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CASE REPORT

Durable Disease-free Survival in a Patient with Metastatic Triple-negative Breast Cancer Treated with Olaparib Monotherapy

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Abstract: ***Background*:** Metastatic triple-negative breast cancer (mTNBC) has a poor prognosis and few effective targeted therapy options. Olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, has been granted accelerated approval by FDA for patients with deleterious BRCA-mutated human epidermal growth factor receptor 2 (HER2)-negative advanced/metastatic breast cancer. However, there is little data demonstrating that patients with particular forms of germline and/or somatic BRCA1/2, such as large fragment variation, can benefit from PARP inhibitors.

***Case Presentation*:** In 2011, a 40-year-old woman was diagnosed with TNBC having pT2N0M0 in the right breast, and a new irregular lesser tubercle in the left breast appeared after approximately 3 years, which was also diagnosed as TNBC. In 2017, computed tomography (CT) showed TNBC metastases to the lung and brain. A next-generation sequencing (NGS) was performed with a lung metastasis sample, and results showed a homologous recombination deficiency (HRD) score of 67, a germline large deletion of exon 2 in BRCA1, a novel somatic BRCA2-STARD13 rearrangement and copy number loss of RAD51. Since September 2017, the patient was treated with olaparib. Till the report date of this case, the patient underwent regular follow-up without disease recurrence.

***Conclusion*:** To our knowledge, this is the first case describing a patient with lung- and brain-metastatic TNBC with combined germline and somatic large rearrangement and a high HRD score who achieved a long-term benefit from olaparib monotherapy. The use of NGS is promising in the treatment of TNBC in clinical practice.

Keywords: BRCA1/2 rearrangement, HRD positive, metastatic triple-negative breast cancer, PARP inhibitor, olaparib, long-term disease-free survival.

1. INTRODUCTION

Triple-negative breast cancer (TNBC) is a highly aggressive subtype of breast cancer, which comprises 10%-15% of all breast cancers [1]. Surgery and chemotherapy are the mainstay treatment for TNBC due to the lack of specific targeted agents. The median overall survival (OS) with conventional cytotoxic agents ranged from 9 to around 12 months [2, 3]. Moreover, TNBC has a high risk of metastasis, particularly the lung and brain [4]. The median survival subsequent to brain metastases was only 2.9 months (95% confidence interval [CI], 2.0-7.6) [5].

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Germline BRCA 1/2 mutations are present in approximately 15% of patients with TNBC [6]. It has been revealed that the inhibition of poly(ADP-ribose) polymerase (PARP) has a synthetic lethal therapeutic effect in the treatment of solid tumors for BRCA mutation carriers [7]. The phase 3 OlympiAD trial showed a significant benefit with PARP inhibitor, olaparib, as monotherapy compared with standard single-agent chemotherapy in patients with HER2-negative metastatic breast cancer with deleterious germline BRCA mutations, with a median progression-free survival (PFS) of 7.0 months versus 4.2 months (hazard ratio, 0.58; 95% CI, 0.43-0.80; $P<0.001$) [8].

Previous randomized, controlled trials (*e.g.* ENGOT-OV16/NOVA and ARIEL2) showed the significant efficacy of PARP inhibitors in patients with ovarian cancer, regardless of the presence or absence of germline BRCA mutations, suggesting the usefulness of PARP inhibitors beyond

BRCA-mutated tumors [9, 10]. For now, the potential of PARP inhibitors in patients with TNBC beyond germline BRCA mutations is unclear.

Here, we presented an advanced patient with TNBC having lung and brain metastases. Next-generation sequencing (NGS) analysis showed a germline large deletion of exon 2 in BRCA1, a novel somatic rearrangement on BRCA2, and a high homologous recombination deficiency (HRD) score. The PARP inhibitor olaparib was initiated and led to an impressive response.

2. CASE PRESENTATION

A 40-year-old woman underwent a lumpectomy for the right breast cancer and right axillary lymph node dissection on August 3, 2011, and was diagnosed with TNBC with disease stage IIA (pT2N0M0). Subsequently, she received postoperative radiotherapy with 95% planned targeted volume, 43.5Gy/2.9Gy/15F, 12MeV, and 8.7Gy/2.9Gy/3F electronic wire radiotherapy from September to October 8, 2011. Six chemotherapy cycles with cyclophosphamide and docetaxel were given from October 25, 2011, to February 2, 2012 (Fig. **1**). Grade 2 nausea, grade 1 vomiting, and grade 1 glutathione abnormalities were observed during chemotherapy.

