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**Case Report** **Internal Medicine**

# An Outstanding Rapid Clinical Response to Olaparib in A Patient with gBRCA2m Fungating Breast Cancer: A Case Report

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## Abstract

***Background*:** Breast cancer is a heterogeneous, phenotypically complex disease made up of various biologic subgroups with unique behaviors and therapeutic responses. Noted that despite lack of a cure for metastatic breast cancer (MBC), there have been appreciable advancements in survival that have occurred at the same time as newer systemic treatments. BRCA1 or BRCA2 mutations cause homologous recombination deficient (HRD) cells, which are vulnerable to PARPi agent treatment. ***Case Report*:** This case report presents a 40 years old single female, known case of multiple co-morbidities who was diagnosed with Bilateral breast cancer in June 2022. She has a Positive family history of malignancy; mother died from endometrial cancer and aunt from paternal side has breast cancer. She underwent needle core biopsy from her Right breast mass, which revealed Invasive high-grade ductal carcinoma with metaplastic features (foci of keratinizing squamous differentiation, and myxoid stromal change). DCIS, of intermediate and high grades and a solid pattern, was noted, focally suspicious for lymphovascular invasion, Triple negative (ER negative (<1%), PR negative (<1%) and her-2 (+2) FISH negative (Her-2 Low), KI 67= 70%. Left breast mass Biopsy done on 12/9/2022 showed Invasive Lobular carcinoma, grade 3, ER negative, PR negative, Her-2 +1, KI 67=70%, BRCA2 POSITIVE & PDL1 CPS score 10%. Staging positron emission tomography scan done on 10 October 2022. She had a Large hypermetabolic fungating right breast mass infiltrating the chest wall, consistent with biopsy-proven malignancy. Additional smaller FDG-avid lesions noted in the right breast. Moreover, she had FDG-avid right axillary and right internal mammary nodal metastases. Mildly FDG-avid left breast mass, consistent with biopsy-proven malignancy. FDG-avid liver and pleural metastases. She was started on PARP inhibitor (Olaparib) on 20/9/2022 after which she had amazing fast clinical response leading to falling off the large fungating mass. ***Conclusion*:** The chance of developing breast and ovarian cancer is extremely elevated if one possesses BRAC 1 or BRCA 2 mutation. In this situation, PARP inhibitors, mutation-targeted therapy, has better outcomes in reducing the morbidity and mortality associated with metastatic breast cancer (Olaparib).

**Keywords:** Olaparib, Breast cancer, fungating, mutation.



## INTRODUCTION

Breast cancer is a significant public health concern that affects more women than any other type of cancer, both in developed and developing countries [1]. Breast cancer accounts for around one-fourth of all cancer diagnoses and fourteen percent of all cancer-related deaths worldwide, culminating in over 500,000 breast cancer deaths in 2008 alone [2]. Despite advancements in treatment and prevention, breast cancer incidence rates continue to climb in the majority of countries.

Locally advanced breast cancer, especially the fungating subtype, is characterized by large, advanced tumors that spread to the chest wall and/or skin and involve regional lymph nodes [3]. In developing nations, delayed diagnosis and presentation of breast lumps are caused by cultural and social hurdles, lack of awareness, and economic restraints. Frequently, women do not seek medical attention until the lump has greatly enlarged, culminating in a big tumor or a fungating mass [4].

Fungating malignant lesions are capable of causing infections, odor, bleeding, necrosis, and ulceration [5]. Not only do these masses carry a high death risk, but they also have a substantial emotional impact. Most frequently, patients with fungating lesions may avoid medical care due to embarrassment, While the disease is aggressive and incurable, palliative care seeks to improve the patient's quality of life [6]. This includes wound cleaning, radiation therapy, topical analgesia, debridement, cauterization, or embolization. These treatment options help in the stoppage of bleeding. Chemotherapy may also be used to diminish the size of a tumor [7], and surgical resections are common.

