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Olaparib in hormone receptor-positive, HER2-negative metastatic breast cancer with a somatic *BRCA2* mutation

Lee S. Schwartzberg and Lesli A. Kiedrowski

***Abstract*:** The oral poly(adenosine diphosphate-ribose) polymerase inhibitor olaparib is approved for the treatment of patients with human epidermal growth factor 2-negative (HER2–) metastatic breast cancer (mBC) and a germline breast cancer susceptibility gene (BRCA) mutation who have been treated with chemotherapy. This case report describes a 63-year-old postmenopausal woman with somatic *BRCA2*-mutated mBC who responded to olaparib treatment following multiple prior lines of therapy. The patient presented in January 2012 with locally advanced, hormone receptor-positive (HR+), HER2– BC which, despite initial response to neoadjuvant chemotherapy, recurred as bone disease in February 2014, and subsequently skin (June 2016) and liver (October 2016) metastases. A comprehensive 592-gene next-generation sequencing panel (Caris Life Sciences), performed on a skin biopsy, detected a pathogenic frameshift mutation in *BRCA2* (H3154fs, c.9460delC), which was not identified in a 28-gene hereditary cancer germline analysis (Myriad Genetics, Inc.), and was therefore considered to be a somatic mutation. In January 2017, cell-free DNA (cfDNA) analysis (Guardant Health, Inc.) confirmed the *BRCA2* H3154fs mutation in plasma. After several lines of chemotherapy and endocrine therapy, deriving clinical benefit from eribulin and capecitabine, the disease progressed by October 2017, and olaparib (300 mg orally twice daily) was initiated in January 2018. By April 2018, the liver lesions had shrunk by 80% and a >90% response in multiple skin lesions was noted. Clinical response was maintained for 8 months, followed by progression in the skin in September 2018. Biopsy of recurrent lesions revealed a novel *BRCA2* mutation, E3152del (c.9455_9457delAGG), predicted to restore the open reading frame and presumably the mechanism of resistance to olaparib. Further likely resistance mutations were noted in subsequent cfDNA analyses. This case demonstrated a clinical response with olaparib as a later-line therapy for HR+, HER2– mBC with a somatic *BRCA2* mutation.

Keywords: breast cancer, metastasis, olaparib, PARP inhibitor, somatic *BRCA2* mutations

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Introduction

Breast cancer (BC) susceptibility genes (*BRCA1* and *BRCA2*) encode proteins essential to high-fidelity repair of DNA double-strand breaks (DSBs).[1] Deletions or mutations in these genes, particularly in breast and ovarian cancer,[2] result in compromised homologous recombination repair (HRR), posing significant risks to genome integrity.[3,4]

Poly(adenosine diphosphate-ribose) polymerase (PARP) is a major factor in the repair of DNA single-strand breaks (SSBs).[5] Olaparib, an oral PARP inhibitor (PARPi),[6] traps PARP at DNA SSBs, thereby stalling replication forks, leading to their collapse and creating irreparable DNA DSBs implicated in tumour-specific cell death in BRCA-mutated cancers.[4,7]

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Table 1. Time course of anticancer therapies before initiating treatment with olaparib.

Treatment	Start treatment	End treatment	Treatment duration, months
Neoadjuvant docetaxel + bevacizumab	13 February 2012	7 June 2012	3.8
Letrozole	12 September 2012	17 March 2014	18.3
Cyclophosphamide + methotrexate + fluorouracil	17 March 2014	28 April 2014	1.4
Dose-dense adriamycin + cyclophosphamide + paclitaxel	30 April 2014	11 June 2014	1.4
Everolimus + exemestane	22 July 2014	21 August 2014	1
Eribulin	17 September 2014	20 July 2016	22
Fulvestrant + palbociclib	27 July 2016	14 December 2016	4.6
Capecitabine	10 January 2017	21 December 2017	11.5
Olaparib, 300 mg twice daily	26 January 2018	25 November 2018	10

In January 2018, olaparib was approved by the United States (US) Food and Drug Administration (FDA) for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated human epidermal growth factor receptor 2-negative (HER2−) metastatic BC (mBC) treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting.[8] Approval was based on the results of the phase III OlympiAD trial, in which olaparib monotherapy improved median progression-free survival (PFS; 7.0 months) compared with standard chemotherapy (4.2 months; hazard ratio [HR], 0.58; 95% confidence interval [CI], 0.43–0.80; $p < 0.001$).[6]

