Scholars Academic Journal of Pharmacy
Abbreviated Key Title: Sch Acad J Pharm
ISSN 2347-9531 (Print) | ISSN 2320-4206 (Online)
Journal homepage: http://saspublishers.com

OPEN ACCESS

Oncology & Hematology

Germline BRCA 1 Positive Breast Ovarian Cancer Syndrome

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DOI: 10.36347/sajp.2023.v12i06.002 | **Received:** 26.04.2023 | **Accepted:** 29.05.2023 | **Published:** 07.06.2023

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Abstract **Case Report**

***Background*:** *BRCA1* (Beast Cancer gene 1) and *BRCA2* (Breast Cancer gene 2) are genes that produce proteins that help repair damaged DNA. Mutations in these genes predispose the person to a substantiable risk of developing breast and ovarian cancers among others. Approximately 10 to 15% of all cases of epithelial ovarian cancer and les than 10 % of Breast cancers are caused by a mutation in the BRCA1 or BRCA2 genes, which when occurs together results in hereditary breast ovarian cancer syndrome. ***Case Presentation*:** This case report presents the clinical course of a 57-year-old female patient who presented with a mass in her right breast in June 2022. The patient's past medical history is significant with a diagnosis of triple-negative non-metastatic left breast cancer that was treated with surgery followed by adjuvant chemotherapy containing Doxorubicin and Taxanes with loco-regional radiotherapy in May 2009. On June 2022 (later after 13 years) patient noticed a Rt breast mass and was evaluated further. A mammography showed an ill-defined micro lobulated lesion 4 cm from the nipple, measuring 43 x 27 mm with a few microcalcifications. Later, an ultrasound right breast confirmed the presence of an ill-defined lesion in her right breast with no significant axillary nodes, True-cut biopsy performed on October 26th, 2022 revealed invasive triple negative ductal carcinoma. Staging work up with Positron Emission tomography and computerized tomography scan showed in addition to the right breast mass, an ovarian mass with peritoneal deposits. This prompted a peritoneal biopsy which confirmed a high grade primary serous carcinoma of ovary. Additionally, BRCA1/2 germline testing showed a positive BRCA1 germline mutation. Following this, the patient was started on neoadjuvant keynote 522 protocol specifically with Epirubicin, Cyclophosphamide, Paclitaxel carboplatin with pembrolizumab. As of the date of reporting she has completed CARBOPLATIN-TAXOL and is now on the third cycle of EC chemotherapy. ***Conclusion*:** This case demonstrates the complexity and difficulty of handling individuals with a history of multiple cancers, particularly in the presence of BRCA1 germline mutation and emphasizes on multidisciplinary care and decision making involving Medical and Radiation Oncologists, Surgeons and in such cases a Clinical Geneticist as well.

Keywords: Beast Cancer gene 1, Doxorubicin, radiotherapy, neoadjuvant keynote, mutation.

INTRODUCTION

Breast cancer is a prevalent cancer type worldwide and is the second leading cause of cancer-related deaths among women [1]. In recent decades, the incidence of breast cancer in India has significantly increased, affecting one in twenty-eight women, particularly young women, with more aggressive clinical behavior [2]. Like breast cancer, ovarian cancer is another common type of cancer. In India, the incidence rate of this cancer is ranging from 5.4 to 8 per 100,000 [3]. Ovarian cancer may manifest as site-specific or occur concomitantly with early-onset breast cancer. When ovarian and breast cancer occurs together, this condition is referred to as hereditary breast and ovarian cancer syndrome [4]. This syndrome is caused by germline mutations in BRCA 2 or BRCA1 genes [5].

Researchers explain that BRCA1 gene participates in the repair of DNA double-strand breaks by interacting with other proteins, such as RAD51. In the DNA mismatch repair process, BRCA1 also interacts with proteins like MSH2, and it's possible that it also does so with poly (ADP-ribose) polymerase (PARP) in single-strand repair [6]. Hence, if any mutation in the BRCA gene occurs, it leads to a deficient DNA repair mechanism, resulting in an increase in mutation rates and encouraging tumor

growth [7]. Consequently, individuals with these mutations are more susceptible to chromosomal instability, creating opportunities for novel treatments such as sensitivity to DNA-damaging agents, poly (ADP-ribose) polymerase inhibitors, and ionizing radiations [8].