PARP inhibitors have also been shown to be effective in the treatment of breast cancer, particularly for tumors with specific DNA-repair defects [8]. Through in vitro and in vivo studies, breast cancer cell lines, which provide an infinite source of homogenous self-replicating materials using simple conventional techniques, have contributed greatly to our understanding of breast carcinomas [3]. Yet, the development of an effective and commercially viable medication involves a multidisciplinary effort throughout the drug discovery process, with the DNA repair process of the cell giving significant insights. Due to their PARP-inhibiting capability, which may induce apoptosis, PARP-1 inhibitors have the potential to be used as a treatment for cancers lacking BRCA1 or BRCA2 genes [4]. The United States Food and Drug Administration has also approved Olaparib, an orally active PARP inhibitor, for patients who have already undergone chemotherapy and who have germline BRCA mutations and HER2-negative metastatic cancer due to its ability to promote cell death in BRCA-deficient cells [9]. This report discusses a case of fungating breast cancer with gBRCA2m which was successfully managed with Olaparib.

## CASE REPORT

This case report presents a 40 years old single female who was diagnosed with bilateral breast cancer in June 2022. She has multiple comorbidities including Single right kidney, status post left nephrectomy (resected 1993), Congenital back and bilateral lower limb skeletal defects, status post multiple surgeries done in Germany. Back surgery complicated by urinary retention, on intermittent self-catheterization. As well, she has a Positive family history of malignancy; mother died from endometrial cancer and aunt from paternal side has breast cancer. With regard to her breast cancer, the patient reports that the right breast lesion started as a small nodule that was about 2 cm in size back in February 2022. It has been progressively increasing in size. In June of 2022, the mass dramatically started increasing in size with ulceration and necrosis.

She underwent needle core biopsy from her Right breast mass, which revealed Invasive high-grade ductal carcinoma with metaplastic features (foci of keratinizing squamous differentiation, and myxoid stromal change). Modified Nottingham grade 3 (tubular differentiation: 3; nuclear pleomorphism: 3, mitotic activity: 2, score = 8/9), DCIS of intermediate and high grades and a solid pattern, was noted, Focally suspicious for lymphovascular invasion, Triple negative (ER negative (<1%), PR negative (<1%) and her-2 (+2) FISH negative (Her-2 Low), KI 67= 70%. The Left breast mass Biopsy done on 12/9/2022 showed Invasive Lobular carcinoma, grade 3, ER negative, PR negative, Her-2 +1 (Her-2 Low), KI 67=70%, BRCA2 POSITIVE & PDL1 CPS score 10%.

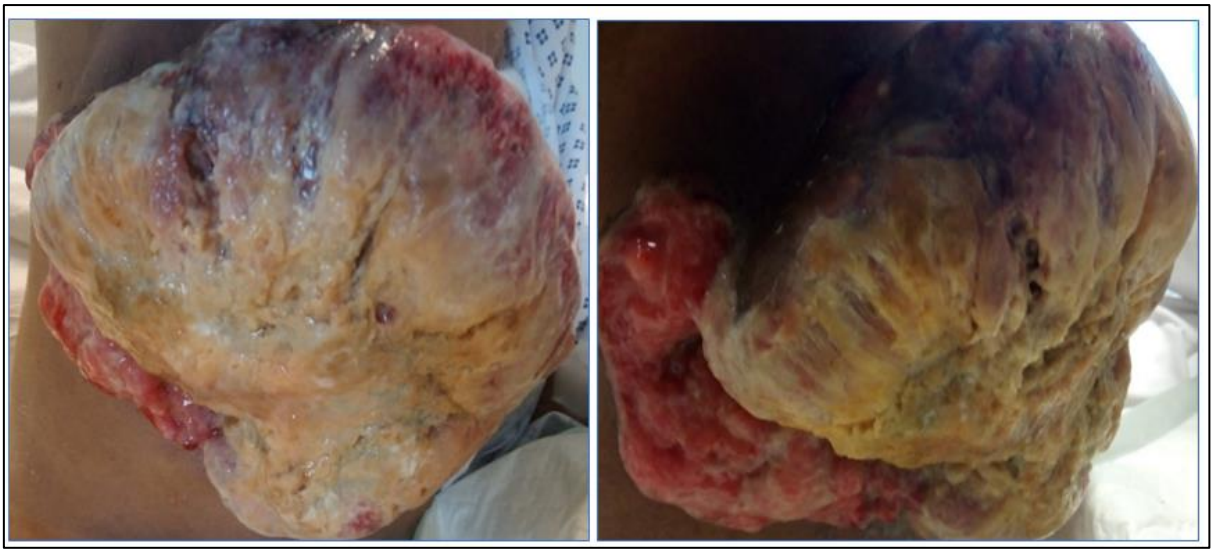
Staging positron emission tomography scan was done on 10 October 2022, reported as follows:

A. Large hypermetabolic fungating right breast mass infiltrating the chest wall, consistent with biopsy-proven malignancy. Additional smaller FDG-avid lesions noted in the right breast.
B. FDG-avid right axillary and right internal mammary nodal metastases.
C. Mildly FDG-avid left breast mass, consistent with biopsy-proven malignancy.
   Metastasis versus synchronous primary.
D. FDG-avid liver and pleural metastases.

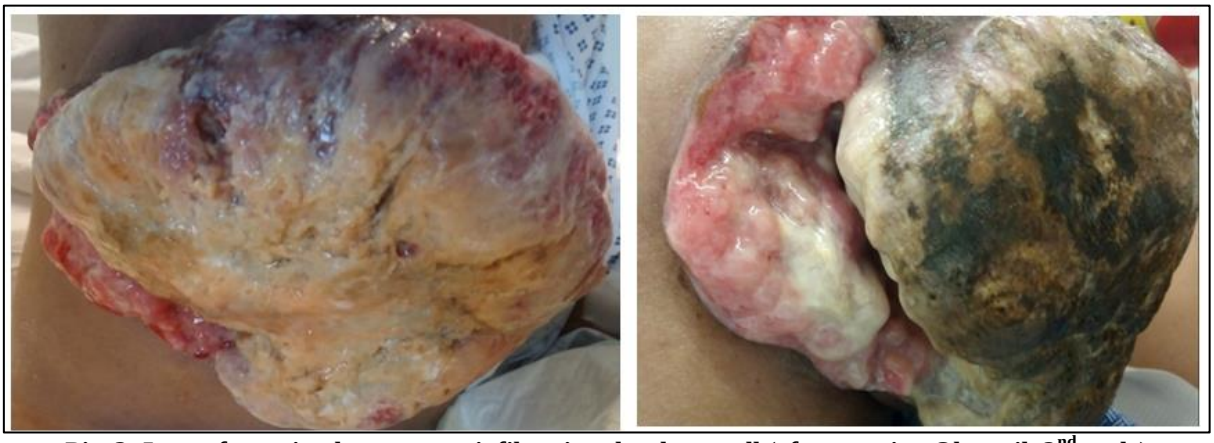
She had a Large hypermetabolic fungating right breast mass infiltrating the chest wall (Pic 1), consistent with biopsy-proven malignancy. Additional smaller FDG-avid lesions noted in the right breast. Additionally she had FDG-avid right axillary and right internal mammary nodal metastases. Also, she had mildly FDG-avid left breast mass, which was consistent with biopsy-proven malignancy. Consequently, she had FDG-avid liver and pleural metastases.

She was offered to start with chemotherapy as she was staged as stage IV disease, but patient was reluctant to start chemotherapy as she has single kidney, and was concerned of the chemotherapy general side effects especially on her kidney & so she tooks the decision not to start chemotherapy.