In a cohort study of 273 unselected patients with BC,[9] germline BRCA mutations were twice as likely as somatic BRCA mutations; 3% of patients harboured only somatic mutations in *BRCA1* or *BRCA2*, for which there is no approved therapy in the USA. HRR deficiency has also been reported in a significant proportion of patients with BRCA-wildtype BC,[7] as hereditary and somatic mutations can occur in other genes involved in the HRR pathway, such as *PALB2* and *PTEN*.[10–13] This suggests the clinical benefit of PARPi in mBC could extend to somatic BRCA mutations, and conceivably to other non-BRCA mutation HRR-deficient cells, regardless of germline *versus* somatic origin.[4,7]

We present the case of a postmenopausal woman with oestrogen receptor-positive (ER+), HER2− mBC and a somatic *BRCA2* mutation in tumour tissues and plasma, who after several lines of chemotherapy, with responses and ultimately progression, had a clinically meaningful response to olaparib.

Case report

In January 2012, a 57-year-old, postmenopausal, white woman presented with a left breast mass and family history of later-onset breast and prostate cancer. Examination revealed a 13 × 13 cm mass, an ulcerating satellite mass in the left inframammary fold and a matted 4 cm mass in the left axillary lymph nodes.

A biopsy of the left breast demonstrated invasive lobular carcinoma, which was ER+ (96%), progesterone receptor-positive (PR+; 95%), HER2− by immunohistochemistry (IHC) and Ki-67 40%.

A computed tomography (CT) scan of the chest and abdomen and a bone scan were negative for distant metastases. The patient was staged as having locally advanced, initially inoperable, stage 3 (cT4, cN3, cM0) cancer. Neoadjuvant chemotherapy with docetaxel and bevacizumab was initiated (Table 1). Complete clinical response was achieved after six cycles of therapy.

Table 2. Summary of common cancer-associated somatic genetic variants detected in skin specimens using NGS.

Gene	592-gene NGS panel #1, 22 June 2016				592-gene NGS panel #2, 16 October 2018			
	Detected variants		Functional classification	VAF, %	Detected variants		Functional classification	VAF, %
	Protein alteration	Nucleotide change			Protein alteration	Nucleotide change		
ALK	P40H	NA	VUS	25	—	—	—	—
BRCA2	H3154fs	c.9460delC	Pathogenic	74	—	—	—	—
BRCA2	—	—	—	—	E3152del	c.9455_9457delAGG	Probable reversion	35
ESR1	Y537S	NA	Pathogenic	36	Y537S	c.1610 _1611delinsCC	Pathogenic	22
NOTCH1	R176Q	NA	VUS	16		—	—	—
RB1	G840R	NA	VUS	14		—	—	—
WT1	E154*	NA	Pathogenic	36	—	—	—	—
WT1	E153D	NA	VUS	37	—	—	—	—
WT1	—	—	—	—	E153 _E154 delinsD*	c.459_460delinsCT	Pathogenic	27

A total of 592 genes was tested using NGS. Alterations prefaced by: p., protein; c., complementary DNA.
ALK, anaplastic lymphoma receptor kinase gene; *BRCA2*, breast cancer type 2 susceptibility gene; *ESR1*, oestrogen receptor alpha gene; NA, not available; NGS, next-generation sequencing; *NOTCH1*, notch homologue 1, translocation-associated gene; *RB1*, retinoblastoma-1 gene; VAF, variant allele frequency; VUS, variant of uncertain significance; WT1, Wilms tumour 1.

In July 2012, the patient underwent a left mastectomy with axillary lymph node dissection and a contralateral right prophylactic mastectomy. Pathologic stage was ypT1a(m), pN2a. Postoperatively, she received left chest wall and regional nodal irradiation; adjuvant letrozole was initiated in September 2012. A bone scan in 2013 was negative for metastatic disease.

Following the development of right hip pain in February 2014, a bone scan revealed multiple new sites of osseous metastatic disease in the right iliac wing, multiple thoracic vertebrae, both scapulae, right ribs and sternum. A CT-guided biopsy of the right iliac crest showed metastatic, poorly differentiated adenocarcinoma consistent with breast origin: ER+ (100%), PR+ (100%) and HER2− (0/3) by IHC. The patient underwent chemotherapy with one cycle of cyclophosphamide, methotrexate and fluorouracil, followed by three cycles of adriamycin, cyclophosphamide and paclitaxel.

