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CONCISE OVERVIEW ON OVARIAN CANCER AND ITS TREATMENT PARP INHIBITOR, TARGETED DRUG THERAPY, IMMUNOTHERAPY AND MORE

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Keywords:

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ABSTRACT: The primary cause of death for women with gynaecological cancer diagnoses is ovarian cancer. It is also, generally speaking, the sixth most common cause of death for women. The majority of cases had advanced diagnoses, which worsens the disease's prognosis. The limited predictive value of the current screening tests adds even more suffering to the situation. The most important early detection techniques, which have not had a discernible positive impact on the morbidity or death of this malignancy, are comprehensive gynaecological evaluation, transvaginal ultrasonography, and laboratory markers such as the cancer antigen-125 (CA-125) assay. However, anti-angiogenic bevacizumab and Poly (ADP-ribose) polymerase (PARP) inhibitors have gained pace in the management of this condition. Traditionally, the treatment regimen involves surgery and platinum-based chemotherapy. Although the exact etiology of ovarian cancer is unknown, there are several factors that have been found to raise the risk of the illness. Experts understand that DNA alterations, or mutations, occur in ovarian cancer-causing cells when they originate within or close to the ovaries. The instructions that inform a cell what to do are encoded in its DNA. The alterations instruct the cells to proliferate rapidly, resulting in a mass of cancerous cells known as a tumour. When healthy cells would perish, malignant cells would not die. They have the ability to infiltrate adjacent tissues and split off from the original tumor to travel (metastasize) to different areas of the body.

INTRODUCTION:

Ovarian Cancer Introduction: Cancer is the leading cause of death in most regions of the world, and it is currently the most prevalent hindrance to obtaining a desirable life expectancy in most countries [1]. Ovarian cancer is one of the most frequent gynaecologic cancers, ranking third after cervical and uterine cancer [2]. It also has the worst prognosis and the highest fatality rate. Although ovarian cancer has a lesser prevalence than breast cancer, it is three times more dangerous, and its mortality rate is expected to climb dramatically by 2040 [2].

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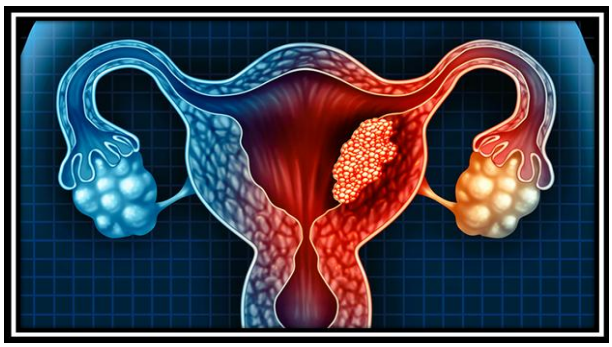


FIG. 1: FIGURE OF OVARIAN CANCER

Different subtypes of ovarian cancer were discussed in nine studies. Studies show that up to 90% of all OC have epithelial origin and the remaining OC have non-epithelial origin [3-5]. Among epithelial OC, 3% are mucinous and others are non-mucinous [6]. Non-mucinous are further found to have serous (70% of non-mucinous), endometrioid (10%), clear cell (10%), and unspecified subtypes (5%) [9-11]. According to recent studies, serous carcinomas are divided into two separate subtypes: high grade and low grade [7-8]. Compared to epithelial cancers, non-epithelial cancers are less invasive [9].

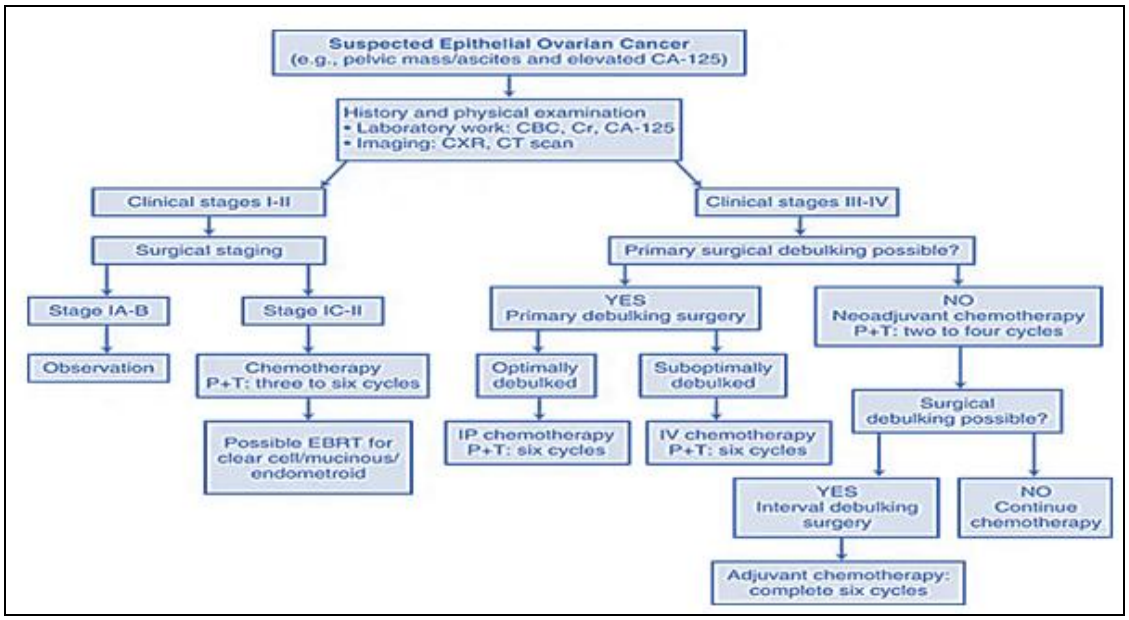


FIG. 2: GENERAL CHART OF ASPECTS OF OVARIAN CANCER

Sign and Symptom: Ovarian symptom awareness level as shown in **Fig. 1**, the most well recognised symptoms were post-menopausal vaginal bleeding (87.4%), abdominal pain (85.0%), and pelvic pain (79.0%). More than half the sample was able to recognise abdominal bloating (71.7%), increased abdominal size (69.4%), back pain (68.3%) and tiredness (59.1%). The least recognised symptoms included a change in bowel habits (49.0%), feeling full quickly (47.7%), difficulty eating (36.3%), and a change in bladder habits (32.0%). The mean symptom recognition score was 6.85 (SD 2.73, range 0–11) [12].

