
Later stage disease (stage III and IV) refers to cancer that has spread from the original site, affecting the lymph nodes or reaching other parts of the body (metastases). Late stage ovarian cancer has a worse prognosis than earlier stage disease.

Section 2: Epidemiology

Incidence & mortality

- Worldwide
- Ovarian cancer is diagnosed in nearly a quarter of a million women each year. It is the eighth most common cancer in women and the seventh leading cause of cancer death among women, responsible for approximately 140,000 deaths each year. These figures confirm that globally, ovarian cancer is the most deadly of the gynaecological cancers.¹

Figure 3: Age standardised mortality rate for ovarian cancer



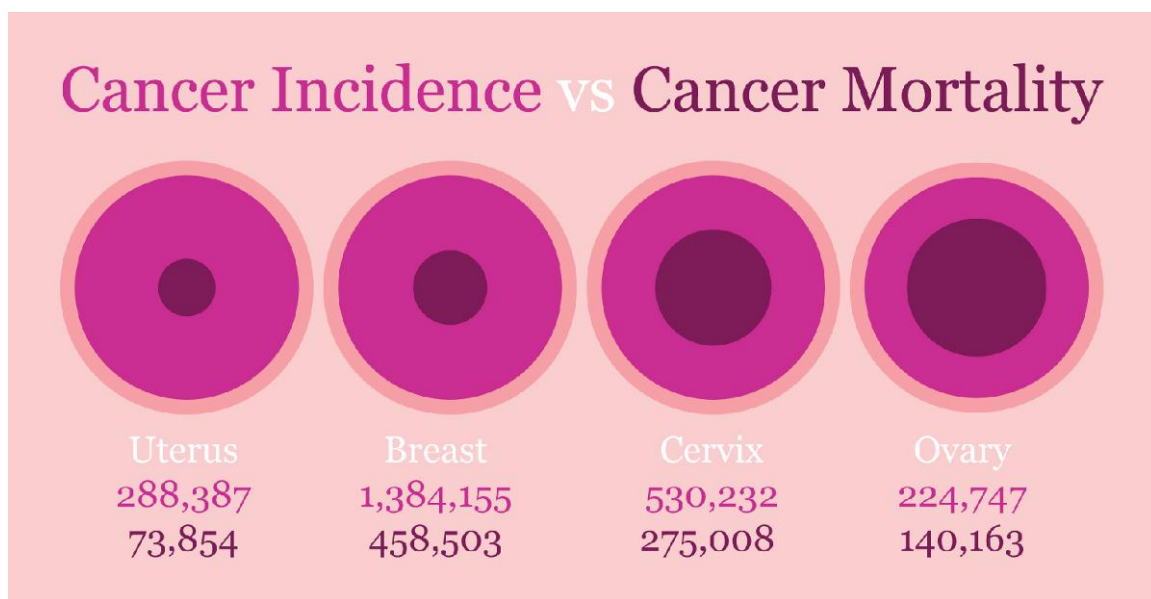
- Europe

In 2008, there were approximately 41,448 deaths from ovarian cancer across Europe, accounting for 5.5% of all female cancer deaths. Europeans have the highest incidence of ovarian cancer and it is the fifth most commonly diagnosed female cancer in Europe.ⁱ

- North America

Ovarian cancer is the eighth most commonly diagnosed cancer in women in North America with 23,895 new cases diagnosed in 2008. It accounts for 3% of female cancer diagnoses but 5.6% of female cancer deaths in North America.ⁱ

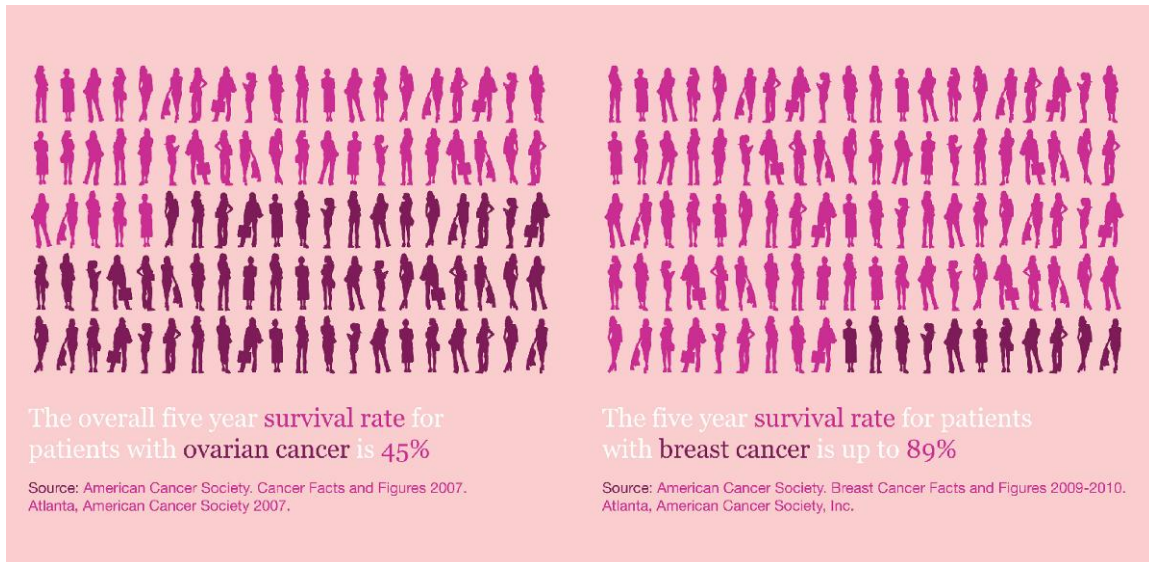
Figure 4: Annual incidence and mortality rates of female cancers worldwide