Re-evaluation in July 2014 showed new metastatic foci in the mid-thoracic spine and right femur. A subsequent switch to everolimus plus exemestane was poorly tolerated, and was discontinued after 1 month.

Eribulin, initiated in September 2014, was generally well tolerated. Bone scans revealed mild improvement at some sites in March 2015 and September 2015, and stable disease in December 2015 and April 2016. CT scans in April 2016 were negative for visceral disease.

Physical examination in June 2016 revealed two new skin lesions on the left chest and back; skin punch biopsies were positive for breast carcinoma. A comprehensive 592-gene next-generation sequencing (NGS) panel (Caris Life Sciences, Phoenix, AZ, USA), performed on the skin biopsy, detected a pathogenic frameshift mutation in *BRCA2* (H3154fs, c.9460delC, variant allele frequency [VAF] 74%). IHC testing confirmed continued ER- and PR-positivity, with HER2− by IHC and chromogenic *in situ* hybridization. Key NGS panel findings are summarized in Table 2. One month later, a 28-gene hereditary cancer germline analysis (Myriad Genetics, Inc., Salt Lake City, UT, USA) of a blood specimen was negative, confirming that the *BRCA2*

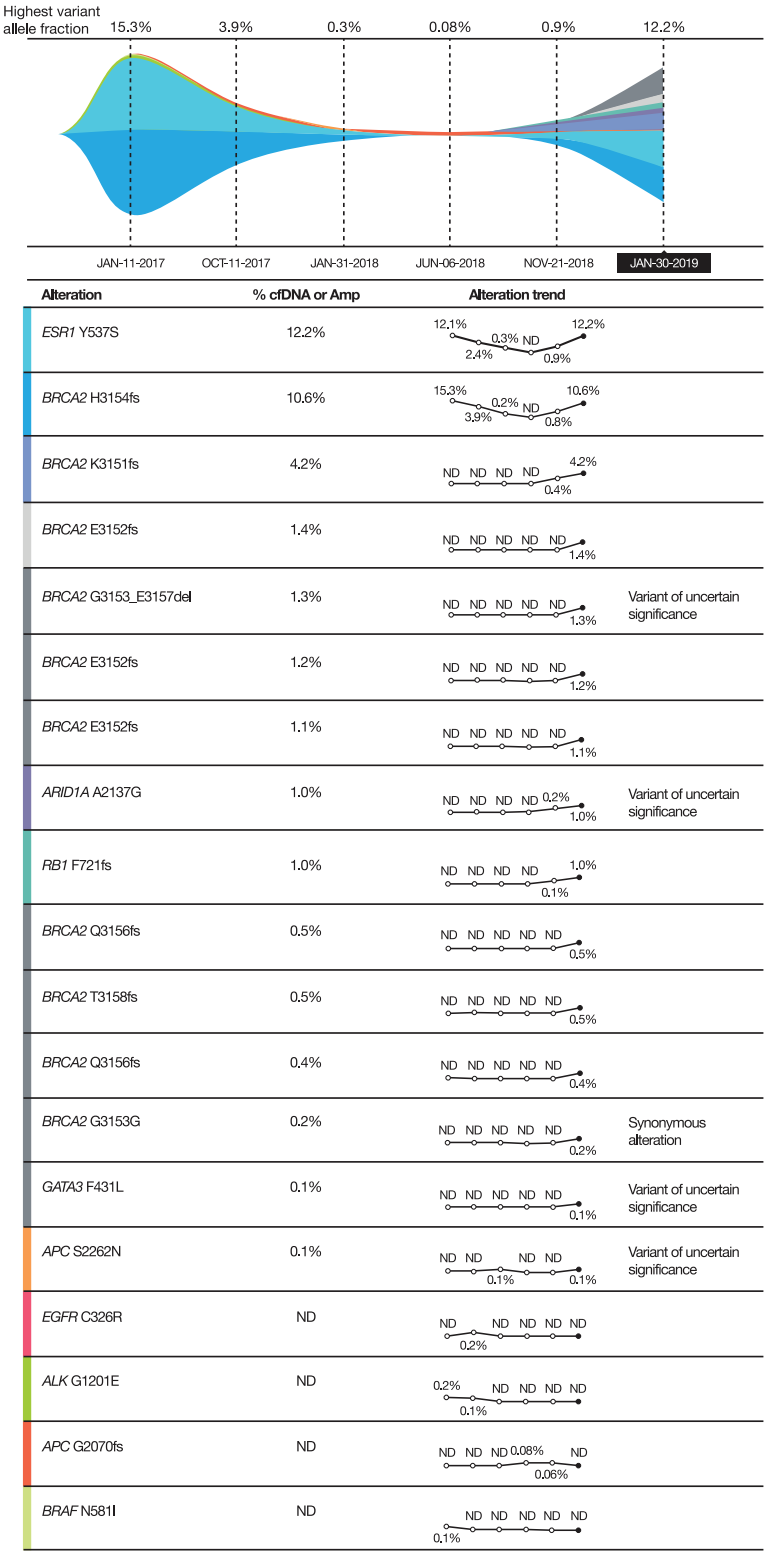

Figure 1. Summary of genetic mutations showing the allele frequencies of cfDNA alterations in plasma across multiple time points.
ALK, anaplastic lymphoma receptor kinase gene; Amp, amplified by polymerase chain reaction; *APC*, adenomatous polyposis coli gene; *ARID*, AT-rich interactive domain gene; *BRAF*, B-Raf gene; *BRCA2*, breast cancer type 2 susceptibility gene; cfDNA, cell-free DNA; *EGFR*, epidermal growth factor receptor gene; *ESR1*, oestrogen receptor alpha gene; *GATA3*, GATA binding protein 3 gene; ND, not detected; *RB1*, retinoblastoma-1 gene.

mutation identified in the tumour tissue was somatic, not hereditary.

Fulvestrant and palbociclib were initiated in July 2016. By October 2016, bone lesions (mixed lytic and blastic disease) were stable, but subtle liver metastases were suspected in a CT scan. A further CT scan in January 2017 showed enlarging liver metastases, with the largest measuring 2.2 × 1.6 cm in segment 6. Plasma cell-free DNA (cfDNA) analysis (Guardant Health, Inc., Redwood City, CA, USA) confirmed the somatic *BRCA2* H3154fs mutation (VAF, 15.3%; Figure 1). The patient was switched to capecitabine chemotherapy, with prompt dose reduction due to hand–foot syndrome.

