

REVIEW ARTICLE

Complete remission with olaparib in *BRIP1*-mutated metastatic high-grade pleomorphic sarcoma: case study and literature review – an example of a genomic profiling-based tumor treatment, in a cancer type with high unmet clinical need

Alexander D. J. Thooft^{a,b,*} , Sofie Joris^{c,*} , Celine Jacobs^{a,b} , David Creyten^d , Sylvie Rottey^{a,b} , Brigitte Maes^{e,f} , Philippe Aftimos^g  and Lore Lapeire^{a,b} 

^aDepartment of Medical Oncology, Ghent University Hospital, Ghent, Belgium; ^bDepartment of Internal Medicine and Pediatrics, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium; ^cDepartment of Medical Oncology, University Hospital Brussels, Brussels, Belgium; ^dDepartment of Pathology, Ghent University Hospital, Ghent University, Ghent, Belgium; ^eLaboratory for Molecular Diagnostics, Jessa Hospital, Hasselt, Belgium; ^fFaculty of Medicine and Life Sciences, LCRC, University of Hasselt, Hasselt, Belgium; ^gClinical Trials Conduct Unit, Institut Jules Bordet – Hôpital Universitaire de Bruxelles, Brussels, Belgium

ABSTRACT

Background and purpose: Patients with high-grade metastatic sarcoma have a poor prognosis and limited treatment options, mostly involving chemotherapy with palliative intent. In the past years, next generation sequencing has proven its benefit in cancer diagnostics and prediction of treatment response to targeted therapy.

Patient/material and methods: We present a case of response and long-term complete remission under treatment with the poly(ADP-ribose) polymerase inhibitor (PARP-inhibitor) olaparib in a patient with metastatic high-grade pleomorphic sarcoma, with an next generation sequencing detected *BRIP1*-mutation. Additionally, a literature search regarding the pathophysiology of *BRIP1*-mutations and the role of PARP-inhibitors in *BRIP1*-mutated cancer was conducted.

Results: A 67-year-old female patient was diagnosed with a high-grade intra-abdominal pleomorphic sarcoma, which was surgically resected. One year later, metastatic lesions in the right lung were observed. Genomic profiling identified a *BRIP1*-mutation. Based on this finding, the patient was included in the PRECISION-2 olaparib study, which evaluates the efficacy of olaparib in advanced cancers of any type harboring mutations in a homologous recombination gene. Within 2 months of olaparib treatment, regression of the pulmonary metastases was observed with ongoing complete remission for currently 36 months. A review of the available literature highlights the importance of *BRIP1* in the homologous recombination repair pathway and its role as a cancer susceptibility gene. Studies in *BRIP1*-mutated breast cancer, ovarian cancer, and prostate cancer suggest a clinical benefit of PARP-inhibitor use.

Interpretation: We here describe the first case of a metastatic *BRIP1*-mutated sarcoma, undergoing a complete radiologic response to olaparib treatment. We highlight an underexplored role of homologous recombination deficiency in non-traditional cancer types and postulate a tumor-agnostic approach to the use of PARP-inhibitors in *BRIP1*-mutated tumors.

ARTICLE HISTORY

Received 15 March 2025
Accepted 3 September 2025
Published 23 September 2025

KEYWORDS

poly(ADP-ribose)
polymerase inhibitors;
BRIP1 protein; human;
sarcoma; recombinational
DNA repair; remission
induction; high-throughput
nucleotide sequencing; precision
medicine

Introduction

Soft-tissue sarcomas (STSs) are a heterogeneous group of mesenchymal tumors with locally destructive growth and high risk of both local and distant recurrences.

The standard of care treatment for high-grade STS in adult patients is a wide surgical excision with R0-margins often followed by adjuvant radiotherapy (RT) and in selected cases adjuvant chemotherapy [1]. Neoadjuvant treatment in the form of chemotherapy or RT can be considered in case of technically unresectable/borderline resectable tumors [2]. In oligometastatic setting, local treatment such as a pulmonary wedge resection,

stereotactic RT, or interventional techniques (radiofrequency- or cryoablation) can be considered [2].