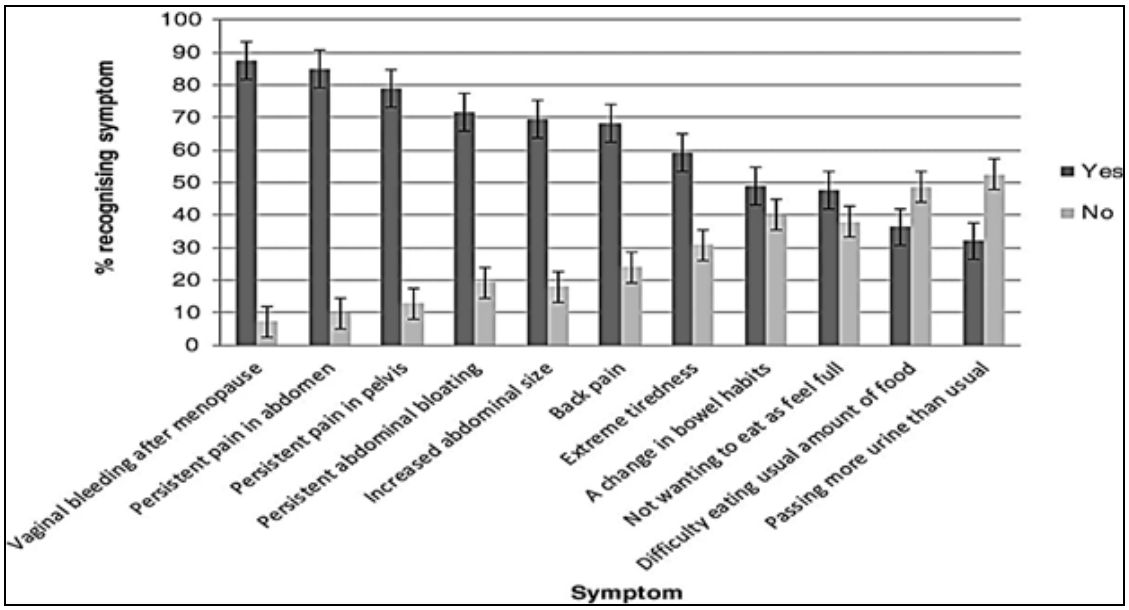


FIG. 3: GRAPHICAL ANALYSIS SYMPTOMS OF OVARIAN CANCER

Ovarian cancer is a type of cancer that arises from different cells of the ovaries the paired female reproductive organ. Early stages of cancer are mostly symptomless, but symptoms are noted during the advanced stages and may include.

1. Abdominal enlargement on swelling
2. Abdominal fullness and pain in lower abdomen
3. Feeling full after eating very little
4. Tiredness
5. Change in bowel
6. Swelling of leg
7. Abnormal menstrual cycle
8. Weight loss or gain
9. Unexpected back pain
10. Clothes not fitting well

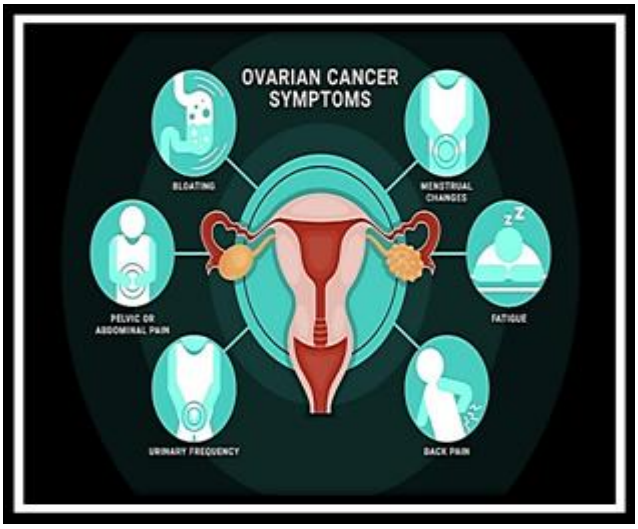


FIG. 4: SYMPTOMS OF OVARIAN CANCER

Stages Ovarian Cancer:

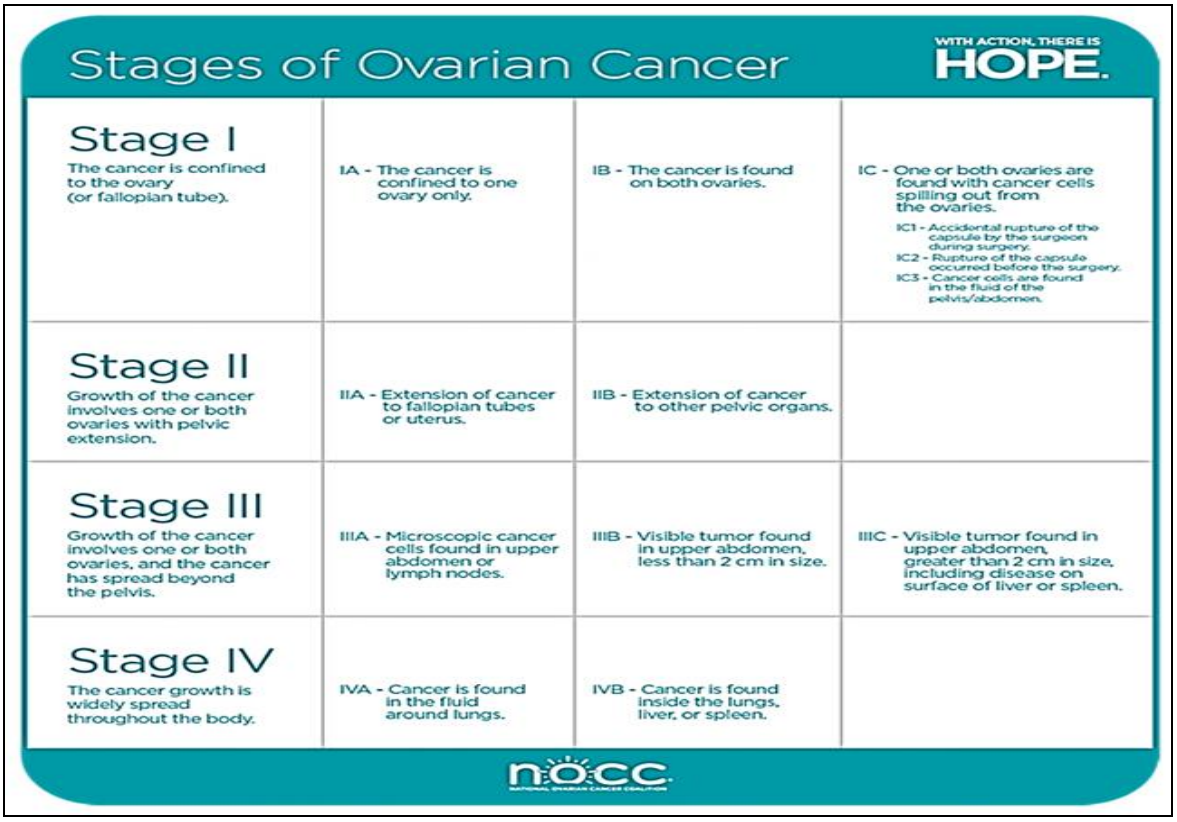


FIG. 5: STAGE OF OVARIAN CANCER

Screening and Diagnosis Test of Ovarian Cancer: A screening test is used to assess an individual's risk of developing a disease, and is generally targeted to large numbers of asymptomatic individuals but could also be specifically targeted to at-risk populations [13]. A diagnostic test is used to determine whether or not an individual has a given disease, and is targeted to individuals who are symptomatic [13]. As such, a diagnostic test must be extremely accurate in determining disease, with particular emphasis on achieving high specificity for disease diagnosis [13]. Alternatively, screening tests should generally be focused on achieving high sensitivity for detecting disease in order to limit the number of false negatives leading to missed diagnoses in the test population [13]. To give an example of this distinction, the Pap test is a widely used screening method for detecting the presence of abnormal cervical cells [13] however, the occurrence of abnormal cells does not always indicate the presence of cancer. Abnormal cells could be caused by a number of factors such as mild inflammation, bacterial, viral, or yeast infections, or cervical dysplasia [14, 15]. When abnormal cells are present in a Pap test, most patients are referred for colposcopy with cervical biopsy, which would serve as a highly accurate diagnostic to determine the presence of cancer [16].

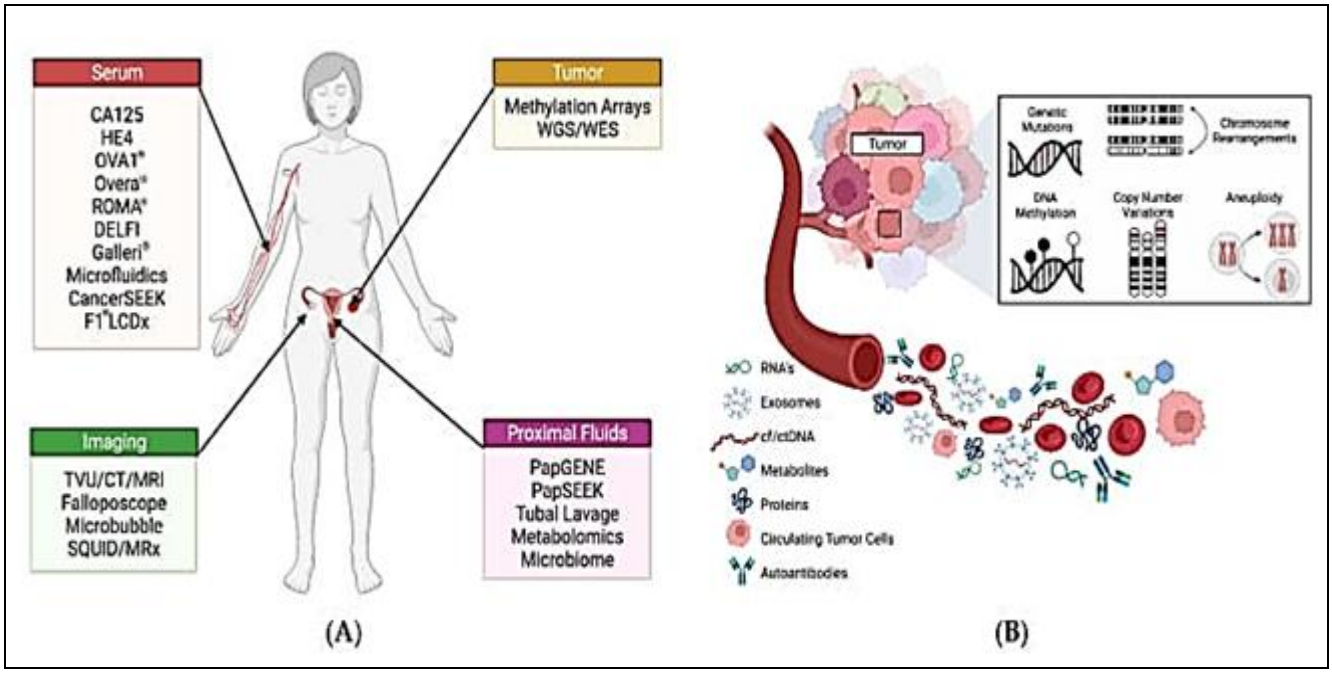


FIG. 6: (A) RELEVANT EMERGING STRATEGIES FOR SCREENING AND DETECTION OF HGSC. (B) CIRCULATING TUMOR BIOMARKERS THAT CAN BE ASSAYED FOR SCREENING AND DIAGNOSTIC PURPOSES

The following tests are used to diagnose ovarian cancer:

Pelvic Exam: During a pelvic exam, your doctor inserts gloved fingers into your vagina and simultaneously presses a hand on your abdomen to feel (palpate) your pelvic organs. The doctor also visually examines your external genitalia, vagina, and cervix.

