Significant Clinical Activity of Olaparib in a Somatic BRCA1-Mutated Triple-Negative Breast Cancer With Brain Metastasis

INTRODUCTION
Breast cancer is a biologically and clinically heterogeneous disease, and patients with similar clinical stage have markedly different outcomes. Triple-negative breast cancer (TNBC) is defined by the lack of expression of estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 (HER2).1,2 This subtype represents 15% to 20% of all breast cancers and is associated with the worst outcome of all subtypes, with greater tendency to distant recurrence in general and visceral metastasis in particular, including brain metastasis.3,4 To date, chemotherapy remains the standard of care for TNBC.5

Molecular stratification of TNBC will have treatment implications.6 For example, approximately 40% of TNBC patients have expression of programmed death-ligand 1 (PD-L1) protein in immune cells, and this biomarker predicts survival benefit from anti-PD-L1 therapy in combination with chemotherapy in the first-line metastatic setting.7 In addition, approximately 10% of patients with TNBC harbor a germline BRCA1/2 mutation, which confers sensitivity to platinum and/or poly (ADP-ribose) polymerase (PARP) inhibitors.8 PARP is involved in the repair of DNA single-strand breaks via the base excision pathway. PARP inhibitors such as olaparib or talazoparib lead to an accumulation of double-strand DNA breaks, resulting in the activation of homologous recombination repair, which can compensate for the lack of activity of the base excision pathway and repair the DNA damage.9 However, patients with defects in the homologous recombination DNA repair pathway cannot repair DNA damages caused by PARP inhibitors, and the tumor cell eventually dies (a term known as synthetic lethality).

Here, we describe a heavily pretreated patient with TNBC brain metastasis and a BRCA1 somatic mutation with a remarkable and durable response to PARP inhibitor therapy. To our knowledge, this is the first case report to demonstrate disease response to PARP inhibition in a TNBC without a germline BRCA1 or BRCA2 mutation.

CASE SUMMARY
The patient is a 46-year-old woman diagnosed in December 2015 with stage IIB (cT3cN1) moderately differentiated invasive papillary carcinoma with marked tumoral infiltrating lymphocytes10 (60%) and the presence of vascular invasion. The tumor was ER-positive, progesterone receptor-negative, and HER2-negative with a Ki-67 of 80%. The patient received neoadjuvant chemotherapy consisting of four cycles of doxorubicin and cyclophosphamide followed by paclitaxel once per week for 12 weeks. She had a mastectomy and lymphadenectomy in June 2016. Analysis of the surgical specimen revealed extensive invasive residual disease (ypT2ypN1) with a TNBC phenotype and abundant images of vascular invasion. She then underwent adjuvant radiation to the breast and started adjuvant endocrine therapy with tamoxifen (clinical decision based on baseline ER positivity).

In August 2017, a positron emission tomography scan revealed multiple pathologic deposits in the bone, lung, and mediastinum and a prepectoral lesion. Physical examination revealed a left prepectoral subcutaneous nodule. Biopsy of the lesion confirmed recurrence of the disease (GATA3 positivity) and a TNBC phenotype with a Ki-67 of 70% and androgen receptor–negative and tumor infiltrating lymphocytes around 10% (Fig 1). PD-L1 immunohistochemistry (DAKO clone 22C3) of immune cells and tumor cells was 0%. At that point, a comprehensive gene panel of 94 genes and 284 single nucleotide polymorphisms (Illumina TruSight Cancer) associated with cancer predisposition was performed. The panel included BRCA1, BRCA2, TP53, PALB2, and CHEK2 among others. No germline mutation was detected.

The patient was treated with carboplatin and gemcitabine for six cycles, and she achieved a partial response (Fig 2). In January 2018, she presented with disease progression in the bone, and she received palliative radiotherapy. Afterward, she began treatment with capecitabine and vinorelbine. After four cycles (12 weeks), the patient presented to the...
emergency department with progressively worsening headache. A brain magnetic resonance imaging scan showed multiple metastases, the largest being found in the right frontal lobe with surrounding edema (Fig 3A).

The patient consented to participate in a research project in which tumor profiling at the DNA and RNA level was performed with results discussed at a molecular tumor board. The prepectoral lesion was used for all the molecular analyses. At the DNA level, a FoundationOne test was performed. The results revealed somatic mutations in \textit{BRCA1} (S1253fs*10 9435_9436delGT) and \textit{TP53} (S37fs*6*), a low tumor mutational burden (four mutations per megabase), and a stable microsatellite status. At the RNA level, an nCounter-based Breast Cancer 360 panel was performed.\textsuperscript{11} This assay includes 752 breast cancer–related genes and 23 signatures, the tumor inflammation signature,\textsuperscript{12} the PAM50 subtype predictor,\textsuperscript{13} and the TNBCtype classifications\textsuperscript{14,15} (Fig 4). Results revealed a PAM50 basal-like subtype with the following features: high expression of BRCA-ness and DNA scar signatures, high expression of proliferation-related genes, low expression of androgen receptor- and estrogen-regulated genes, low expression of CD8 T cells and PD-L1, high expression of immunosuppressive genes or signatures such as transforming growth factor-\(\beta\) and regulatory T-cell signatures, and a TNBCtype mesenchymal subtype.