In June 2014, a breast ultrasound showed an irregular lesser tubercle (1.2 × 1.1 cm) in the caudate lobe of the left breast, which was considered malignant tumors. Puncture aspiration biopsy of the nodule of the left breast showed invasive breast carcinoma. The patient underwent an extensive resection of left breast mass and left axillary lymph node dissection in our hospital. The postoperative pathology showed TNBC with stage IA (pT1cN0M0). The patient received 6 cycles of weekly paclitaxel liposomes combined with carboplatin from August 21, 2014, to December 16, 2014. During the adjuvant chemotherapy, she suffered grade 2 nausea, vomiting, and grade 3 neutropenia.

In July 2017, the computed tomography (CT) scan of the patient's neck and chest showed new nodular shadows in the right middle lobe of the lung, with the maximum cross-section of 2.3 × 1.8 cm (Fig. **2**). Then she underwent thoracoscopic right middle lung lobectomy + hilar mediastinal lymph node dissection. Postoperative pathology showed poorly differentiated cancer infiltration with necrosis in the right middle lung tissue, primarily considered as breast cancer metastasis, tumor size of 2 × 1.5 × 1 cm, visceral pleural involvement, and LNM 0/10. Immunohistochemistry: NapsinA-, TTF1-, ER-, PR-, HER2-, CK5/6-, GATA3-, ki-67 70%+.

However, in August 2017, the patient was admitted to the hospital again due to headache, speech difficulty, right limb weakness, and walking instability 1 month after surgery Fig. (**3**). The head magnetic resonance imaging (MRI) revealed metastatic lesions in the left frontal lobe with surrounding edema, watching for subfalcine herniation and metastatic tubercle to the right cerebellum (Figs. **3A-D**). The patient underwent surgery to remove the left frontal lobe lesion and radiotherapy for the postoperative tumor bed area and the metastatic nodule in the right cerebellum. The postoperative pathology showed poorly differentiated carcinoma infiltrates with necrosis on the left frontal lobe of the brain, which was considered as breast cancer metastasis due to the morphological characteristics of medullary carcinoma. Immunohistochemical staining showed negative results of ER, PR, HER2, GATA3, and no expression of typical markers.

In September 2017, NGS was performed on a lung metastasis sample from the patient using a 381-gene panel performed in a CAP-certificated laboratory to explore other potential therapeutic opportunities. Genetic testing of lung metastases revealed that the HRD score was high (67, ≥cutoff of 30), and she carried a germline large deletion of exon 2 in BRCA1, a novel somatic BRCA2-STARD13 rearrangement (Fig. **4A** and **B**) and copy number loss of RAD51. The novel mutation of BRCA2-STARD13 was thought to be possibly pathogenic because it led to BRCA2 protein C-terminal deletion. The patient was not willing to receive chemotherapy and was given the PARP inhibitor olaparib (300 mg twice daily) since September 2017 and reviewed every 3 to 6 months. During treatment, the inhibitor (treatment) was well tolerated by the patient, with only grade 1 nausea and grade 1 anemia. At 45 months after the last surgery, the patient did not report any clinical manifestation, and imaging monitoring confirmed the absence of carcinoma recurrence. Till the report date of this case, the patient presented cerebral edema after postoperative radiotherapy, which was resolved with symptomatic treatment (Fig. **3E** and **F**).

3. DISCUSSION

Central nervous system (CNS) metastases account for 10%-30% of all breast cancers. The median survival time of breast cancer with brain metastases is about 7 months, and the OS of TNBC with CNS metastases is even shorter. Those with BRCA1/2 germline mutations are more likely to develop brain metastases and have a worse prognosis. This case report highlighted a long disease-free survival (more than 40 months) with olaparib monotherapy in a patient with metastatic TNBC with germline large deletion of exon 2 in BRCA1, a novel BRCA2-STARD13 somatic rearrangement, and an HRD score of 67.