By March 2017, near-complete resolution of skin lesions was noted. CT scans demonstrated 80% reduction in liver lesion diameters and stable bone disease. CT scans in July 2017 were stable.

In October 2017, skin lesions recurred and progressed, with a CT scan revealing substantial progression of multiple metastases in the liver. The capecitabine dosage was increased, and the cutaneous lesions responded briefly, but a CT scan in January 2018 showed multiple new liver lesions and doubling in size of the largest lesion (Figure 2). The skin lesions had progressed, and new satellite nodules were detected. Bone scan results remained stable. Capecitabine was discontinued after almost 12 months of therapy.

Olaparib therapy (300 mg orally twice daily) was initiated on 26 January 2018. A cfDNA assay on 31 January 2018 again showed the original *BRCA2* H3154fs (c.9460delC), this time at a much lower VAF of 0.2%. Skin lesions improved by 50% within 3 weeks. Initial symptomology (nausea, fatigue, irritated mouth) also improved. Olaparib treatment was paused briefly in February 2018, during hospitalization for *Klebsiella* bacteraemia complicating febrile pancytopenia, and was restarted at a full dose (300 mg twice daily) following recovery of the white blood cell count.

In April 2018, a CT scan showed liver lesion shrinkage of 80% (Figure 2). Multiple lytic lesions in the spine remained unchanged. Physical examination showed >90% response in multiple skin lesions. Olaparib treatment was continued, with

mild fatigue and resolution of nausea. Periodic packed red blood cell transfusions were required.

By June 2018, a >95% improvement in the metastatic skin lesions and further reduction in liver lesions was noted; bone scan results remained stable. A cfDNA analysis at this time demonstrated undetectable levels of *BRCA2* and of other mutations, including *ESR1* and *ALK* (Figure 1). CT scans on 30 August 2018 showed further reduction in the hepatic metastases.

