case report

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

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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.[2,8] 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 lymphocytes[10] (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

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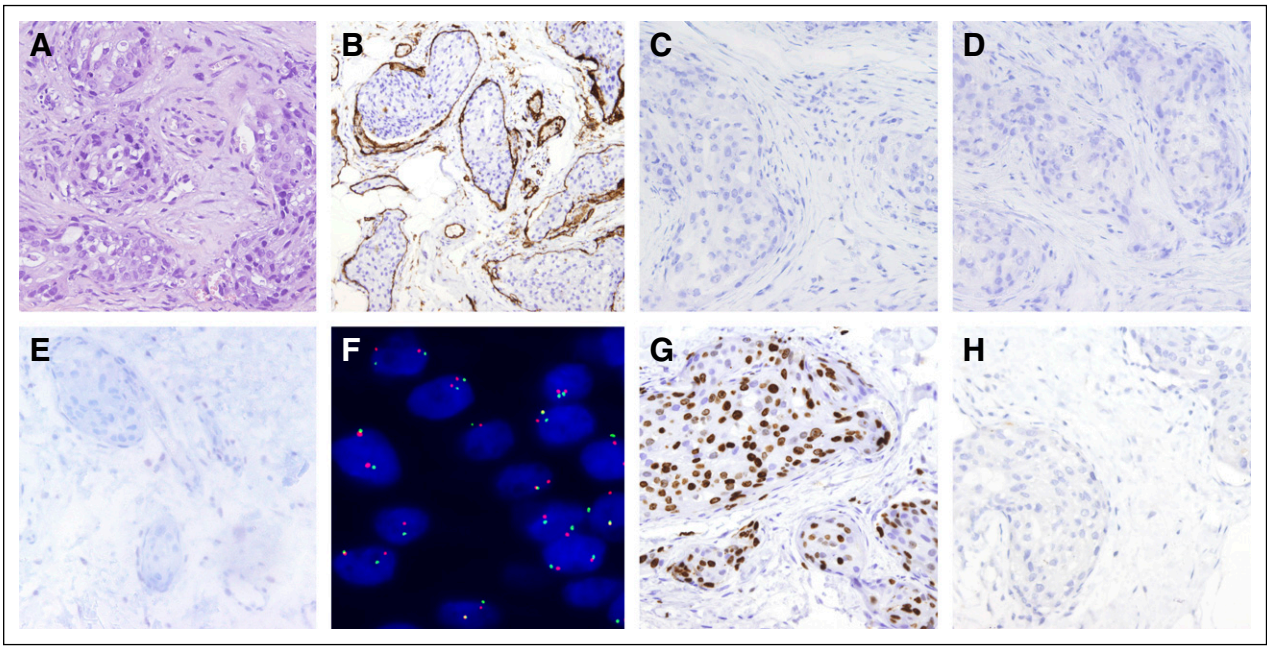

FIG 1. Morphologic and immunohistochemical features. (A) The tumor (hematoxylin and eosin stain) was composed of neoplastic infiltrative nests with scattered stromal tumor-infiltrating lymphocytes with many images of (B) lymphovascular invasion (CD31). The neoplastic cells were negative for (C) estrogen 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.

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 *BRCA1* (S1253fs*10 9435_9436delGT) and *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.[11] This assay includes 752 breast cancer–related genes and 23 signatures, the tumor inflammation signature,[12] the PAM50 subtype predictor,[13] and the TNBCtype classifications[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-β 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 *BRCA1/2* mutations are ideal candidates for PARP inhibition. BRCA proteins play a critical role in the homologous recombination DNA repair pathway.[16] In the presence of a *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.[9] To date, two phase III clinical trials have shown that PARP inhibition with olaparib[17] or talazoparib[18] is superior to standard chemotherapy in terms of progression-free survival in HER2-negative advanced breast cancer harboring a *BRCA* germline mutation. Olaparib and talazoparib are now approved by the US Food and Drug Administration in