Numerous researchers have also investigated the application of neoadjuvant chemotherapy in breast cancer patients with mutations of BRCA genes, with an emphasis on "pathologic complete response" (PCR) rates as an indicator of clinical efficacy and prognosis [9]. According to major observational research, ten out of twelve (83%) patients with BRCA1 positive breast cancer who underwent neoadjuvant cisplatin achieved PCR [10]. In contrast, the PCR rates for patients with BRCA1 mutated breast cancer who were treated with fluorouracil, methotrexate, doxorubicin, and cyclophosphamide with or without fluorouracil were significantly lower (7%, 8%, and 22%, respectively) [11].

Additionally, individuals with "invasive breast cancer" caused by genetic breast cancer syndromes, such as the "BRCA-related breast cancer syndrome" are offered treatment options that are tailored to their individual needs [12]. These patients respond very well to DNA damaging medicines such as platinum-based therapies and "poly-ADP ribose polymerase" inhibitors that prevent the recruitment of DNA damage repair by inhibiting the production of ADP-ribose polymers at the place of breakage area of DNA single-strand [13].

Other potential treatments investigated in patients with invasive breast cancer having BRCA 1 mutation include trabectedin, which has demonstrated specific activity against intact metastatic breast cancer albeit not a recommended treatment currently [14].

This case report presents a case of 57 years old female who initially developed breast cancer in 2009 and later after 13 years, was diagnosed with recurrent breast cancer with associated primary ovarian Ca and positive germline BRCA 1 mutation.

CASE REPORT

This case report presents the clinical course of a 57-year-old female patient who presented with a mass in her right breast in June 2022.

She had a diagnosis of left nonmetastatic triple negative breast Ca in 2009 for which she underwent Left mastectomy and axillary clearance in May of 2009.

She had a pT2N3M0 disease with high-risk features such as extranodal capsular invasion and lympho-vascular invasion.

Surgery was followed by chemotherapy with AC 4 and Paclitaxel 12 cycles, and adjuvant radiation 50.4 Gy to left chest wall and left supraclavicular area in 28 fractions. Treatment was completed in early quarter of 2010 and she remained disease free until 2022.

In June 2022she noticed a mass in the Rt breast and a mammography done revealed an ill-defined micro lobulated lesion 4 cm from the nipple, measuring 43 x 27 mm with a few microcalcifications.

Ultrasound revealed an ill-defined hypoechoic lesion measuring 35 x 26 mm with no obvious internal mammary or right axillary suspicious lymph nodes.

17/11/2022

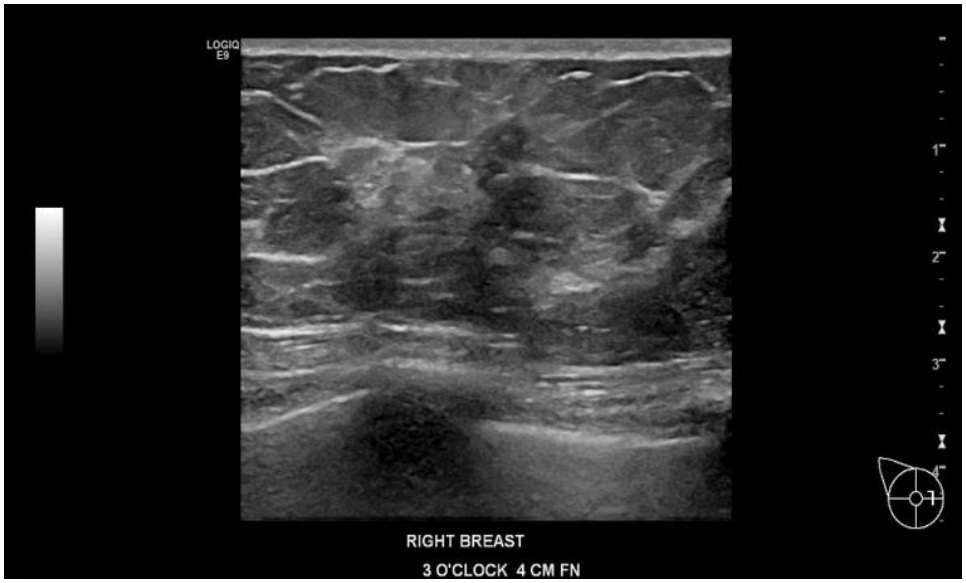

Fig 1: Right breast US Ultrasound

A True-cut biopsy was performed in India on October 26th, 2022, which reported invasive mammary carcinoma grade 3 score 8/9, ER negative, PR negative, HER2/neu negative, KI 67 90 percent, and E-cadherin positive in the neoplastic cells.