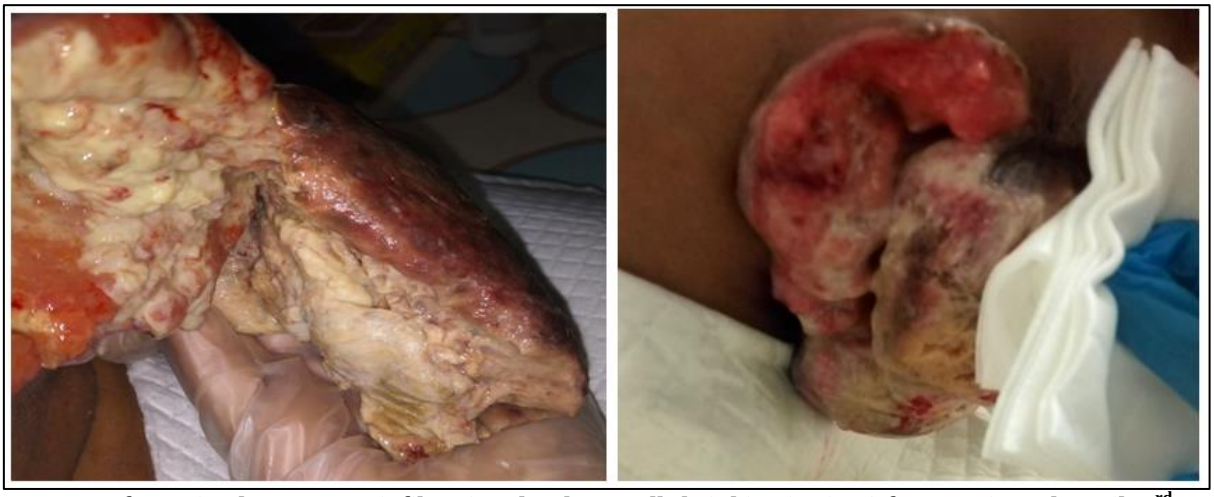
Overtime, her condition deteriorated , the breast lesion increased in size, became ulcerated extending to right lateral axilla & the breast as such is replaced by a proliferative cauliflower growth with some degree of cellulitis and pain.



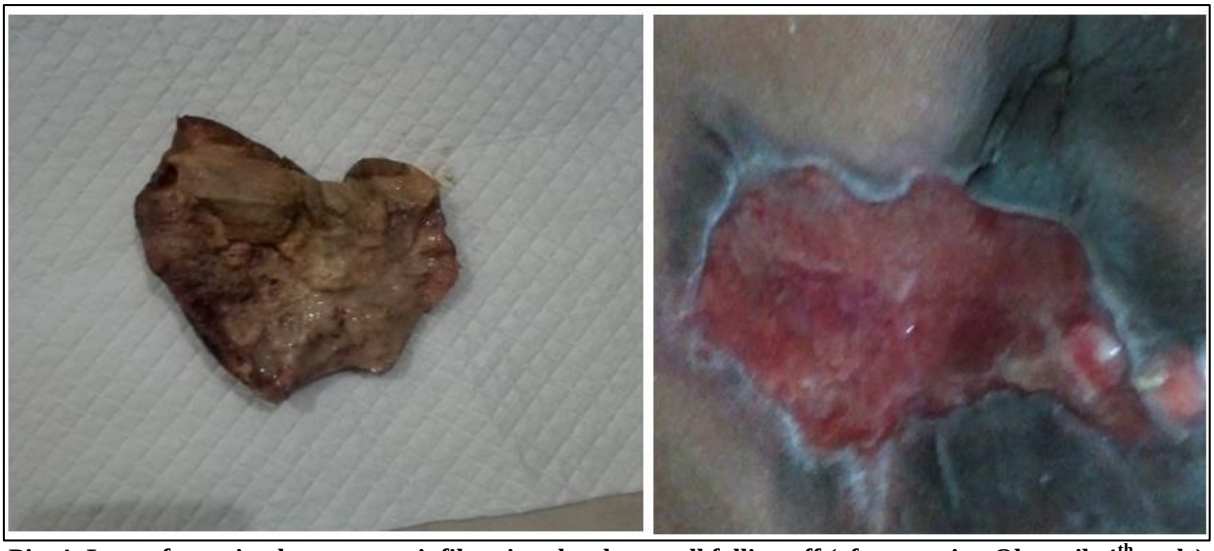
**Pic–1: Large fungating breast mass infiltrating the chest wall (before starting Olaparib)**