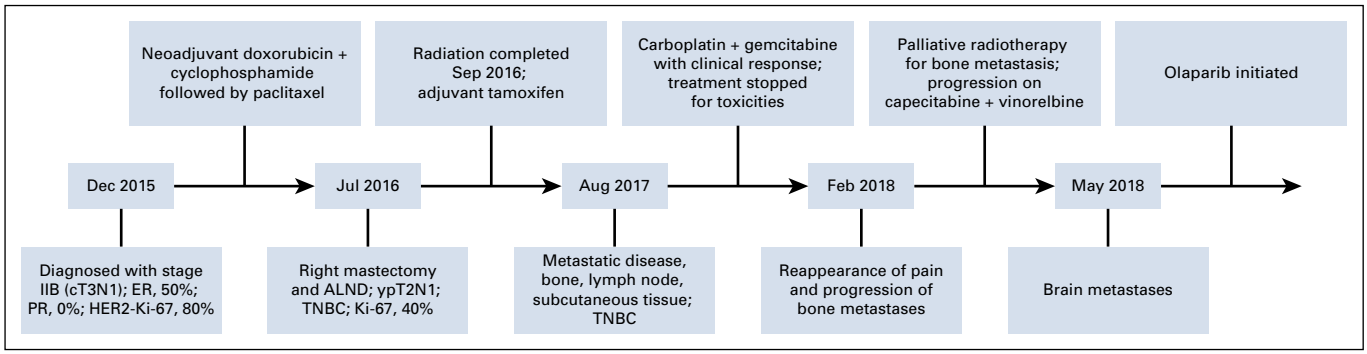

FIG 2. Patient treatment timeline. ALND, axillary lymph node dissection; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; TNBC, triple-negative breast cancer; yp, pathologic staging after neoadjuvant therapy.

patients with germline *BRCA1/2*-mutated advanced breast cancer. PARP inhibitors have also been shown to have significant activity in patients with metastatic prostate[19] or ovarian[20] 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*.[21-23]

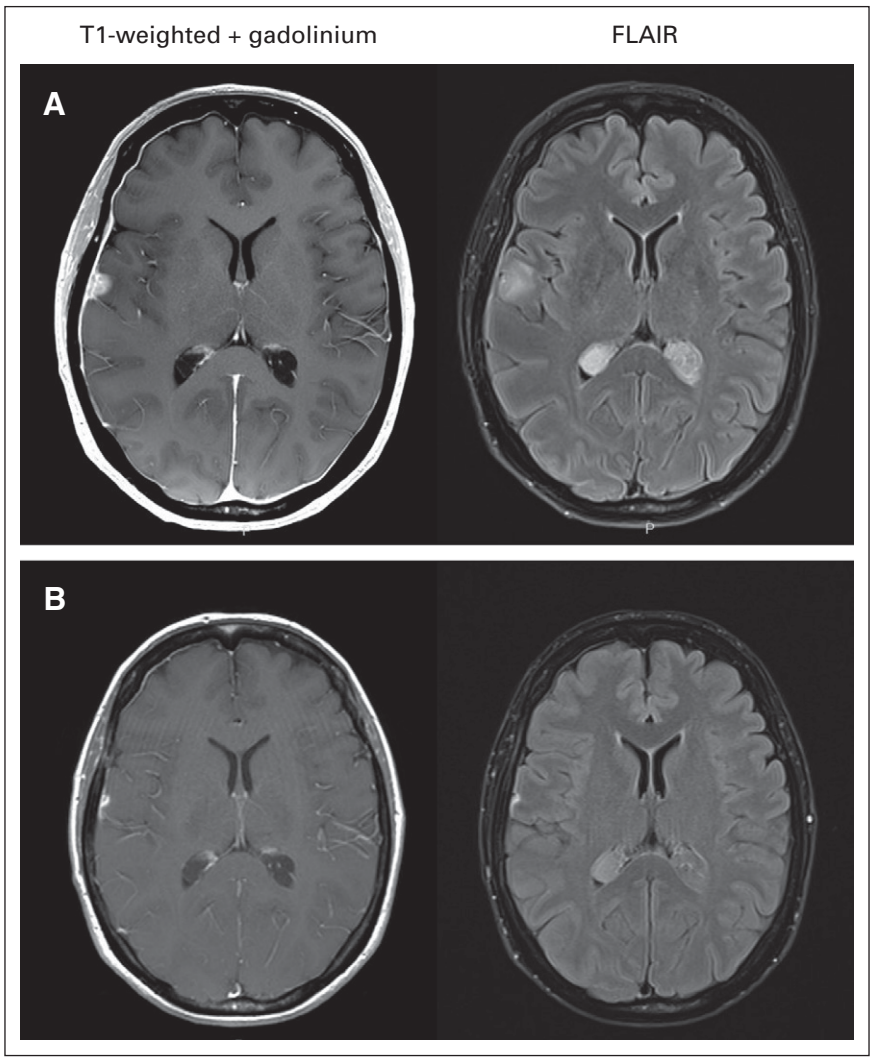

FIG 3. Brain magnetic resonance imaging before and after olaparib monotherapy. (A) Images before olaparib therapy show a cortical enhancing lesion on gadolinum-enhanced T1-weighted imaging in the inferior frontal gyrus with perilesional edema visualized on fluid-attenuated inversion recovery (FLAIR) 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.