On the basis of these results, off-label use of olaparib 300 mg twice per day was indicated. Consideration was given to introducing corticosteroids or delivering whole-brain radiotherapy (WBRT), but after discussion with the patient, a clinical decision was made to start olaparib under close observation and without the addition of either radiotherapy or corticosteroids. After 2 weeks of treatment, neurologic symptoms improved, and a restaging magnetic resonance imaging scan at week 8 demonstrated a significant reduction in the size of the brain lesions and disappearance of associated cerebral edema (Fig 3B). Computed tomography and bone scans demonstrated stable disease. No evidence of disease progression has been observed after 4 months.

**DISCUSSION**

Patients harboring germline \textit{BRCA1/2} mutations are ideal candidates for PARP inhibition. BRCA proteins play a critical role in the homologous recombination DNA repair pathway.\textsuperscript{16} In the presence of a \textit{BRCA} germline mutation, one allele is affected, and the occurrence of a genetic alteration in the other allele (eg, through methylation or loss of heterozygosity) leads to a nonfunctional BRCA and the appearance of breast cancer, among other cancers.\textsuperscript{9} To date, two phase III clinical trials have shown that PARP inhibition with olaparib\textsuperscript{17} or talazoparib\textsuperscript{18} is superior to standard chemotherapy in terms of progression-free survival in HER2-negative advanced breast cancer harboring a \textit{BRCA} germline mutation. Olaparib and talazoparib are now approved by the US Food and Drug Administration in

**FIG 1.** Morphologic and immunohistochemical features. (A) The tumor (hematoxylin and eosin stain) was composed of neoplastic infiltrative nests with scattered stromal tumor-infiltrating lymphocytes with many images of (B) lymphovascular invasion (CD31). The neoplastic cells were negative for (C) estrogen receptor, (D) progesterone receptor, and (E) androgen receptor. (F) Human epidermal growth factor receptor 2 (HER2) studied by fluorescence in situ hybridization showed a normal pattern without gene amplification. (G) The tumor had a high proliferation index (Ki-67), and (H) programmed death-ligand 1 (PD-L1) was negative in both the neoplasm and the stromal cells.
patients with germline BRCA1/2-mutated advanced breast cancer. PARP inhibitors have also been shown to have significant activity in patients with metastatic prostate or ovarian cancer who harbor germline mutations in BRCA1/2. In addition, cases of response in other tumors to PARP inhibitors have been reported in the context of mutations in other homologous recombination genes such as RAD51D or RAD51C.

**FIG 3.** Brain magnetic resonance imaging before and after olaparib monotherapy. (A) Images before olaparib therapy show a cortical enhancing lesion on gadolinium-enhanced T1-weighted imaging in the inferior frontal gyrus with perilesional edema visualized on fluid-attenuated inversion recovery (FLAIR) sequencing, as well as diffuse dural enhancement in the right hemisphere. (B) Images after 8 weeks of treatment with olaparib show decreased size of the brain lesions, edema, and dural enhancement.
whether germline and somatic BRCA1/2 mutations are biologically equivalent. What seems clear is that a subset of patients with TNBC without a germline BRCA1/2 mutation have a genetic profile similar to those with a germline BRCA mutation (so-called BRCA-ness). For example, Davies and colleagues recently derived a predictor, using whole-genome sequencing, of BRCA1/2 deficiency called Homologous Recombination Deficiency Detect (HRDetect), which is composed of six mutational signatures. HRDetect identified 12.4% of breast cancers as being BRCA1/2 deficient despite not having a BRCA1/2 germline mutation. Early-phase clinical trials of PARP inhibitors in metastatic TNBC and germline BRCA1/2 wild-type HER2-negative breast cancer with specific somatic genomic alterations such as BRCA1/2 mutations are underway (eg, NCT02401347; Phase II Talazoparib in BRCA1 + BRCA2 Wild-Type & Triple-Neg/HER2-Negative Breast Cancer/Solid Tumors and NCT03330847; To Assess Safety and Efficacy of Agents Targeting DNA Damage Repair With Olaparib Versus Olaparib Monotherapy).

The long-lasting response of breast cancer brain metastasis to olaparib in the absence of any other treatment is worth discussing. First, this suggests that olaparib, which had not previously been thought to cross the blood-brain barrier, is able to get to the site of the tumor. Concordant with this, other case reports with olaparib monotherapy have described regression of brain metastasis. Second, olaparib, and other highly effective targeted systemic therapies, allow the delay of WBRT. This is important because WBRT can have a negative impact on quality of life and long-term neurocognitive functioning. Thus, strategies to avoid, delay, or abrogate the effects of WBRT using systemic targeted therapies should be prioritized.

In summary, comprehensive genomic alteration testing may provide novel clinical strategies for personalized therapy in advanced TNBC with improvement in overall survival and quality of life. More trials regarding molecular targeted therapy are expected to be conducted in the future, and at the same time, mechanisms regarding resistance are expected to be explored and understood, which will aid the development strategies to resensitize tumor cells to PARP inhibitors and improve long-term effectiveness.
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