Right breast mass biopsy 11/11/ 2022:

CASE SUMMARY: (INVASIVE CARCINOMA OF THE BREAST: Biopsy)
Mitotic Rate: score 2
Overall Grade: Grade 3
- Ductal Carcinoma In Situ: Not Present
- Necrosis: Present
- Lobular Carcinoma In Situ (LCIS): Not identified.
Lymph-Vascular Invasion: No definite

Predictive markers:
Estrogen Receptor (ER) Status: Negative
Status of internal controls: Not present
Progesterone Receptor (PgR) Status:
Specify percentage of cells with nuclear positivity: Negative
HER2 by Immunohistochemistry :1+
Percentage of cells with uniform intense complete membrane staining: 5%
+ Ki-67
+ Percentage of cells with nuclear positivity (specify): Up to 70% in some areas.
Diagnosis
Right breast mass, biopsy:
- Invasive carcinoma of no special type, Grade 3.

Staging work up with computerized tomography scan showed an ovarian mass with peritoneal deposits in addition to the rt breast mass.

Further examination through a Positron Emission Tomography-Computerized Tomography (PET-CT) scan revealed a right breast mass with a right axillary lymph node and a right ovarian mass with peritoneal deposits.

PET CT 15/11/2022:
IMPRESSION: 1. Intensely FDG-avid right breast mass, consistent with biopsy-proven malignancy. 2. Mildly FDG-avid right axillary node with thickened cortex, suspicious. 3. Intensely FDG-avid right ovarian mass with FDG-avid peritoneal deposits, highly suspicious for synchronous primary ovarian malignancy with peritoneal spread. 4. Rest of the study shows no evidence of FDG-avid malignancy.

Considering the clinical features and history we did a true cut biopsy of the peritoneal deposit which revealed a primary high grade serous carcinoma of Ovary.
FNAC peritoneal nodule
Descriptive Diagnosis

Left Peritoneal Nodule - FNA:

Evaluation of this aspirate shows scattered clusters and cohesive groups/acini of neoplastic cells, depicted by pleomorphic nuclei with increased nucleocytoplasmic ratios, hyperchromatic chromatin patterns with irregular nuclear contours, visible nucleoli and small to moderate amounts of cytoplasm.

Diagnosis
Malignant cells present.

The cell block was prepared. Sections show serous carcinoma with papillary architecture. There is moderate cytological atypia and occasional mitotic figures. The grading of serous carcinoma is not possible on the available material.

The tumor cells are:

CK7: Positive
GATA3: Negative
TTF one: Negative
PAX8: Positive
WT1: Positive
P 16: Diffuse positivity
ER: Positive

The cytological features and immunohistochemical profile are in keeping with serous carcinoma of primary Mullerian origin.

As is recommended this was followed by germline testing of BRCA1/2 genes. The results came positive for BRCA1 mutation.

MOLECULAR GENETIC ANALYSIS OF *BRCA1/2* GENES

Reason for request / clinical indication
Breast cancer.
Test requested
BRCA1/2 NGS panel.

Method summary: To the peripheral blood sample received it was performed: α) DNA extraction using QIAamp DNA Mini kit (QIAGEN) β) appropriate libraries preparation according to the manufacturer's protocol with the AmoyDx® BRCA1 and BRCA2 Gene Mutation Detection Kit (Amoy Diagnostics Co., L td.) (see Appendix) and sequenced on a NextSeq500 system (Illumina). Bioinformatic analysis was performed using the AmoyDx NGS data analysis system software - ANDAS Data Analyzer to obtain the related gene variant information (Amoy Diagnostics Co., L td.).