Prognosis

Cancer statistics often use an ‘overall 5-year survival rate’ to give a better idea of the longer term outlook for people with a particular cancer. Over half of women diagnosed with ovarian cancer will not live beyond five years.^{vi} The overall 5-year survival rate for women with ovarian cancer is 45%. This compares to a 5-year survival rate of up to 89% in women diagnosed with breast cancer.^{vi,vii} The reasons for this poor prognosis are that there is no effective screening for ovarian cancer and symptoms can be ambiguous, leading to a high percentage of cases being diagnosed at an advanced stage when the disease is more difficult to treat. Treatment options are limited to surgery and chemotherapy.

Figure 5: 5-year survival rate of ovarian cancer vs. breast cancer



Section 3: Treatment

Treatment options vary depending on the stage of the cancer, and are assessed taking into account the following variables:

- Tumour size
- Tumour position
- Degree of spread
- Patient's physical condition

In general, the current treatment options for ovarian cancer are limited to surgery and chemotherapy. Radiotherapy is not frequently used to treat ovarian cancer.

Surgery

Surgery is used to remove as much of the tumour as possible. This is known as debulking surgery or cytoreduction. Patients most commonly have both ovaries removed (bilateral oophorectomy) and a hysterectomy (removal of the uterus). In young women who wish to remain fertile, only the affected ovary is removed and the uterus is left in place. In patients diagnosed with early disease, surgery alone is usually sufficient but in advanced disease, debulking surgery followed by chemotherapy is recommended.^{xv}

Chemotherapy

Chemotherapy after surgery is referred to as 'front-line' or 'first-line' treatment and involves a combination

of a platinum and taxane-based chemotherapy (usually carboplatin and paclitaxel). Patients with advanced ovarian cancer who aren't initially able to undergo surgery due to large ascites or invasive tumours can be treated with chemotherapy before being considered for surgery (neoadjuvant treatment).^{viii}

Ovarian cancer usually responds to chemotherapy but unfortunately, in the majority of cases the cancer returns (known as "relapse" or "recurrence"), resulting in half of patients eventually dying from the disease.ⁱⁱ When the cancer returns, the only currently available treatment option is further chemotherapy. The choice of chemotherapy at this stage depends on how quickly the cancer has returned.

Section 4: Avastin[®] (bevacizumab) and ovarian cancer

What is Avastin and angiogenesis?

Angiogenesis is a process that occurs naturally in the body and involves the growth of new blood vessels during, for example, development and wound healing. Growing tumours can release chemicals to encourage this blood vessel growth (known as tumour angiogenesis) so that the new blood supply brings oxygen and nutrients that the tumours need to grow. Tumour angiogenesis is a fundamental process required for a tumour to grow and to spread (metastasise) to other parts of the body.^{xviii, xix}

Avastin is an anti-angiogenic therapy that specifically binds and blocks the biological effects of VEGF^{xx} (vascular endothelial growth factor), the key driver of tumour angiogenesis.^{xxi} Inhibiting the formation of these new blood vessels helps starve the tumour of the essential oxygen and nutrients it needs to grow and spread.^{xxii} By controlling angiogenesis, tumour growth is controlled.

Avastin in ovarian cancer – the rationale

Ovarian tumours in particular have large blood supplies and high levels of VEGF protein. Increased levels of VEGF contribute to the build up of fluid in the abdomen known as ascites which are a common complication of ovarian cancer that can cause swelling, fatigue and shortness of breath.^{xxiii,xxiv,xxv} Research has also shown that high VEGF levels are associated with poor outcome in women with ovarian cancer, making it a prime treatment target.^{xxvi}

Phase II trials of Avastin in ovarian cancer indicated promising activity and led to further investigation in large, randomised phase III studies.^{xxvii,xxviii}

Roche has an extensive research and clinical trial programme investigating Avastin in patients with ovarian cancer in both the front-line and second-line setting (when the cancer has returned after initial therapy), in order to help improve treatment outcomes for women with ovarian cancer.