The patient with TNBC underwent 4 surgeries from August 2011 to August 2017, and different degrees of progression and metastases occurred after various chemotherapies, including docetaxel, cyclophosphamide, paclitaxel, and platinum-based chemotherapy. Consequently, the NGS analysis of the patient lung metastasis sample revealed an HRD characteristic with a high HRD score and BRCA mutations. Since September 2017, the patient was given the PARP inhibitor, olaparib, and the cancer-related symptoms basically disappeared without disease recurrence for more than 3 years.

Pre-clinical studies showed that PARP inhibitors could activate the cGAS-cGAMP-STING pathway, inducing the recruitment of T-cells in TNBC [11]. They can also upregulate the interferon response in breast cancer with BRCA mutations [12]. Recently, these effects of PARP inhibitors were found in HRD-positive TNBC [13], supporting the use of olaparib in the current case.

The deleterious BRCA mutation has emerged as a paragon for PARP inhibitor sensitivity, with BRCA deficiency leading to synthetic lethality in PARP inhibitor-exposed can-

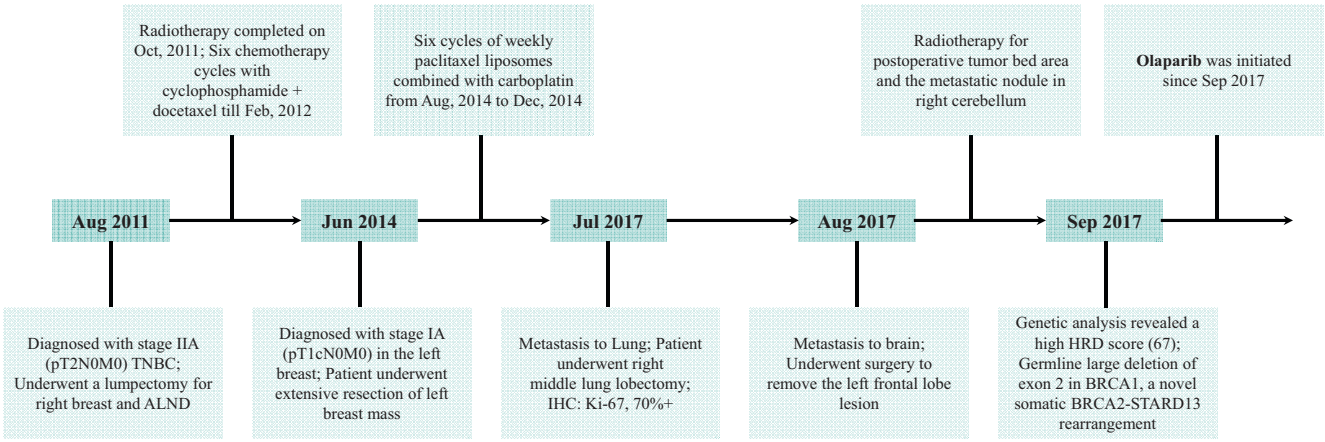

Fig. (1). Patient course of disease progression and various treatment timelines. ALND, axillary lymph node dissection; IHC, Immunohistochemistry; HRD, homologous recombination deficiency; STARD13, StAR-related lipid transfer domain protein 13; TNBC, triple-negative breast cancer.