Results summary

A pathogenic variant was detected in *BRCA1* gene.
No pathogenic or likely pathogenic variants were detected in *BRCA2* gene.
PARPi drugs are approved.

Results
The following variant was detected in the sample tested:

Gene	Variant Coordinates	dbSNP	Variant Frequency	Exon	Classification
BRCA1	NM_007294.4, c.68_69del, p.(E23Vfs*17)	rs80357914	47.16%	2	Pathogenic

We had an extensive discussion of her case in the multidisciplinary tumor board about the treatment plan and sequencing of Surgery for the breast as well as the Ovary.

We started her on neoadjuvant keynote 522 protocol with (Epirubicin. Cyclophosphamide and Taxol Paclitaxel carboplatin with pembrolizumab).

We omitted doxorubicin as she had received the same before to avoid cardiotoxicity and opted to have Epirubicin.

A review ultrasound after 12 cycles of paclitaxel and platinum showed good partial response.

10/2/2023

Significant size reduction of known malignant lesion at 3:00/4 cm FN. It measures in the current study 22 x 6 x 10 mm previously measured 39 x 25 x 24 mm. No post biopsy clip noted. No axillary lymphadenopathy.

Impression/recommendation

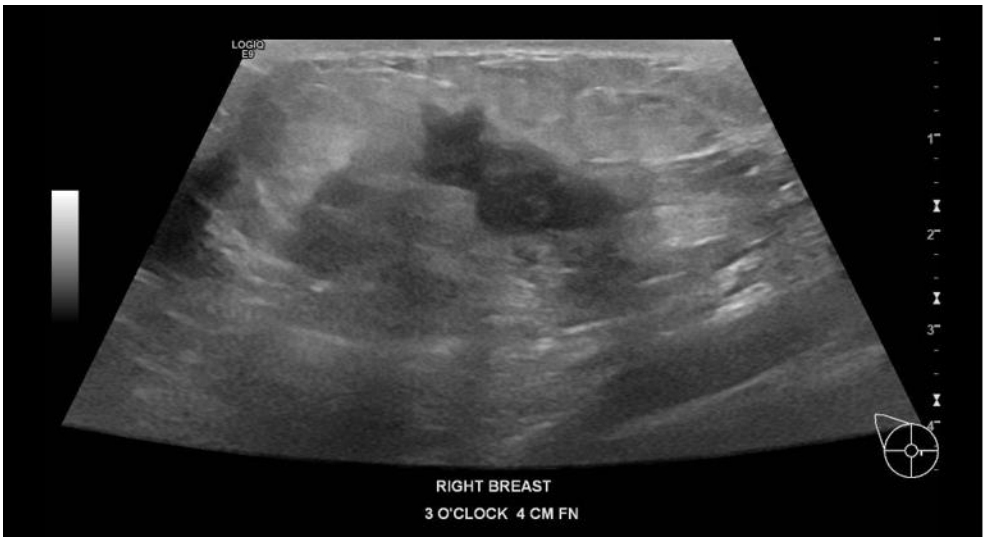

Fig 2: Right breast US Ultrasound showed marked partial response

As of the date of reporting this she has completed taxol carboplatin and is now on the third cycle of EC.

She will undergo reassessment with Ultrasound after completing 4 cycles of EC followed by Surgical management of Breast and ovary sequentially.

Patient has opted for a total Mastectomy and hence after the completion of chemo she will have a Right mastectomy with axillary/sentinel LN biopsy.

This will be followed by adjuvant treatment with Olaparib if she does not have a complete pCR (Pathological complete response) as per OlympiA Trial with or without Capecitabine as needed.

As of the date of reporting this case she has completed taxol carboplatin protocol and is now on the third cycle of EC with pembrolizumab.

Option of adjuvant radiotherapy will be discussed after final Pathology (after surgery).

DISCUSSION

This case demonstrates the difficulties and complexity of handling individuals with a history of triple negative breast cancer, especially in the context of BRCA1 mutation. In 2009, our patient was initially diagnosed with non-metastatic triple-negative breast cancer that was treated with chemotherapy with anthracyclines and paclitaxel and radiotherapy. In 2022, the patient appeared with a mass in her right breast and further evaluations revealed a mass in her right ovary and mildly avid lymph node in her right axilla which was considered reactive by US and mammogram. Biopsies from Rt breast mass and Peritoneal nodule confirmed the presence of invasive breast cancer and high grade "primary serous" ovarian cancer respectively, and germline genetic testing revealed a positive BRCA1 diagnosis.