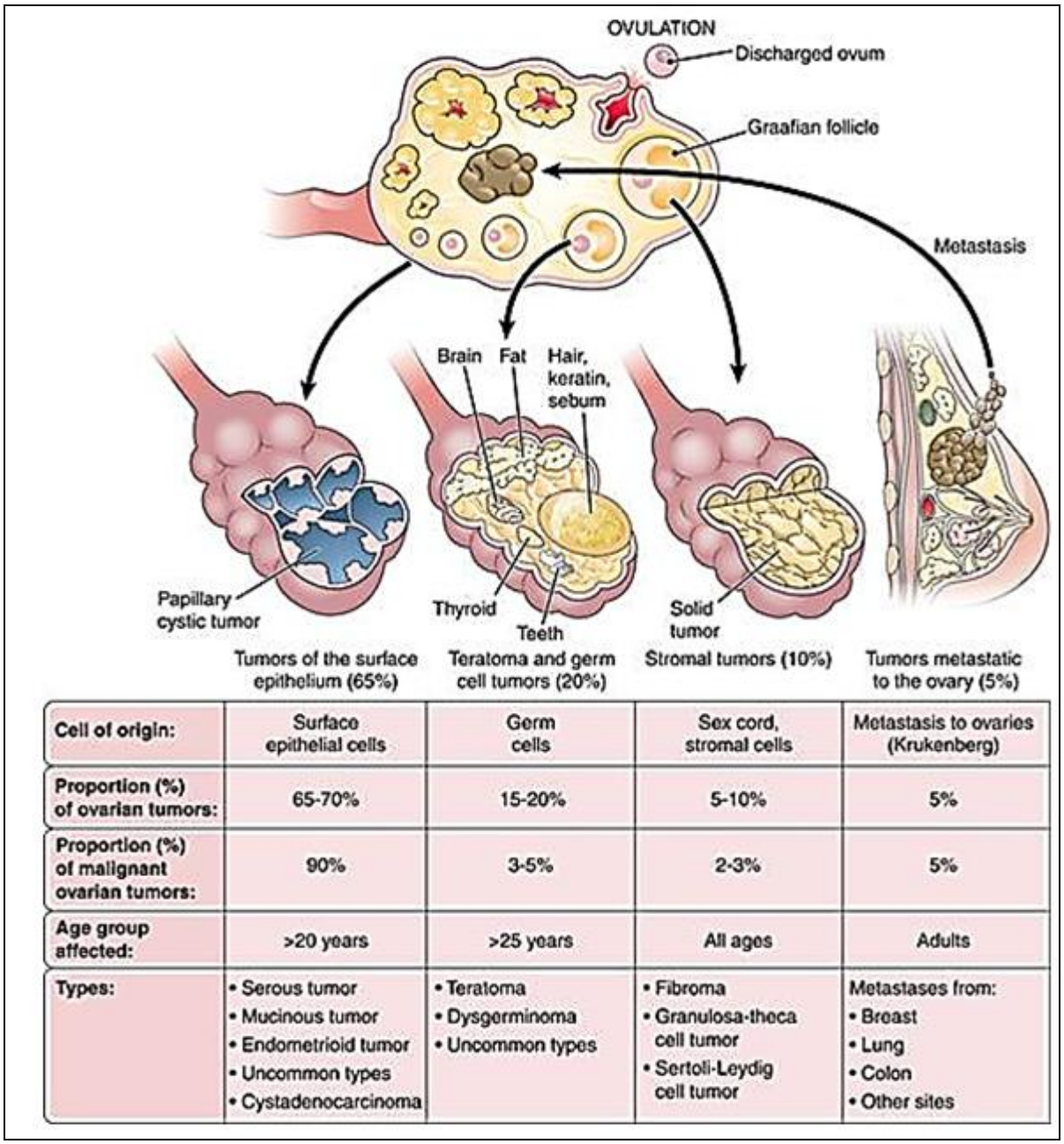
Imaging Tests: Tests such as ultrasound or CT scans of your abdomen and pelvis may help determine the size, shape, and structure of your ovaries.

Blood Tests: Blood tests might include organ function tests that can help determine your overall health. Your doctor might also test your blood for tumour markers that indicate ovarian cancer.

For example, a cancer antigen (CA) 125 test can detect a protein that's often found on the surface of ovarian cancer cells. These tests can't tell your doctor whether you have cancer, but they may provide clues about your diagnosis and prognosis.

Biopsy: A small piece of the ovarian tissue is examined under the microscope to check for any cancer characteristics and its type.

Types of Ovarian Cancer:



Cell of origin:	Surface epithelial cells	Germ cells	Sex cord, stromal cells	Metastasis to ovaries (Krukenberg)
Proportion (%) of ovarian tumors:	65-70%	15-20%	5-10%	5%
Proportion (%) of malignant ovarian tumors:	90%	3-5%	2-3%	5%
Age group affected:	>20 years	>25 years	All ages	Adults
Types:	• Serous tumor • Mucinous tumor • Endometrioid tumor • Uncommon types • Cystadenocarcinoma	• Teratoma • Dysgerminoma • Uncommon types	• Fibroma • Granulosa-theca cell tumor • Sertoli-Leydig cell tumor	Metastases from: • Breast • Lung • Colon • Other sites

FIG. 7: TYPES OF OVARIAN CANCER

Types of Treatment on Ovarian Cancer: Doctors usually treat ovarian cancer with a combination of surgery and chemotherapy. However they may also treat ovarian cancer using radiation therapy, targeted therapy, hormone therapy and immunotherapy.

The treatment option for ovarian cancer include:

- Targeted Drug Therapy

Chemotherapy: Chemotherapy uses one or more drugs to kill cancer cells.

Radiation: Radiation therapy kills cancer cells and shrinks tumours with high-energy beam.

- Targeted Drug Therapy

1. PARP Inhibitor
2. Anti-Angionic Drugs
3. Immunotherapy

PARP Inhibitor: In gynaecologic malignancies, potential therapeutic targeted agents include antiangiogenic agents, poly (ADP-ribose)

polymerase (PARP) inhibitors, tumor-intrinsic signalling pathway inhibitors, selective oestrogen receptor down regulators, and immune checkpoint inhibitors.