One month later, a lesion on the left back had grown from approximately 7 mm to 20 mm, although no new skins lesions were noted. A skin biopsy (16 October 2018) showed GATA3-positive, ER+ (90%), PR+ (90%), HER2− mBC. A repeat 592-gene NGS panel on the skin biopsy detected a novel *BRCA2* mutation, E3152del (c.9455_9457delAGG), at a VAF of 35%, predicted to restore the open reading frame and potentially lead to resumption of functional activity (Table 2).

cfDNA analysis on 21 November 2018 showed co-occurring *BRCA2* H3154fs (c.9460delC; VAF, 0.8%) and emerging K3151fs (c.9452_9453delAA; VAF, 0.4%) mutations (Figure 1). A CT scan showed minimal liver disease, stable bone disease, and small left pleural effusion. New satellite skin lesions on the back were detected on physical examination. Olaparib treatment was discontinued after 10 months of therapy, and vinorelbine was initiated.

By January 2019, multiple skin nodules had progressed, with unchanged bone disease. Eastern Cooperative Oncology Group performance status remained at 1. Pain was controlled with long-acting narcotics, vinorelbine treatment was discontinued and liposomal doxorubicin treatment was initiated, with poor tolerance. A subsequent cfDNA analysis (30 January 2019) showed VAF increases in the original *BRCA2* H3154fs to 10.6% and in the recently emerging *BRCA2* K3151fs to 4.2%, as well as three new genomically distinct variants of *BRCA2* E3152fs (c.9453dupA, c.9450_9454delAAAAGinsCAAAAA, and c.9455_9456delAG) at 1.4%, 1.2% and 1.1% VAF, respectively, and three genomically distinct *BRCA2* Q3156fs variants (c.9465dupT, c.9471_9472insT, and c.9466delCinsAA), at 0.5%, 0.4%, and 0.2% VAF, respectively (Figure 3). A CT scan demonstrated a slight increase in pleural effusion, with stable liver and bone disease. Carboplatin and radiation therapy for ulcerated skin lesions began on 30 January 2019, and continued until April 2019, when hepatic progression was observed. The patient received palliative care and died in August 2019.

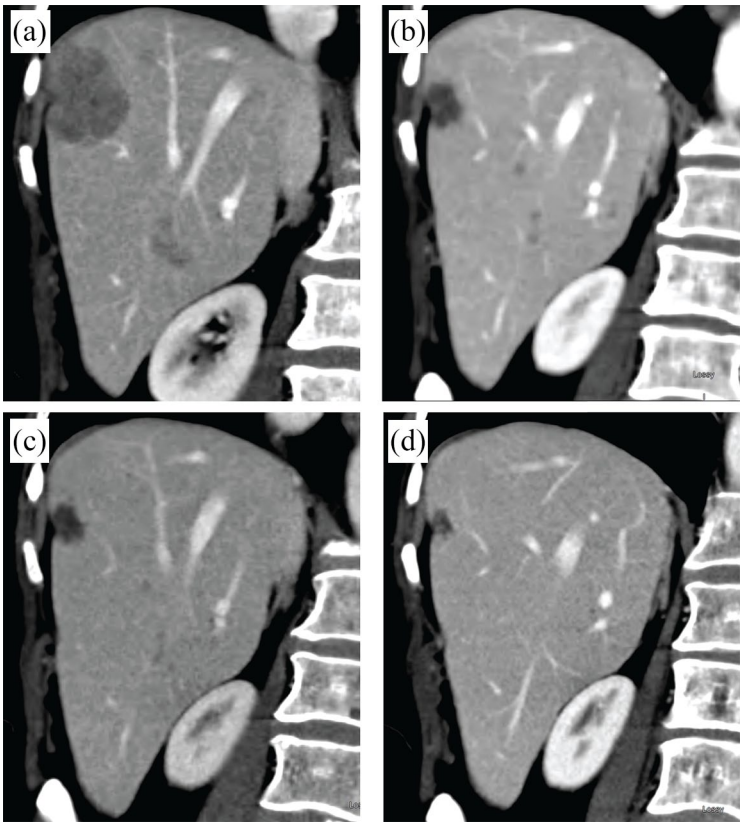

Figure 2. CT scans of liver metastases. (a) January 2018, before olaparib therapy. (b) April 2018, following interruption to olaparib therapy. (c) June 2018, during olaparib therapy. (d) January 2019, after stopping olaparib therapy.
CT, computed tomography

Discussion

These findings indicate that olaparib was effective as later-line therapy in a 63-year-old woman with a somatic *BRCA2* mutation, who was diagnosed 7 years earlier with ER+, PR+ and HER2− invasive lobular carcinoma. Metastatic recurrence in bone developed <2.5 years after neoadjuvant chemotherapy, while she was receiving adjuvant endocrine therapy. She subsequently received multiple therapeutic lines, deriving clinical benefit from eribulin and capecitabine, followed by cutaneous and hepatic progression prior to olaparib treatment.