The Triple negative phenotype is the most commonly detected histological subtype in breast cancer subjects with BRCA1/2 mutations or 'BRCAness' [15]. 'BRCAness breast cancers are sporadic tumors with similar characteristics to tumors with BRCA1/2 mutations [16]. In fact, over 70 percent of breast cancers having "BRCA1 germline mutations" are of the "TN subtype" [17], and roughly 20% of TNBC patients are diagnosed with BRCA1 mutations. Including morphological characteristics and immunohistochemical profiles, BRCA1 mutant tumors and TNBC share a number of similarities [18]. Morphologically, BRCA1 tumors, and TNBC have an unusual medullary characteristic, high histological grade, extensive lymphocytic infiltration, high pushing margins, and high proliferation indices. Numerous BRCA1 mutation tumors exhibit negative estrogen receptor/progesterone receptor status, negative human epidermal growth factor receptor 2 (HER2) status, overexpression of epidermal growth factor receptor (EGFR), and mutations in TP53 at the immunohistochemical level [15]. Our patient also had triple negative breast cancer, ER negative, PR negative, and HER2/neu negative, associated with BRCA1 genetic mutation.

Molecular genetic testing can discover abnormalities in the BRCA1 gene that may increase the risk of developing triple-negative breast and ovarian cancers. This information can be used to inform screening, preventive, and treatment decisions [19]. Individuals who test positive for BRCA1 mutations may be advised to undergo more frequent screenings, to consider prophylactic surgery to remove the breasts and/or ovaries, or to get BRCA1-specific targeted therapy.

In addition, molecular genetic testing has emerged as a useful approach for predicting treatment responses, especially with the advent of novel targeted therapeutic drugs such as poly inhibitors and the reporting of platinum-based sensitivity [10]. This testing can help physicians select the most effective treatment options for patients with TNBC with BRCA1 mutations, such as targeted treatments or chemotherapy.

To address this complex and challenging case, our patient was initiated on the neoadjuvant keynote 522 protocol with epirubicin, cyclophosphamide, and Taxol carbo with pembrolizumab. The KEYNOTE-522 trial was a phase 3, prospective, randomized, and placebo-controlled study of neoadjuvant and adjuvant pembrolizumab treatment for patients with early-stage triple-negative breast cancer [20]. One of the significant strengths of this trial was the incorporation of a control group that received standard-of-care chemotherapy containing carboplatin, paclitaxel, followed by either AC (doxorubicin hydrochloride, cyclophosphamide) or EC (epirubicin cyclophosphamide). This enabled a direct comparison between the chemotherapy plus pembrolizumab and neoadjuvant chemotherapy regimen without pembrolizumab which has been shown to provide a high response rate in subjects with early stage TNBC.

Patients with early triple-negative breast cancer who received pembrolizumab in addition to neoadjuvant chemotherapy showed a significantly higher rate of pathological complete response compared to those who received neoadjuvant chemotherapy with a placebo. The findings of the study provide evidence in favor of utilizing pembrolizumab in conjunction with carboplatin, paclitaxel, AC, or EC containing neoadjuvant chemotherapy, followed by adjuvant pembrolizumab post-surgery, as a treatment protocol for patients diagnosed with high-risk early triple-negative breast cancer.

The recent findings on the use of neoadjuvant pembrolizumab to treat triple-negative breast cancer are consistent with those of previous studies. For example, a KEYNOTE-173 phase 1b trial evaluated the efficacy of neoadjuvant pembrolizumab coupled with chemotherapy with or without carboplatin for locally advanced TNBC, 60% (90% confidence interval [CI]:

30 to 85%) of subjects obtained a "pathological complete response" [21].

Similarly, an I-SPY2 phase 2 trial compared pembrolizumab with neoadjuvant chemotherapy without platinum, in patients with HER2-negative and HR-positive breast cancer, the pembrolizumab-chemotherapy group had an estimated "pathological complete response" (PCR) rate that was twenty one percent higher than the subjects group who received only chemotherapy regiment [22].