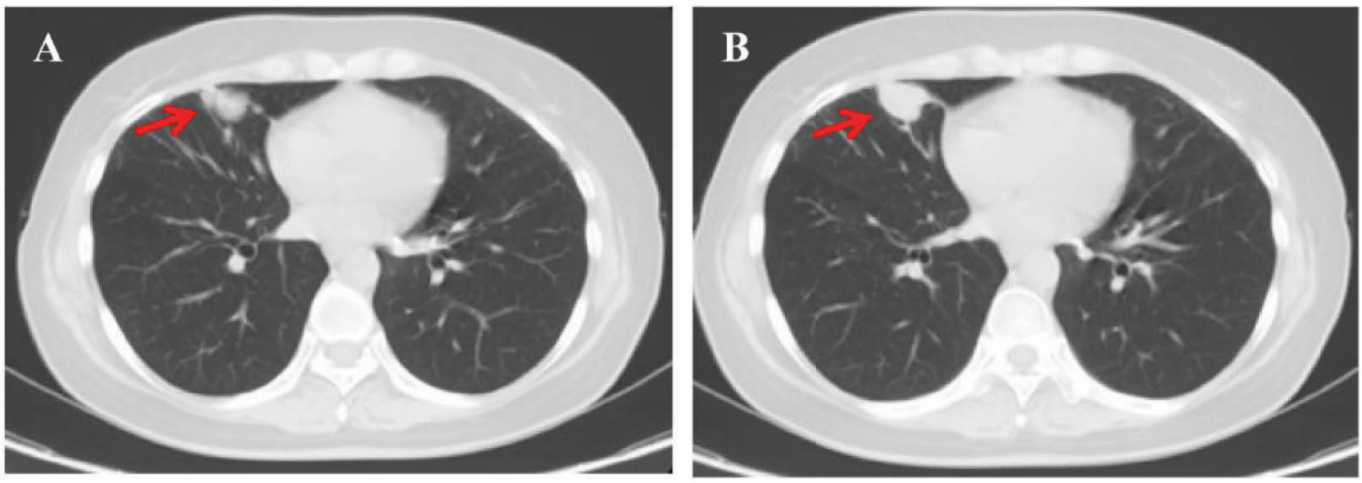

Fig. (2). Chest computed tomography (CT) images. (**A, B**) Preoperative chest CT scan showed a new pulmonary nodule (about 2.3 × 1.8 cm, arrow) in the right middle lobe of the lung. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

cer cells [14]. Currently, olaparib and talazoparib were FDA-approved PARP inhibitors for the treatment of patients with HER2-negative, germline BRCA1/2-mutated metastatic breast cancer who had previously received chemotherapy [15]. Recently, PARP inhibitors received attention as a viable treatment and had shown a potential curative effect in TNBC [16, 17]. For now, the germline BRCA mutation is still the only valid predictive biomarker for the efficacy of PARP inhibitors in breast cancer. However, this case suggested that PARP inhibitors may be of benefit in the treatment of TNBC beyond BRCA mutations. Further large-scale clinical studies are warranted.

HRD status plays a potential role as a predictive biomarker for response to PARP inhibitors in several clinical trials, especially in ovarian cancer. The MyChoice of Myriad Genetics is the FDA-approved test for patients with ovarian cancer to determine HRD status and provides information on the magnitude of benefit with PARP inhibitor (olaparib and niraparib) therapy [9, 18, 19]. According to the myChoice HRD test, high HRD could predict long PFS with niraparib maintenance therapy and provide significant clinical benefits regardless of BRCA status [9]. For TNBC, HRD positivity can be identified in two-thirds of the patients [13, 20]. HRD status in metastatic TNBC may identify more suitable patients who would receive greater benefit from PARP inhibitors and should be evaluated further in prospective studies. However, there are no standard criteria to determine the HRD status in breast cancer at present. The 3DMed-HRD algorithm was developed, which combines the loss of heterozygosity score, telomeric allelic imbalance score, and large-scale state transition score to characterize genomic instability using over 10,000 single nucleotide polymorphisms (SNPs), adjusted by tumor ploidy and purity [21]. HRD positive is defined by a deleterious mutation in BRCA1/2 or HRD score no less than the threshold (≥30). The reliability of this novel algorithm still needs time for verification.

CONCLUSION

To our knowledge, this is the first reported case with combined genomic alterations of a germline large deletion of