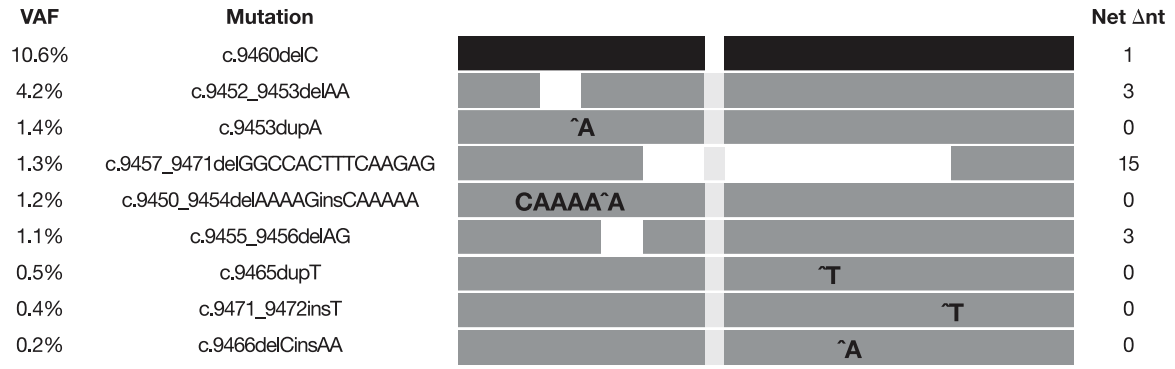

Figure 3. Summary of *BRCA2* genetic mutations showing the allele frequencies of cfDNA alterations in plasma from the analysis on 30 January 2019 and predicted net change in nucleotides highlighting predicted restoration of the open reading frame.
BRCA2, breast cancer type 2 susceptibility gene; cfDNA, cell-free DNA; Net Δnt, net change in nucleotides; VAF, variant allele frequency.

Genomic alterations were detected in skin biopsies performed more than 2 years apart and in sequential plasma cfDNA analyses. The most pertinent and potentially actionable mutation found was *BRCA2* H3154fs, a pathogenic mutation leading to a non-functional BRCA2 protein. A subsequent multigene panel for germline mutations in blood was negative for *BRCA2*, confirming the somatic origin of the *BRCA2* pathogenic mutation, concordant with genomic testing across breast, skin and plasma specimens (Table 2 and Figure 1). The mutational analyses provided a strong rationale for treatment with olaparib, considering the known sensitivity of germline BRCA mutations to the effects of PARPi therapy.[14] The patient had a clinical response to olaparib that lasted 8 months, with tolerable toxicity.

Non-detection of the original somatic *BRCA2* H3154fs mutation in skin in the second NGS panel and in sequential plasma cfDNA assays suggests a positive effect of olaparib in suppressing the pathogenic clone, leading to prolongation of the clinical response.

Somatic *BRCA2* reversion mutations and treatment resistance have been reported in metastatic prostate cancer exposed to PARPi.[15,16] cfDNA analysis has the advantage of detecting heterogeneous alterations from multiple tumour sites with a minimally invasive approach, and quantitative VAFs can serve as a measure of the tumour burden and therapeutic response, especially when used sequentially.[15,17]

In this patient, sequential cfDNA analyses revealed multiple mutations over time, each predicted to restore the open reading frame. Concurrent identification of the original H3154fs mutation with reversion mutations likely represents differing subclonal tumours' responses to olaparib. These polyclonal alterations were probable mechanisms of resistance, emerging after months of olaparib therapy, as previously reported in patients with pathogenic germline and somatic BRCA mutations in breast and ovarian cancers.[18–21] To our knowledge, this is the first case of clinical response to olaparib documented for somatic *BRCA2*-mutated mBC, with presumed resistance emerging from reversion mutations. Further research into PARPi therapy in patients with somatic BRCA-mutated, germline BRCA-wildtype mBC is underway.

This case report demonstrates clinical response to olaparib as later-line therapy for ER+, HER2− mBC, with germline wildtype BRCA genes and an actionable somatic BRCA mutation, for which PARPi could provide substantial clinical benefit.

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Conflict of interest statement

Lee S. Schwartzberg is a consultant for AstraZeneca, Genentech, Helsinn, Lilly, Novartis, Pfizer and Spectrum. He has received research funding from Amgen and Pfizer and is on the speakers' bureau for Amgen and Puma. Lesli A. Kiedrowski is an employee and shareholder of Guardant Health, Inc.