In patients with TNBC, the pembrolizumab-chemotherapy group had an estimated rate of PCR that was forty percent points greater than the patient group that only received chemotherapy.

Also to be mentioned is that the inclusion of the PARP inhibitor veliparib with carboplatin neoadjuvant chemotherapy resulted in robust pCR benefit for triple-negative breast cancer patients to the tune of 51% vs 26% [23].

Based on these results, it can be inferred that incorporating "immune checkpoint inhibitors" with "neoadjuvant chemotherapy" could enhance the rate of PCR among patients with a "triple negative" phenotype and the addition of PARP inhibitors could be an upcoming option as well for the Triple negative subtype.

CONCLUSION

In conclusion, the management of patients with a history of triple-negative breast cancer, particularly in the context of a rare hereditary BRCA1 mutation, is a complex and difficult task which includes multidisciplinary input from Oncologists, Surgeons and Geneticists. BRCA1 mutations are frequently related to the triple-negative phenotype, and molecular genetic testing can assist to identify specific germline mutations that may increase the risk of developing triple-negative breast and ovarian cancers.

Regarding treatment, our case report supports the use of neoadjuvant pembrolizumab as a treatment protocol for individuals diagnosed with early TNBC with a high-risk profile and BRCA 1 mutation as well.

However Further research is ongoing to elucidate the option of adding other potentially useful agents such as PARP inhibitors in the neoadjuvant setting for BRCA 1 patients especially the triple negative subtypes.

REFERENCES

1. Ben Ayed-Guerfali, D., Ben Kridis-Rejab, W., Ammous-Boukhris, N., Ayadi, W., Charfi, S., Khanfir, A., ... & Mokdad-Gargouri, R. (2021). Novel and recurrent BRCA1/BRCA2 germline mutations in patients with breast/ovarian cancer: a series from the south of Tunisia. *Journal of Translational Medicine*, *19(1)*, 1-10.
2. Parada Jr, H., Sun, X., Tse, C. K., Olshan, A. F., & Troester, M. A. (2019). Lifestyle patterns and survival following breast cancer in the Carolina Breast Cancer Study. *Epidemiology (Cambridge, Mass.)*, *30*(1), 83-92.
3. Siegel, R. L., Miller, K. D., & Jemal, A. (2020). Cancer statistics, 2020. *CA Cancer J Clin*, 70(1), 7-30.
4. Kwong, A., Ho, C. Y., Shin, V. Y., Au, C. H., Chan, T. L., & Ma, E. S. (2021). A case report of germline compound heterozygous mutations in the BRCA1 gene of an ovarian and breast cancer patient. *International Journal of Molecular Sciences*, *22*(2), 889.
5. Goldgar, D. E., Easton, D. F., Deffenbaugh, A. M., Monteiro, A. N., Tavtigian, S. V., & Couch, F. J. (2004). Integrated evaluation of DNA sequence variants of unknown clinical significance: application to BRCA1 and BRCA2. *The American Journal of Human Genetics*, *75*(4), 535-544.
6. Maresca, L., Lodovichi, S., Lorenzoni, A., Cervelli, T., Monaco, R., Spugnesi, L., ... & Galli, A. (2018). Functional interaction between BRCA1 and DNA repair in yeast may uncover a role of RAD50, RAD51, MRE11A, and MSH6 somatic variants in cancer development. *Frontiers in Genetics*, *9*, 397.
7. Yoshida, K., & Miki, Y. (2004). Role of BRCA1 and BRCA2 as regulators of DNA repair, transcription, and cell cycle in response to DNA damage. *Cancer science*, *95*(11), 866-871.
8. Caramelo, O., Silva, C., Caramelo, F., Frutuoso, C., & Almeida-Santos, T. (2019). The effect of neoadjuvant platinum-based chemotherapy in BRCA mutated triple negative breast cancers-systematic review and meta-analysis. *Hereditary cancer in clinical practice*, *17*, 1-10.
9. Lambertini, M., Olympios, N., Lequesne, J., Calbrix, C., Fontanilles, M., Loeb, A., ... & Clatot, F. (2019). Impact of taxanes, endocrine therapy, and deleterious germline BRCA mutations on anti-müllerian hormone levels in early breast cancer patients treated with anthracycline-and cyclophosphamide-based chemotherapy. *Frontiers in oncology*, *9*, 575.
10. De Talhouet, S., Peron, J., Vuilleumier, A., Friedlaender, A., Viassolo, V., Ayme, A., ... & Labidi-Galy, S. I. (2020). Clinical outcome of breast cancer in carriers of BRCA1 and BRCA2 mutations according to molecular subtypes. *Scientific reports*, *10*(1), 7073.
11. Byrski, T., Gronwald, J., Huzarski, T., Grzybowska, E., Budryk, M., Stawicka, M., ... & Narod, S. (2010). Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy. *Journal of Clinical Oncology*, *28*(3), 375-379.