Avastin has already demonstrated a significant improvement in the time women with ovarian cancer live without the disease getting worse (progression free survival; PFS) in three large phase III studies (GOG 0218 and ICON7 in the front-line setting, OCEANS in the relapsed platinum-sensitive setting).

The GOG 0218 study^{xxix}

GOG 0218 was the first of two encouraging phase III trials investigating Avastin front-line in ovarian cancer (first-line after surgery). The trial showed that Avastin in combination with carboplatin and paclitaxel chemotherapy followed by the continuation of Avastin alone (for up to 15 months) significantly improved the time women lived without their disease getting worse.

- Women who continued Avastin alone after receiving it in combination with chemotherapy:
 - Had a median PFS of 18.0 months in comparison to 12.0 months in the chemotherapy alone arm
 - Had a 54% improvement in the likelihood of living longer without the disease worsening compared to chemotherapy alone
- Adverse events were consistent with those observed in previous pivotal trials of Avastin in other cancer types.

The trial involved 1,873 women with previously untreated advanced ovarian cancer who had undergone surgery to remove as much of the tumour as possible. Patients were randomised to one of three arms, for a total treatment duration of up to 15 months:

- **Arm 1:** Placebo in combination with carboplatin and paclitaxel followed by placebo
- **Arm 2:** Avastin (15mg/kg every 3 weeks) in combination with carboplatin and paclitaxel followed by placebo
- **Arm 3:** Avastin (15mg/kg every 3 weeks) in combination with carboplatin and paclitaxel followed by the Avastin alone, continued as a single agent

There was no statistically significant difference between the shorter duration of Avastin and the chemotherapy arm. The significant benefit was only seen when Avastin was started with chemotherapy and

continued beyond it for a total of 15 months or until disease progression.

The study was conducted by a network of researchers led by the Gynecologic Oncology Group (GOG). This trial was a pivotal study of Avastin front-line in ovarian cancer.

The ICON7 study^{xxx}

ICON7 was the second phase III trial of Avastin front-line in ovarian cancer, and further supports the use of Avastin in this setting. The trial showed that Avastin in combination with carboplatin and paclitaxel chemotherapy followed by the continuation of Avastin alone (for up to 12 months) significantly improved the time women lived without their disease getting worse.

- Women who continued Avastin alone after receiving it in combination with chemotherapy:
 - Had a 27% improvement in the likelihood of living longer without the disease worsening compared to chemotherapy alone
 - Had a median PFS of 18.3 months in comparison to 16.0 months in the chemotherapy alone arm
- Adverse events were consistent with those observed in previous pivotal trials of Avastin in other cancer types.

The trial involved 1,873 women with previously untreated advanced ovarian cancer who had undergone surgery to remove as much of the tumour as possible. Patients were randomised to one of two arms, for a total treatment duration of up to 12 months:

- **Arm 1:** Placebo in combination with carboplatin and paclitaxel followed by placebo
- **Arm 2:** Avastin (7.5mg/kg every three weeks) in combination with chemotherapy carboplatin and paclitaxel followed by the continuation of Avastin alone

In ICON7 the majority of patients had advanced stage ovarian cancer but the trial also included patients with earlier stage disease.

Although the two trials cannot be directly compared due to significant differences in trial design, ICON7 supports the results from GOG 0218 and taken together the results suggest that a higher magnitude of benefit for patients with previously untreated stage III/IV ovarian cancer is achieved by combining Avastin 15mg/kg with carboplatin/paclitaxel followed by continued use of Avastin alone for a total of 15 months.

An analysis of patient types in ICON7 demonstrated that those with later stage disease derived greater benefit than those with earlier stage disease.^{xxx}

The ICON7 study is sponsored by the Medical Research Council (MRC) in the United Kingdom, led by the MRC Clinical Trials Unit and conducted through an international network of researchers in the Gynaecologic Cancer InterGroup (GCIIG).

Other key phase III studies of Avastin in ovarian cancer

The OCEANS study is a US based phase III trial of approximately 480 patients with platinum-sensitive ovarian cancer. Patients received Avastin or placebo in combination with gemcitabine and carboplatin chemotherapy followed by continued use of Avastin as single-agent therapy or placebo alone until progression of disease.

The time between receiving the last dose of platinum-based chemotherapy and disease recurrence is used to help determine the choice of chemotherapy used in the second-line of treatment. Patients are said to have 'platinum-sensitive' disease if disease recurrence occurred more than six months after completing their initial platinum-based chemotherapy.

OCEANS demonstrated that Avastin based therapy extended the time patients with platinum-sensitive ovarian cancer lived without their disease getting worse, compared to chemotherapy alone. Adverse events were consistent with those seen in previous pivotal trials of Avastin.

The results from OCEANS build on findings from the two previous phase III studies (GOG 0218 and ICON7), establishing the key role for Avastin in ovarian cancer.

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