Pharmacokinetic of PARP Inhibitors:

TABLE 1: PHARMACOKINETIC CHARACTERISTICS OF PARP INHIBITORS

	Olaparib	Niraparib	Rucaparib
Posology	300 bid	300 mg	600 bids
Bioavailability	NA	73%	30–45%
AUC 0-24	42,000 h ng/mL	NA	1690 h ng/mL
Cmax	58,000 ng/mL	3 h	1940 ng/mL
Tmax	1–3 h	NA	1.9 h
Plasmatic Clearence	8.6 L/h	16.5 L/h	13.9–18.4 L/h
Volume of Distribution	167 L	1311 L	113–262 L
Half-life	11.9 h	48-51 h	25.9 h
Co-Administration with Food	Food assumption delays Tmax of about 2 h	No influence	After a highly lipidic meal, Cmax is increased by 20% and AUC of 38%, while Tmax is delayed by 2.5 h
Plasmatic Protein Binding	Dose-dependent: bound fraction decreases from 91% at 1 microg/mL concentration to 82% to qo microg/mL and to 70% at 40 microg/mL	83%	70.2%
Metabolism	CYP3A4/5 are enzymes primarily responsible for metabolism	Carboxilestherasis are the enzymes primarily responsible for metabolism	CYP2D6 and CYP1A2 e CYP3A4 are the enzymes primarily involved in metabolism
Substrate of	P-gp (clinically non-significant)	P-gp, BRCP, MATE1/2 (clinically non-significant)	P-gp and BCRP
Cytochromes and Transporters Inhibition	Induction of CYP1A2, 2B6 e 3A4	Inhibition of MATE1/2 e and mild inhibition of OCT1	Moderate inhibition of CYP1A2
Cytochromes and Transporters Inhibition	Moderate inhibition of CYP3A, P-gp, BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K	None	Mild inhibition of CYP2C9, CYP2C19, CYP3A E P-gp
Renal Impairment	Severe renal impairment (ClCr< 30 mL/min): not recommended Moderate renal impairment (CrCl 31–50 mL/min): dose reduction to 300 mg × 2 Mild renal impairment (ClCr 51–80 mL/min): no dose adjustment	Severe renal impairment (ClCr< 30 mL/min): not recommended Moderate renal impairment (CrCl 31–50 mL/min): no dose adjustment Mild renal impairment (ClCr 51–80 mL/min): no dose adjustment	Severe renal impairment (ClCr< 30 mL/min): not recommended Moderate renal impairment (CrCl 31–50 mL/min): no dose adjustment Mild renal impairment (ClCr 51–80 mL/min): no dose adjustment
Hepatic Impairment	Mild or moderate hepatic impairment (child pug A or B): no dose adjustment Severe hepatic impairment (child pug C): not recommended	Mild or moderate hepatic impairment (child pug A or B): no dose adjustment Severe hepatic impairment (child pug C): not recommended	Mild or moderate hepatic impairment (child pug A or B): no dose adjustment Severe hepatic impairment (child pug C): not recommended

Mechanism of Action: PARP inhibitors (Olaparib, rucaparib, and niraparib) are used as maintenance monotherapies for recurrent epithelial ovarian cancer in women who have BRCA1 / BRCA2 mutations [17, 18, 19, 20]. BRCA1 and BRCA2 genes are involved in the repair of DNA double-strand breaks through the process of homologous recombination [21]. Ovarian cancers with BRCA1 / BRCA2 mutations depend on error-prone alternative pathways like the base excision pair (BER) pathway to repair single-strand breaks in DNA damage [21]. PARP is a family of DNA-repairing enzymes that play an important role in DNA damage repair via BER [22]. PARP inhibitors destroy

cancer cells by inhibiting the BER pathway and creating a buildup of damaging double-strand breaks within cancer cells when given to patients with BRCA1 / BRCA2 mutations [23, 24]. PARP inhibitors were found to improve progression-free survival but not overall survival [19]. Furthermore, the use of olaparib, the first licensed PARP inhibitor, in combination with platinum-based chemotherapy is limited by overlapping hematologic toxicities, necessitating medication dose reduction. Furthermore, acquired drug resistance mechanisms such as BRCA mutant reversions and ABCB1 fusions for PARP inhibitor treatment resistance have been observed in some patients.

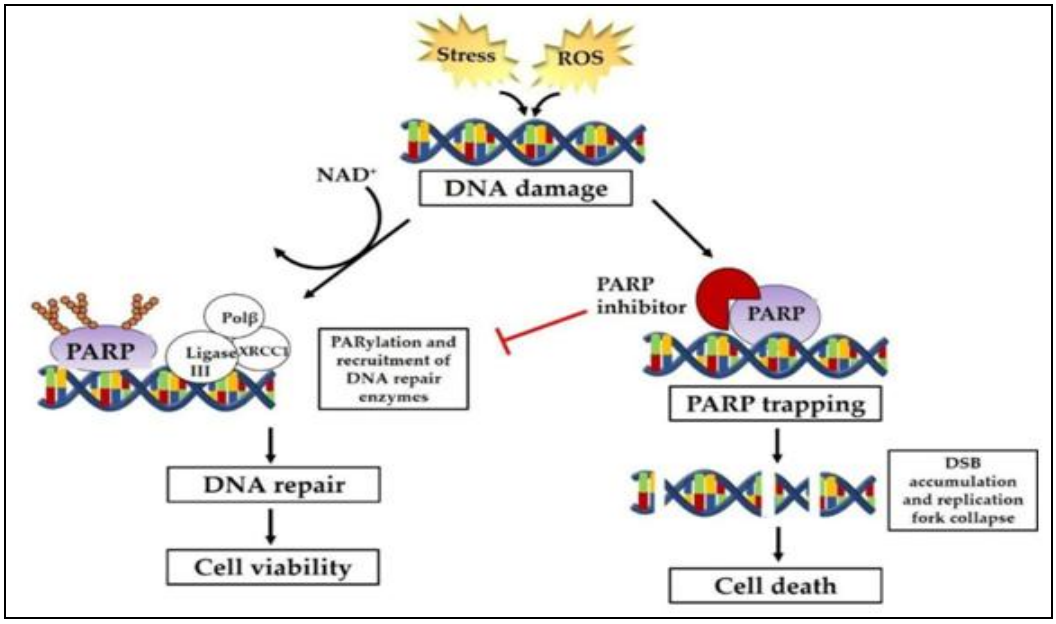


FIG. 8: MECHANISM OF ACTION OF PARP INHIBITORS

Adverse Effect of Ovarian Cancer:

Common Adverse Effects:

Gastrointestinal Toxicities: Patients should be counselled about the high potential for nausea and to be vigilant or even prophylactically prevent its occurrence. Nausea was reported by 148 (76%) of 195 patients treated with Olaparib, 280 (75%) of 372 patients treated with rucaparib and 270 (74%) of 367 patients treated with niraparib. Having a light meal with an antiemetic 60 min before taking the PARP inhibitor can also be helpful.