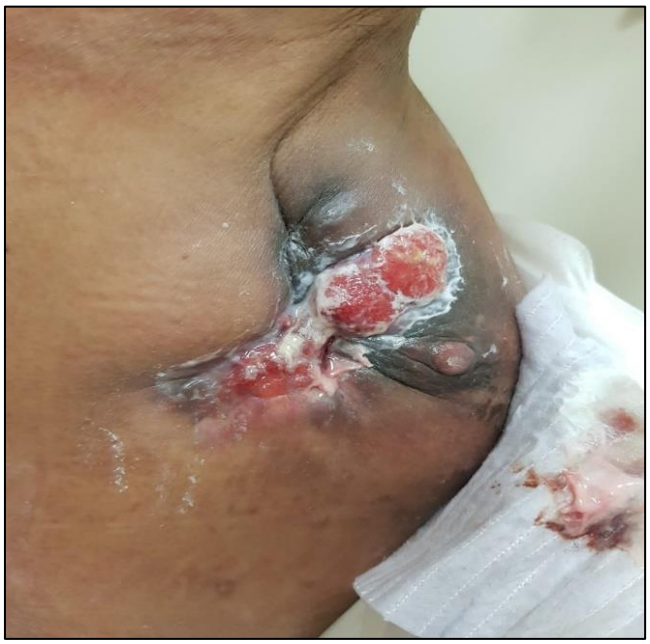
**Pic–2: Large fungating breast mass infiltrating the chest wall (after starting Olaparib 2nd cycle)**



**Pic–3: Large fungating breast mass infiltrating the chest wall shrinking in size (after starting Olaparib 3rd cycle)**



**Pic–4: Large fungating breast mass infiltrating the chest wall falling off (after starting Olaparib 4th cycle)**



**Pic–5: Amazing results after 4th cycle of Olaparib. The Large fungating breast mass fell down, breast tissue is healing**

Her case was discussed in tumor board & multidisciplinary team meeting. The nutshell of the meeting was that Surgery is unlikely to result in negative margins and will be a major one requiring a free flap for coverage. In addition to multiple other risks of the surgery in terms of long operation, infection, poor / delayed healing / non-viability of any graft / flap, given all those potential hazards, it's reasonable to go for oncologic treatment (radiotherapy / chemo / immunotherapy) which is believed to be the best for her quality of life. So the patient was planned to be transferred under the care of oncology team to re-discuss & consider chemotherapy, but she was unsuitable for that due to multiple admissions with recurrent catheter related Urinary tract infections and persistent patient chemotherapy denial.

Here came the decision to start her on PARP inhibitors , & hence she was started on Olaparib 300 mg BID on 20/9/2022 & was discharged home 3 days later.

We based our treatment on the OlympiAD which is a Phase III study investigating olaparib vs TPC (Treatment of Physician Choice) in gBRCAm HER2-negative metastatic breast. She had her first visit in oncology clinic on 28/9/22 post discharge , she was doing well on Olaparib & still refusing chemotherapy .

**Disease course while on Olaparib:**

- On 2/11/22 the breast mass seen healing ( Pic 2).
- On 18/11/22 the left: lump disappeared, no nipple retraction, no discharge, The fungating and ulcerating mass which was ocuupying the

whole right breast was healing and shrinking in size (Pic 3)

- On the following visit , the breast mass has already fallen down , & the underlying breast tissue was in a healing process (Pic 4-5)

As well there was a major decline in tumor markers after initiation of Olaparib, Fig 1 illustrates the change in CD 15 – 3 tumor marker over time while on Olaparib.