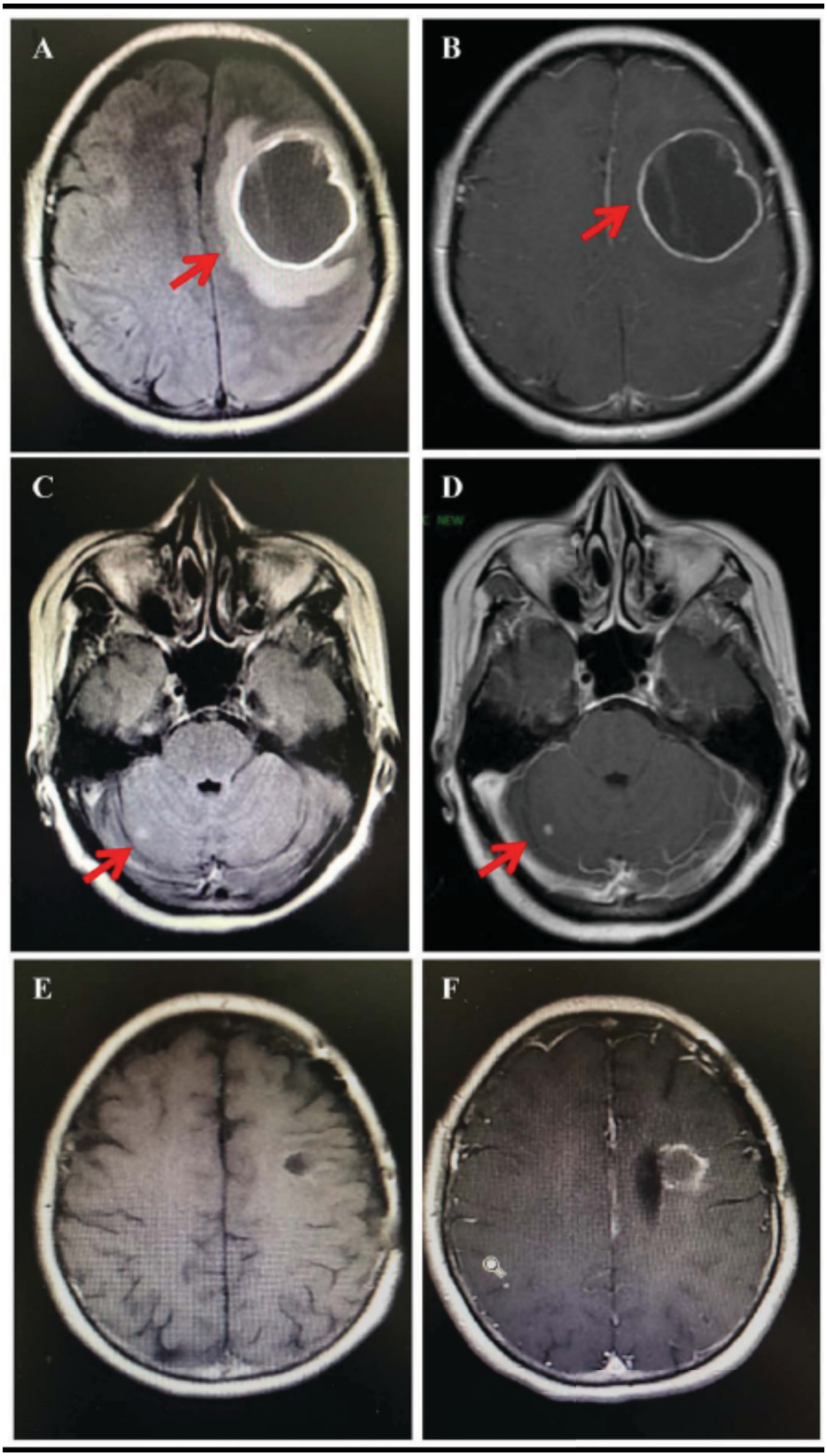

Fig. (3). Brain metastasis at subfalcine herniation and metastatic tubercle to the right cerebellum by brain magnetic resonance imaging (MRI). (**A**) Enhanced MRI showing a lesion with ring-like enhancement in the left frontal lobe with peritumoral edema. (**B**) Post-gadolinium weighted MRI revealed a cystic-solid mass with a size of 4.8 × 4.4 cm in the left lateral ventricle. (**C**, **D**) MRI showing brain metastasis at subfalcine herniation and metastatic tubercle to right cerebellum (0.4 × 0.3 cm, arrow). (**E**, **F**) The brain MRI showed recovery after surgery (1.5 × 1.0 cm). *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