Fatigue: Fatigue is a nearly universal toxicity for all PARP inhibitors. 59–69% of patients had fatigue of any grade with the three approved PARP inhibitors, and grade 3 or higher fatigue was seen in 30 (8%) of 367 patients using niraparib, 25 (7%) of 372 patients using rucaparib, and 8 (4%) of 195 patients using Olaparib.

Expert opinion recommends that non-pharmacological treatments, such as exercise, massage therapy, and cognitive behavioural therapy, can be effective in reducing symptoms.

Effects on the Blood: PARP inhibitors can temporarily affect the number of blood cells in the body. You'll have regular blood tests to check your blood count. Blood is made up of red cells, white cells and platelets. If the number of blood cells is too low, your next treatment may be delayed or the dose reduced.

Anaemia: Having too few red blood cells is called anaemia. If you feel particularly tired, breathless or dizzy, let your treatment team know.

Risk of Infection: Not having enough white blood cells (neutropenia) can increase the risk of getting an infection such as a urine infection, pneumonia and bronchitis.

Non common adverse effects:

- ✓ Neurological toxicities
- ✓ Respiratory toxicities
- ✓ Musculoskeletal toxicities
- ✓ Cardiovascular toxicities

Anti-Angionic Drug: Targeting the angiopoietin axis with non-VEGF inhibitors is an alternate strategy in ovarian cancer and is still undergoing early clinical trials [25]. Trebananib, a peptide-Fc fusion protein (peptibody) inhibiting the interaction of angiopoietin-1 and -2 to the Tie2 receptor, has been evaluated in combination with paclitaxel in recurrent ovarian cancer [26]. The results of a Phase III trial have been promising. Participants were treated with paclitaxel alone or paclitaxel and trebananib [27].

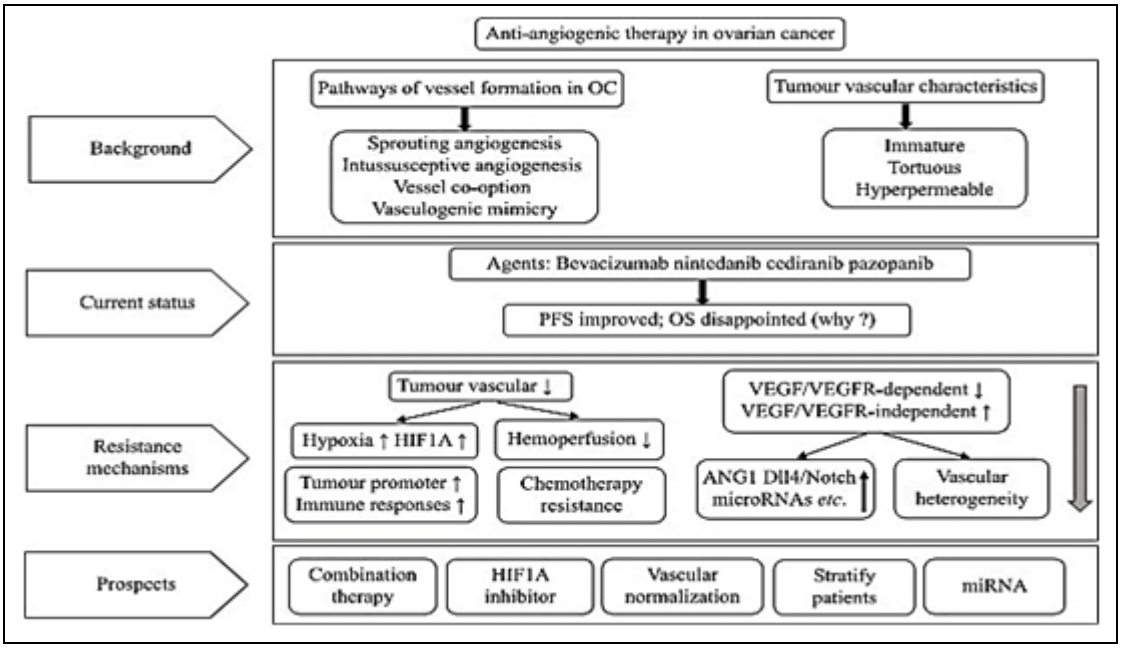


FIG. 9: CHART OF GENERAL ASPECTS OF ANTIANGIONIC DRUG

Mechanism of Action:

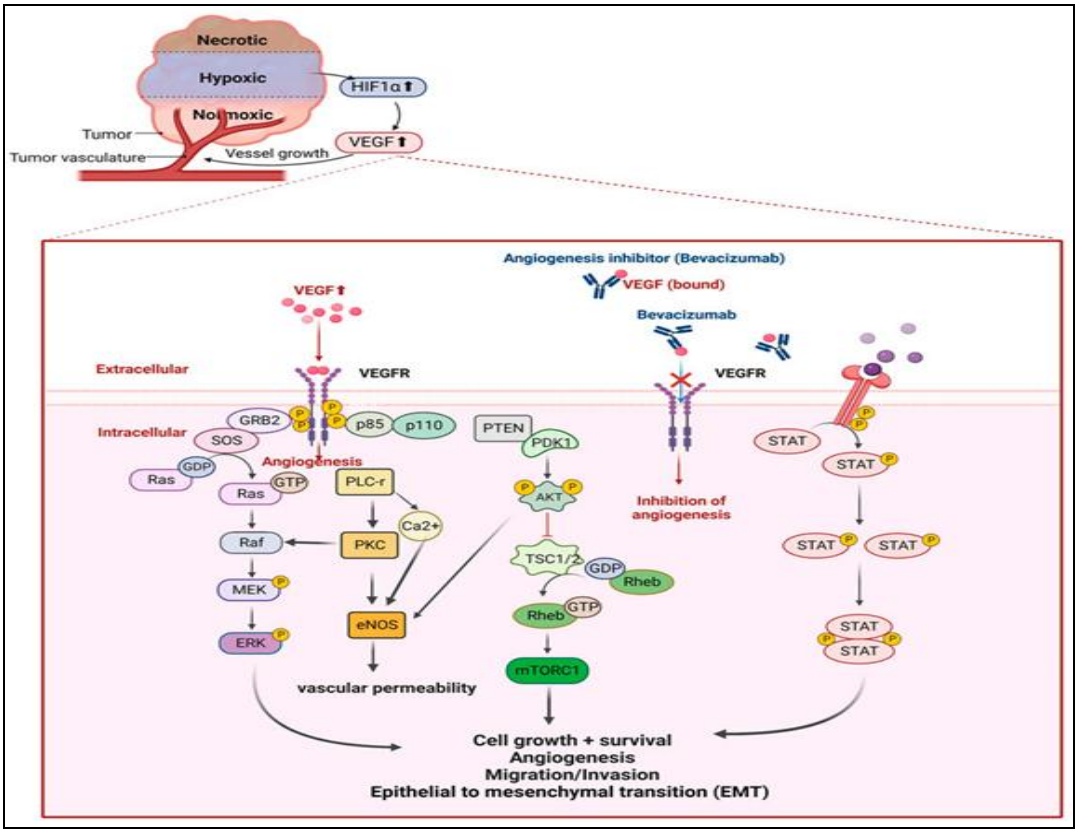


FIG. 10: MECHANISM OF ACTION OF ANTIANGIONIC DRUG

Angiogenesis, the process of new blood vessel formation, plays a pivotal role in normal ovarian physiology, as well as ovarian cancer progression [28]. VEGFs A-D and their receptors (VEGFRs 1-3) are among the many factors that regulate angiogenesis and are expressed at varying levels on epithelial ovarian cancer cells; additionally, increased VEGF signalling has been linked to the development of malignant ascites and tumor progression [28, 29]. Two angiogenesis inhibitors, bevacizumab and cediranib, with distinct mechanisms of action [30], have shown antitumor activity in patients with ovarian cancer [31, 32, 33, 34; bevacizumab is a monoclonal antibody that targets VEGF-A, while cediranib is a small-molecule inhibitor that targets multiple factors, including VEGFRs 1-3 and c-Kit [35].

Following the results of the GOG-0218 and ICON7 studies, the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved bevacizumab in combination with platinum-based chemotherapy, followed by bevacizumab alone as maintenance, for the treatment of patients with FIGO (International Federation of Gynaecology and Obstetrics) stage III or IV epithelial ovarian cancer after initial surgical resection **Table 1**. For patients with platinum-sensitive recurrent/relapsed (PSR) ovarian cancer, bevacizumab is also approved in combination with, and as maintenance after, platinum-based chemotherapy. The FDA and EMA have approved bevacizumab in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for patients with platinum-resistant recurrent ovarian cancer who have had two prior chemotherapy regimens. For both relapsed disease indications, the EMA specifies that patients must not have received prior bevacizumab or other antiangiogenic treatment [36].

Approved angiogenesis inhibitors include:

1. Bevacizumab (Avastin®)

2. Axitinib (Inlyta®)

3. Cabozantinib (Cometriq®)

4. Everolimus (Afinitor®)

5. Lenalidomide (Revlimid®)

6. Lenvatinib mesylate (Lenvima®)

7. Pazopanib (Votrient®)

8. Ramucirumab (Cyramza®)

9. Regorafenib (Stivarga®)

10. Sorafenib (Nexavar®)

11. Sunitinib (Sutent®)

12. Thalidomide (Synovir, Thalomid®)

13. Vandetanib (Caprelsa®)

14. Ziv-aflibercept (Zaltrap®)

Immunotherapy: Your immune system would be able to protect you from cancer cells, too. But unlike a virus, which your immune system recognizes as a foreign invader, cancer cells are still a part of you. Because of this, the immune system doesn't effectively recognize and respond to cancer [37].

Immunotherapy is a form of cancer treatment that helps your immune system learn how to identify and respond to cancer cells.

There are several types of immunotherapy, including [37]:

Immune Checkpoint Inhibitors: These are drugs that help the immune system better detect cancer cells.

Monoclonal Antibodies: These are manufactured antibodies that can target specific aspects of cancer cells.

Chimeric Antigen Receptor T-Cell Therapy: CAR T-cell therapy trains certain immune cells, called T cells, to find and destroy cancer cells.

Cytokines: These are proteins that can stimulate the immune system.

Immunomodulators: These are drugs that help boost the immune system.

Cancer Vaccines: These are vaccines that trigger the immune system to respond to cancer.

Oncolytic Viruses: These are modified viruses that are designed to infect and kill cancer cells.

Current immunotherapy treatment of ovarian cancer:

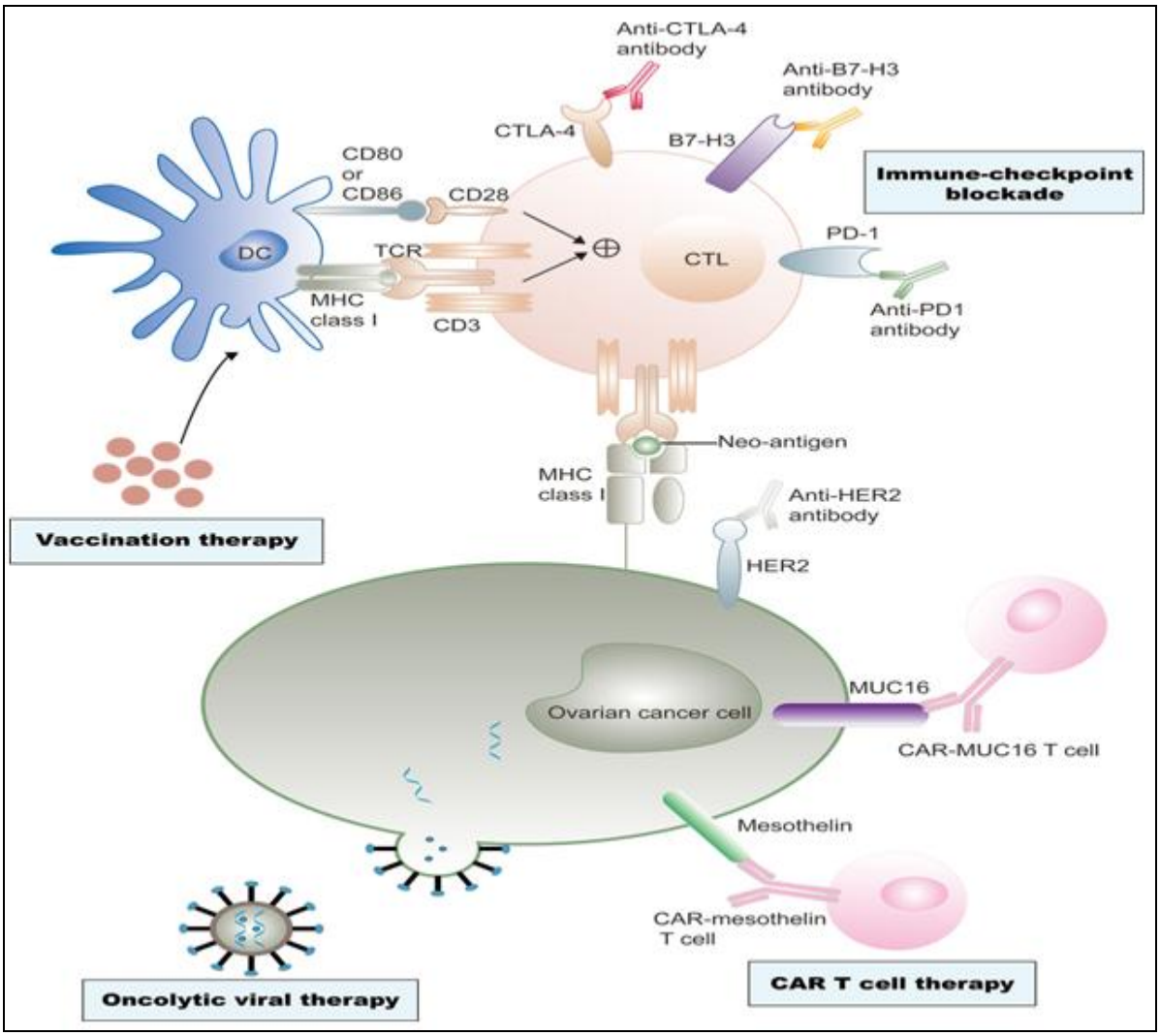


FIG. 11: CURRENT IMMUNOTHERAPY TREATMENT OF OVARIAN CANCER

Chemotherapy: Chemotherapy uses one or more drugs to kill cancer cells.

A randomized control trial of elderly patients over the age of 70 with comorbidities and stage III-IV ovarian cancer found that carboplatin monotherapy was associated with worse survival outcomes than carboplatin-paclitaxel three weekly/weekly [38]. However, when used in combination therapy, a modified dose-dense regimen of weekly carboplatin plus paclitaxel has been shown to be better tolerated with a lower toxicity profile than the standard dosing (three weeks schedule). Despite this, it did not improve progression-free survival in the MIT07 phase III trial, which can also be used in elderly patients with comorbidities [39, 40]. It was discovered that the elderly, frail patients had lower levels of neuropathy, thrombocytopenia, febrile neutropenia, and high-grade neutropenia [39]. Our ability to predict chemotherapy tolerance will be aided by an ongoing prospective trial involving older women who are at least 70 years old and receiving various combinations of chemotherapy regimens. Preliminary findings, however, indicate that patients with higher baseline instrumental activities on the daily living score are less likely to experience high-grade toxicity and are more likely to finish four cycles of chemotherapy [41].

Radiation Therapy: Radiation therapy kills cancer cells and shrinks tumours with high-energy beam.

In the past, total abdominal radiation was used, but because of a higher risk of toxicity and complications, it was eventually abandoned. Radiation therapy for ovarian cancer is currently

only used in palliative care, either to treat localized disease spread or to manage symptoms. Including a subset of patients at high risk, adjuvant radiation therapy has not demonstrated a survival benefit in cases of early-stage clear cell carcinoma [42].

Radiation therapy for ovarian cancer has become less common due to the development of sophisticated systemic therapies. The newest method of palliative radiation therapy is stereotactic body radiotherapy (SBRT). Even when local control is achieved, there is ongoing evidence that the use of this medication increases the rate of distant progression of lesions [43]. The role of radiation in the treatment of locally recurrent ovarian cancer, particularly in chemotherapy-resistant lesions, is currently being strongly considered. This is due to the introduction of new techniques such as SBRT, intensity-modulated radiotherapy and low-dose hypo-fractionation [44, 45].

CONCLUSION: A woman's risk of getting ovarian cancer during her lifetime is about one in 67. Ovarian cancer is the type of cancer that begin in the ovaries. these cells multiply quickly and can invade and destroy healthy body tissue over the past 40 years, the treatment of ovarian cancer has undoubtedly improved as a result of better multi-modality care and more recently, the introduction of anti-angionic therapy, PARP inhibitor have achieved significant clinical efficacy in the treatment of recurrent ovarian cancer. Targeted drugs called PARP inhibitors stop cancer cells' PARP enzymes from functioning properly. This results in the cancer cells dying since it prevents them from mending during cancer treatment. One sort of targeted therapy called anti-angiogenic medicines prevents tumor from growing new blood vessels, which are necessary for the tumor to spread and grow. They function by inhibiting the proteins that aid in the formation of blood vessels or by halting the impulses that cause blood vessels to expand and divide.

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CONFLICT OF INTEREST: There is No conflict of interest in this article.

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