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References

1. Ledermann JA, Drew Y and Kristeleit RS. Homologous recombination deficiency and ovarian cancer. *Eur J Cancer* 2016; 60: 49–58.
2. Chen CC, Feng W, Lim PX, *et al*. Homology-directed repair and the role of BRCA1, BRCA2, and related proteins in genome integrity and cancer. *Annu Rev Cancer Biol* 2018; 2: 313–336.
3. Gunderson CC and Moore KN. BRACAnalysis CDx as a companion diagnostic tool for Lynparza. *Expert Rev Mol Diagn* 2015; 15: 1111–1116.
4. Murata S, Zhang C, Finch N, *et al*. Predictors and modulators of synthetic lethality: an update on PARP inhibitors and personalized medicine. *Biomed Res Int* 2016; 2016: 2346585.
5. O'Connor MJ. Targeting the DNA damage response in cancer. *Mol Cell* 2015; 60: 547–560.
6. Robson M, Im SA, Senkus E, *et al*. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med* 2017; 377: 523–533.
7. den Brok WD, Schrader KA, Sun S, *et al*. Homologous recombination deficiency in breast cancer: a clinical review. *JCO Precis Oncol* 2017; 1: 1–13.
8. US Food and Drug Administration. Lynparza prescribing information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s014lbl.pdf. (accessed 7 September 2020).
9. 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* 2016; 27: 1532–1538.
10. Mendes-Pereira AM, Martin SA, Brough R, *et al*. Synthetic lethal targeting of *PTEN* mutant cells with PARP inhibitors. *EMBO Mol Med* 2009; 1: 315–322.
11. Ming M and He Y-Y. PTEN in DNA damage repair. *Cancer Lett* 2012; 319: 125–129.
12. Nepomuceno TC, De Gregoriis G, de Oliveira FMB, *et al*. The role of *PALB2* in the DNA damage response and cancer predisposition. *Int J Mol Sci* 2017; 18: 1886.
13. Ngeow J, Sesock K and Eng C. Breast cancer risk and clinical implications for germline *PTEN* mutation carriers. *Breast Cancer Res Treat* 2017; 165: 1–8.
14. Yi T, Feng Y, Sundaram R, *et al*. Antitumor efficacy of PARP inhibitors in homologous recombination deficient carcinomas. *Int J Cancer* 2019; 145: 1209–1220.
15. Quigley D, Alumkal JJ, Wyatt AW, *et al*. Analysis of circulating cell-free DNA identifies multiclonal heterogeneity of *BRCA2* reversion mutations associated with resistance to PARP inhibitors. *Cancer Discov* 2017; 7: 999–1005.
16. Carneiro BA, Collier KA, Nagy RJ, *et al*. Acquired resistance to poly (ADP-ribose) polymerase inhibitor olaparib in *BRCA2*-associated prostate cancer resulting from biallelic *BRCA2* reversion mutations restores both germline and somatic loss-of-function mutations. *JCO Precis Oncol* 2018; 2: 1–8.
17. Lupini L, Moretti A, Bassi C, *et al*. High-sensitivity assay for monitoring *ESR1* mutations in circulating cell-free DNA of breast cancer patients receiving endocrine therapy. *Sci Rep* 2018; 8: 4371.
18. Noordermeer SM and van Attikum H. PARP inhibitor resistance: a tug-of-war in BRCA-mutated cells. *Trends Cell Biol* 2019; 29: 820–834.
19. Weigelt B, Comino-Mendez I, de Bruijn I, *et al*. Diverse *BRCA1* and *BRCA2* reversion mutations in circulating cell-free DNA of therapy-resistant breast or ovarian cancer. *Clin Cancer Res* 2017; 23: 6708–6720.
20. Gornstein EL, Sandefur S, Chung JH, *et al*. *BRCA2* reversion mutation associated with acquired resistance to olaparib in estrogen receptor-positive breast cancer detected by genomic profiling of tissue and liquid biopsy. *Clin Breast Cancer* 2018; 18: 184–188.
21. Christie EL, Fereday S, Doig K, *et al*. Reversion of *BRCA1/2* germline mutations detected in circulating tumor DNA from patients with high-grade serous ovarian cancer. *J Clin Oncol* 2017; 35: 1274–1280.