12. Marchetti, C., Ataseven, B., Cassani, C., Sassu, C. M., Congedo, L., D'Indinosante, M., ... & Fagotti, A. (2023). Ovarian cancer onset across different BRCA mutation types: a view to a more tailored approach for BRCA mutated patients. *International Journal of Gynecologic Cancer*, *33*(2).
13. Livraghi, L., & Garber, J. E. (2015). PARP inhibitors in the management of breast cancer: current data and future prospects. *BMC medicine*, *13*(1), 1-16.
14. Delaloge, S., Wolp-Diniz, R., Byrski, T., Blum, J. L., Gonçalves, A., Campone, M., ... & Lubinski, J. (2014). Activity of trabectedin in germline BRCA1/2-mutated metastatic breast cancer: results of an international first-in-class phase II study. *Annals of oncology*, *25*(6), 1152-1158.
15. Bianchini, G., Balko, J. M., Mayer, I. A., Sanders, M. E., & Gianni, L. (2016). Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. *Nature reviews Clinical oncology*, *13*(11), 674-690.
16. Li, M., Zhang, J., Ouyang, T., Li, J., Wang, T., Fan, Z., ... & Xie, Y. (2016). Incidence of BRCA1 somatic mutations and response to neoadjuvant chemotherapy in Chinese women with triple-negative breast cancer. *Gene*, *584*(1), 26-30.
17. Xie, Y., Gou, Q., Wang, Q., Zhong, X., & Zheng, H. (2017). The role of BRCA status on prognosis in patients with triple-negative breast cancer. *Oncotarget*, *8*(50), 87151-87162.
18. Chen, H., Wu, J., Zhang, Z., Tang, Y., Li, X., Liu, S., ... & Li, X. (2018). Association between BRCA status and triple-negative breast cancer: a meta-analysis. *Frontiers in pharmacology*, *9*, 909.
19. Fostira, F., Tsitlaidou, M., Papadimitriou, C., Pertesi, M., Timotheadou, E., Stavropoulou, A. V., ... & Fountzilas, G. (2012). Prevalence of BRCA1 mutations among 403 women with triple-negative breast cancer: implications for genetic screening selection criteria: a Hellenic Cooperative Oncology Group Study. *Breast cancer research and treatment*, *134*, 353-362.
20. Rizzo, A., Cusmai, A., Acquafredda, S., Giovannelli, F., Rinaldi, L., Misino, A., & Palmiotti, G. (2022). Keynote-522, impassion031 and geparnuevo: changing the paradigm of neoadjuvant immune checkpoint inhibitors in early triple-negative breast cancer. *Future Oncology*, *18*(18), 2301-2309.
21. Schmid, P., Park, Y. H., Munoz-Couselo, E., Kim, S. B., Sohn, J., Im, S. A., ... & Cortes, J. (2017). Pembrolizumab (pembro)+ chemotherapy (chemo) as neoadjuvant treatment for triple negative breast cancer (TNBC): Preliminary results from KEYNOTE-173. *American Society of Clinical Oncology*.
22. Nanda, R., Liu, M. C., Yau, C., Asare, S., Hylton, N., Veer, L. V. T., ... & Esserman, L. (2017). Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer (BC): results from I-SPY 2. *American Society of Clinical Oncology*.
23. Schmid, P., Cortes, J., Pusztai, L., McArthur, H., Kümmel, S., Bergh, J., ... & O'Shaughnessy, J. (2020). Pembrolizumab for early triple-negative breast cancer. *New England Journal of Medicine*, *382*(9), 810-821.