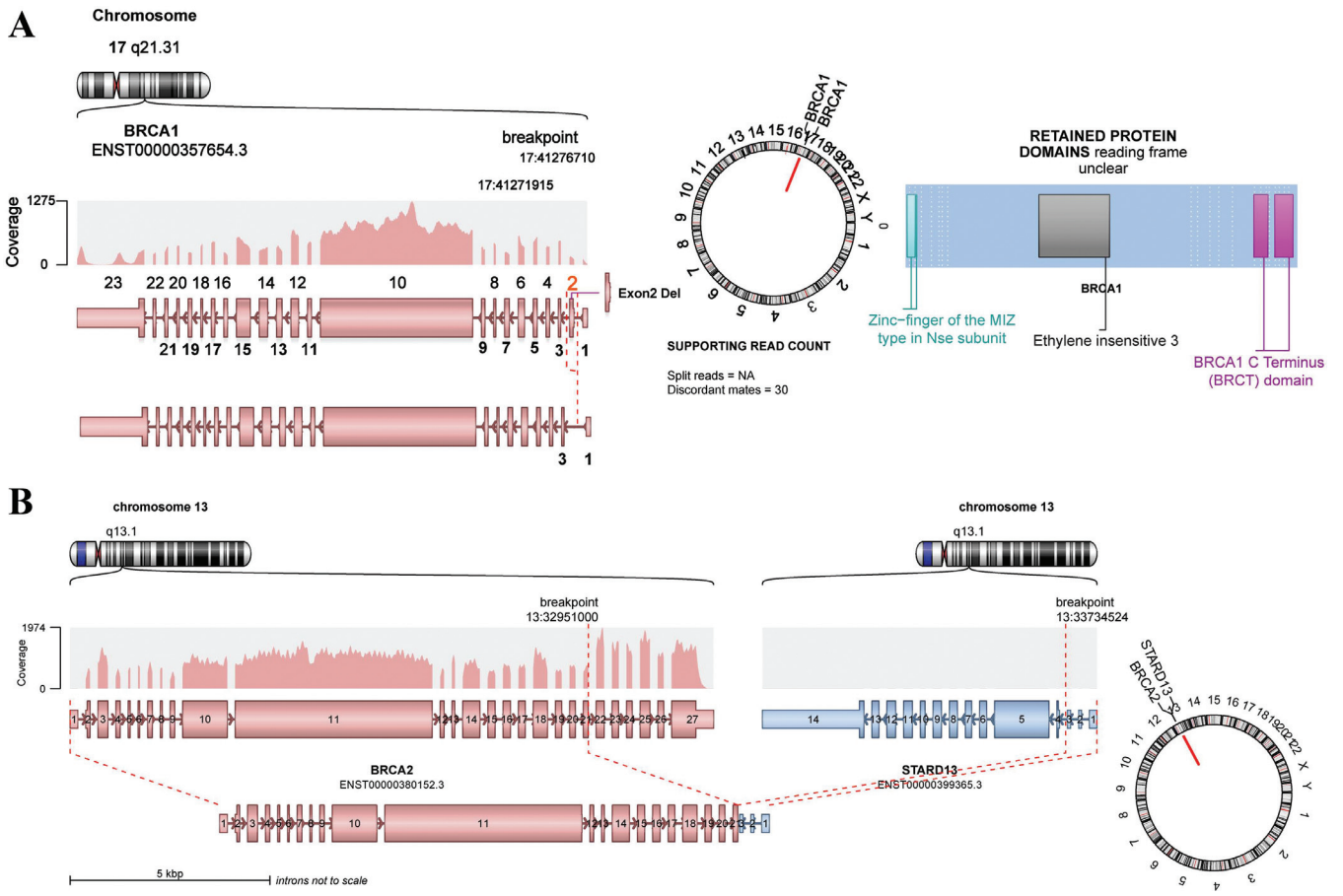

Fig. (4). BRCA gene mutations. (**A**) A germline large deletion of exon 2 in BRCA1. (**B**) The novel somatic BRCA2-STARD13 rearrangement. BRCA2 lost the C-terminal and deleted the exon from 22 to 27. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

exon 2 in BRCA1, a novel somatic rearrangement of BRCA2-STARD13, and an HRD score of 67, achieving a long disease-free survival (>38 months) in a lung- and brain-metastatic TNBC patient treated with olaparib monotherapy. The success of this case suggested that PARP inhibitors might bring clinical benefits for patients with HRD-positive TNBC. Further studies evaluating the efficacy and safety of PARP inhibitors in patients with HRD-positive TNBC are needed, particularly in those with chemotherapy-resistant advanced disease. The use of NGS is promising in clinical practice to detect multiple genomic alterations and HRD scores for individualized TNBC treatment.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the institutional research committee National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, China.

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, China and were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

CONSENT FOR PUBLICATION

Written informed consent was obtained from patients.

STANDARDS OF REPORTING

The CARE guidelines have been followed for this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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