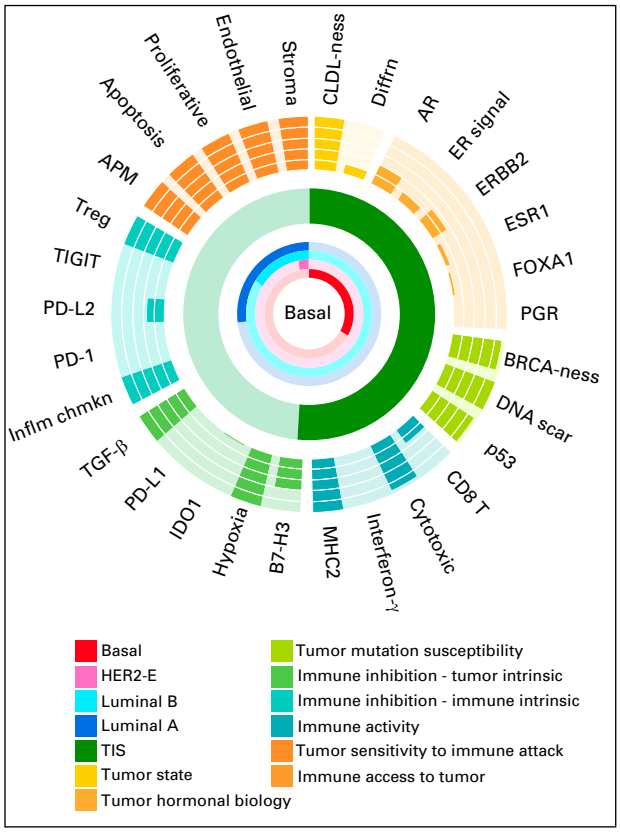

FIG 4. Gene expression summarized results after using the Breast Cancer 360 nCounter-based gene panel. Selected signature scores are shown with the tumor inflammation signature (TIS) and PAM50 signatures at the core; the other signature scores are shown as bars around the rim. Scores range from 0 to 1 mapped to quantiles of the population with invasive breast carcinoma in The Cancer Genome Atlas (TCGA). As an example, a value of 0.5 matches the median expression in the TCGA. Color denotes each signature's biologic function. APM, antigen processing machinery; AR, androgen receptor; BRCA-ness, BRCAness signature; CLDL-ness, Claudin-Low subtype signature; Diffrn, differentiation; DNA scar, DNA scar signature; ER, estrogen receptor; HER2-E, HER2-enriched; Inflm chmkn, inflammatory chemokines; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PGR, progesterone receptor; TIGIT, T cell immunoreceptor and Ig and ITIMS domains; Treg, regulatory T cell.

Somatic mutations may also arise in genes involved in homologous recombination. For example, somatic mutations in *BRCA1/2* occur in approximately 3% of all sporadic breast cancers.[24,25] At this point, it is not known whether germline and somatic *BRCA1/2* mutations are biologically equivalent.[16] 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).[26] For example, Davies and colleagues[27] 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,[28] 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.[29,30] Second, olaparib, and other highly effective targeted systemic therapies, allow the delay of WBRT.[31-35] This is important because WBRT can have a negative impact on quality of life and long-term neurocognitive functioning.[36] 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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REFERENCES