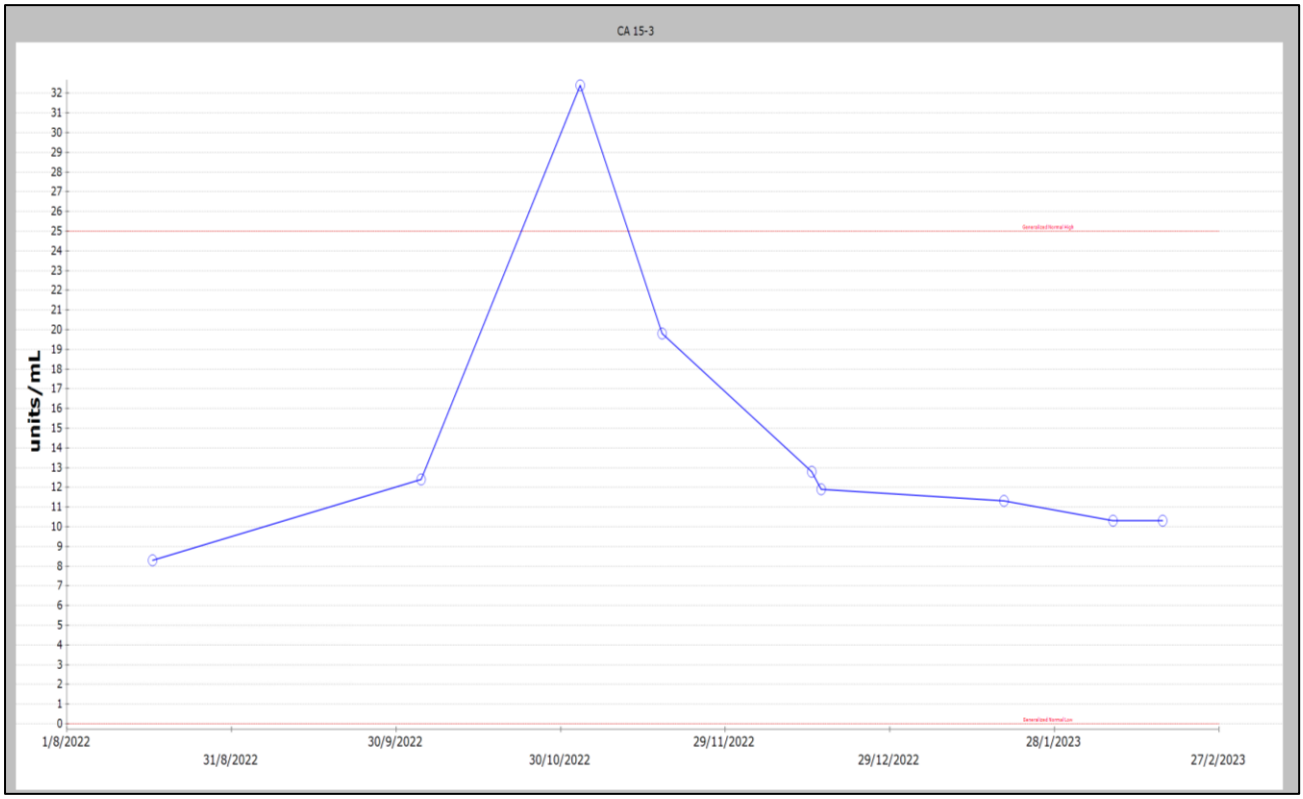



**Fig 1: Changes in serum tumor marker levels before and after treatment**

## DISCUSSION

This case report highlights the complexity of managing fungating breast cancer in a patient with multiple comorbidities and a positive family history of cancer. Fungating breast cancers are relatively uncommon but can pose a formidable management issue for medical professionals [10]. These malignant wounds are often accompanied by crusting, bleeding, pruritic, exudation, and aesthetic disturbance and can have severe consequences [11].