1. Bauer KR, Brown M, Cress RD, et al: Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: A population-based study from the California Cancer Registry. Cancer 109:1721-1728, 2007
2. Cancer Genome Atlas Network: Comprehensive molecular portraits of human breast tumours. Nature 490:61-70, 2012
3. Carey LA, Perou CM, Livasy CA, et al: Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 295:2492-2502, 2006
4. Dent R, Trudeau M, Pritchard KI, et al: Triple-negative breast cancer: Clinical features and patterns of recurrence. Clin Cancer Res 13:4429-4434, 2007
5. Cardoso F, Senkus E, Costa A, et al: 4th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 4). Ann Oncol 29:1634-1657, 2018
6. Prat A, Adamo B, Cheang MC, et al: Molecular characterization of basal-like and non-basal-like triple-negative breast cancer. Oncologist 18:123-133, 2013
7. Schmid P, Adams S, Rugo HS, et al: Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 379:2108-2121, 2018
8. Ahn SG, Kim SJ, Kim C, et al: Molecular classification of triple-negative breast cancer. J Breast Cancer 19:223-230, 2016
9. Ashworth A: A synthetic lethal therapeutic approach: Poly(ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. J Clin Oncol 26:3785-3790, 2008
10. Salgado R, Denkert C, Demaria S, et al: The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: Recommendations by an international TILs working group 2014. Ann Oncol 26:259-271, 2015
11. NanoString: nCounter Breast Cancer 360 panel. https://www.nanostring.com/products/gene-expression-panels/gene-expression-panels-overview/ncounter-breast-cancer-360-panel
12. Ayers M, Lunceford J, Nebozhyn M, et al: IFN-γ-related mRNA profile predicts clinical response to PD-1 blockade. J Clin Invest 127:2930-2940, 2017
13. Parker JS, Mullins M, Cheang MC, et al: Supervised risk predictor of breast cancer based on intrinsic subtypes. J Clin Oncol 27:1160-1167, 2009
14. Lehmann BD, Bauer JA, Chen X, et al: Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest 121:2750-2767, 2011
15. Lehmann BD, Jovanović B, Chen X, et al: Refinement of triple-negative breast cancer molecular subtypes: Implications for neoadjuvant chemotherapy selection. PLoS One 11:e0157368, 2016
16. den Brok WD, Schrader KA, Sun S, et al: Homologous recombination deficiency in breast cancer: A clinical review. JCO Precis Oncol doi:10.1200/PO.16.00031
17. Robson M, Im SA, Senkus E, et al: Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med 377:523-533, 2017
18. Litton JK, Rugo HS, Ettl J, et al: Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med 379:753-763, 2018
19. Mateo J, Carreira S, Sandhu S, et al: DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 373:1697-1708, 2015
20. Mirza MR, Pignata S, Ledermann JA: Latest clinical evidence and further development of PARP inhibitors in ovarian cancer. Ann Oncol 29:1366-1376, 2018
21. Chandran EA, Kennedy I: Significant tumor response to the poly (ADP-ribose) polymerase inhibitor olaparib in heavily pretreated patient with ovarian carcinosarcoma harboring a germline RAD51D mutation. JCO Precis Oncol doi:10.1200/PO.18.00253
22. Sweis RF, Heiss B, Segal J, et al: Clinical activity of olaparib in urothelial bladder cancer with DNA damage response gene mutations. JCO Precis Oncol doi:10.1200/PO.18.00264

23. Ngoi NYL, Tay D, Heong V, et al: Reversal of bowel obstruction with platinum-based chemotherapy and olaparib in recurrent, short platinum-free interval, RAD51C germline mutation–associated ovarian cancer. JCO Precis Oncol doi:10.1200/PO.18.00008
24. Nik-Zainal S, Davies H, Staaf J, et al: Landscape of somatic mutations in 560 breast cancer whole-genome sequences. Nature 534:47-54, 2016
25. Winter C, Nilsson MP, Olsson E, et al: Targeted sequencing of BRCA1 and BRCA2 across a large unselected breast cancer cohort suggests that one-third of mutations are somatic. Ann Oncol 27:1532-1538, 2016
26. Turner N, Tutt A, Ashworth A: Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer 4:814-819, 2004
27. Davies H, Glodzik D, Morganella S, et al: HRDetect is a predictor of BRCA1 and BRCA2 deficiency based on mutational signatures. Nat Med 23:517-525, 2017
28. Chalmers A, Jackson A, Swaisland H, et al: DDIS-19. Olaparib penetrates tumour margins as well as contrast enhancing regions of glioblastoma at therapeutic levels: Interim results of the Oparatic Trial NCT01390571. Neuro-Oncol 18:vi51, 2016
29. Fong PC, Boss DS, Yap TA, et al: Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 361:123-134, 2009
30. Forster MD, Dedes KJ, Sandhu S, et al: Treatment with olaparib in a patient with PTEN-deficient endometrioid endometrial cancer. Nat Rev Clin Oncol 8:302-306, 2011
31. Sahgal A, Soliman H, Larson DA: Whole-brain radiation therapy of brain metastasis, in Kim DG, Lunsford LD (eds): Current and Future Management of Brain Metastasis. Basel, Switzerland, Karger Publishers, 2012, pp 82-95
32. Gaspar LE, Mehta MP, Patchell RA, et al: The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline. J Neurooncol 96:17-32, 2010
33. Gaspar LE, Scott C, Murray K, et al: Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys 47:1001-1006, 2000
34. Cairncross JG, Kim JH, Posner JB: Radiation therapy for brain metastases. Ann Neurol 7:529-541, 1980
35. Bachelot T, Romieu G, Campone M, et al: Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): A single-group phase 2 study. Lancet Oncol 14:64-71, 2013
36. O'Sullivan CC, Davarpanah NN, Abraham J, et al: Current challenges in the management of breast cancer brain metastases. Semin Oncol 44:85-100, 2017