Due to the severity of their condition, many of these individuals are ineligible for initial surgical resection, preventing adequate wound closure. Systemic treatment may result in cytoreduction [12]. However, not every patient can be transformed successfully into a surgical candidate. Our patient was not a viable surgical candidate. Surgery was not recommended in our case due to the considerable risks associated with surgery, such as lengthy operation time, the risk of infection, and the possibility of problems with healing and graft viability. Additionally, her prolonged refusal to take chemotherapy and frequent urinary tract infections caused by catheterization exacerbated the difficulty of managing her condition. Hence, it was decided to initiate PARP inhibitors to treat fungating breast cancer.

Olaparib is an FDA-approved treatment for patients with metastatic, HER2-negative breast cancer who also contain the BRCA1/2 mutation and have had chemotherapy in the past (and endocrine therapy, if appropriate) [13]. Also, we recommend it for persons with severe somatic BRCA1/2 mutations and germline PALB2 mutations who have previously had chemotherapy. Therefore, our patient was to be transferred under the care of the oncology team to re-discuss and consider chemotherapy, but she was unsuitable for this due to multiple admissions with catheter-related UTIs and persistent patient chemotherapy refusal.

PARP inhibition has a molecular basis as a cancer treatment. PARP is required for the metabolic pathways that lead to a cell's recovery from DNA damage [14]. When PARP1, the most common member of the PARP family, is inhibited, double-strand DNA breaks and accumulates. Under normal circumstances, these breaks are repaired by the "BRCA pathway-dependent homologous recombination mechanism" [15]. Their predictions have been validated in both clinical and preclinical settings [16, 17].

For example, a study examined the effectiveness and safety of PARP inhibition in both TNBCs and BRCA-mutated breast cancer cancers [18]. Olaparib exhibited improved progression-free survival (PFS) to chemotherapy in a survey of 121 BRCA mutation carriers with "metastatic triple-negative disease" who had all received a taxane or an anthracycline in either a metastatic or an adjuvant setting (HR for progression or death 0.43, 95% CI 0.30-0.63) [18]. The overall findings of the study, which included patients with HER2-negative, "hormone receptor-positive disease", were promising, although the advantages of olaparib were more obvious in the triple-negative group. Our patient also belonged to a triple negative group.

Additionally, MEDIOLOA and TOPACIO trials investigated the efficacy and safety of Olaparib in conjunction with immune system checkpoint inhibitors. In the MEDIOLOA trial, Olaparib was administered to patients for a 4-week run-in period before being combined with durvalumab. By examining the data from the first 32 patients, it was discovered that the disease control rate (DCR) at 12 weeks was 81% [18]. Similarly, in other research the phase I/II TOPACIO study examined the safety and efficacy of combining treatments with the PARP inhibitor, pembrolizumab, and niraparib in patients with triple-negative breast cancer or recurrent ovarian cancer, In the 60 patients who could be evaluated, the ORR/DCR was 25%/68%, and in the 11 patients who could be evaluated for tumor BRCA mutations, it was 45%/73% [19, 20]. However, more research is needed in the future to confirm the effectiveness of Olaparib in the treatment of fungating breast cancer caused by gBRCA2 mutation. Although, Olaparib is a targeted therapy and is helpful in treating patients with BRCA gene mutations. It is more and more important to take into account mutation screenings of breast cancer patients as new therapeutic modalities and Next generation sequencing development progress.

## CONCLUSION

Over two million cases of breast cancer are diagnosed worldwide each year, making it the most common malignancy. Additionally, it is the primary global cause of cancer death in women. Treatment modalities are diverse. For those with BRAC 1 or BRCA 2 mutation, triple negative disease, PARP inhibitors (Olaparib), mutation-targeted therapy, has better outcomes in reducing the morbidity and mortality associated with metastatic breast cancer.

### CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

**Ethical Approval:** As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

**Competing Interests:** Authors have declared that no competing interests exist.

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