Unresectable metastatic disease is treated with chemotherapy, most commonly with an anthracycline-based therapy. For doxorubicin at a dosing schedule of 75 mg/m² every 3 weeks, the overall response rate is 10–25%, and the stable disease rate is 20–40% [3]. The median progression-free survival (PFS) and overall survival (OS) for doxorubicin are 4–5 months and 8–14 months, respectively [3]. Combination therapy on an anthracycline backbone has a higher response rate but is associated with greater toxicity without OS benefit [3]. With

CONTACT Alexander D. J. Thooft  alexander.thooft@uzgent.be  Corneel Heymanslaan 10, 9000 Ghent, Belgium

*Shared first author.

 Supplemental data for this article can be accessed online at <https://doi.org/10.2340/1651-226X.2025.43374>

© 2025 The Author(s). Published by MJS Publishing on behalf of Acta Oncologica. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>).

doxorubicin, there is a dose limiting cardiotoxicity risk, and a maximum lifetime cumulative dose of 450–550 mg/m² needs to be respected. Therefore, patients can only safely receive up to six cycles of doxorubicin [4].

Second-line chemotherapy regimes may include gemcitabine-docetaxel, trabectedin, and pazopanib [3].

During the course of systemic treatment, surgery or RT of responding metastases may be considered taking into account the site, tumor extent, and natural history of the disease in the individual patient [1, 2, 5].

Treatment of metastatic high-grade STS in adults remains highly challenging, as the prognosis is poor with an overall survival of 5% at 5 years [6, 7] and a median survival of approximately 12–19 months from the onset of metastatic disease [5, 8]. This stresses the importance of further research on additional treatment options. One potential route of research involves the role of homologous recombination deficiency (HRD).

Material and methods

We present a case of complete remission under treatment with olaparib in a patient with metastatic high-grade pleomorphic sarcoma with a germline *BRIP1*-mutation. All information in the case report was – with consent of the patient – extracted from the electronic patient record management system used at Ghent University Hospital, Belgium. The case report was written in accordance with the Consensus-based Clinical Case Reporting (CARE) guidelines. Figures were created using either Microsoft PowerPoint or GIMP 2.10.38.

Additionally, an extensive review was performed of the available literature on the pathophysiology of *BRIP1*-mutations, the use of poly(ADP-ribose) polymerase inhibitors (PARP-inhibitors) in *BRIP1*-mutated ovarian, breast, prostate, and

pancreatic cancer, as well as the use of PARP-inhibitors in STS and other cancer types. Several search engines (including but not limited to PubMed, Google Scholar, and Embase) were employed. Used entry terms included *BRIP1*, *BAHC1*, *FANCI*, Fanconi anemia, Poly(ADP-ribose) Polymerase Inhibitors, Olaparib, Talazoparib, Rucaparib, Niraparib, HRD, Soft-tissue sarcoma, Pleomorphic sarcoma, Ovarian cancer, Breast cancer, Prostate cancer, Pancreatic Cancer, Comprehensive genomic Profiling (CGP), and Precision medicine.

As high-grade pleomorphic sarcoma is a rare cancer type, and the available data on the use of PARP-inhibitor in *BRIP1*-mutated tumors stem mainly from case reports, we performed a narrative review as opposed to a systematic review, as this seemed the best way to summarize the limited available literature.

Results

Case description

In March 2021, a 67-year-old female patient with no relevant medical history but with a family history of early-onset breast cancer (sister at the age of 37) was diagnosed with an undifferentiated pleomorphic sarcoma presenting as a large tumoral mass in the mesentery of the small intestine at the Angle of Treitz (Figure 1). No metastases were visualized on imaging. Surgical removal of the tumoral mass with a maximal diameter of 10 cm was performed. Histology showed spindle-shaped and polygonal poorly differentiated tumor cells with marked pleomorphism, arranged in a haphazard to fascicular growth pattern. Large, bizarre multinucleated cells and numerous mitotic figures were identified. The tumor cells lacked any evidence of epithelial differentiation. Immunohistochemistry showed absence of specific line of differentiation: the tumor

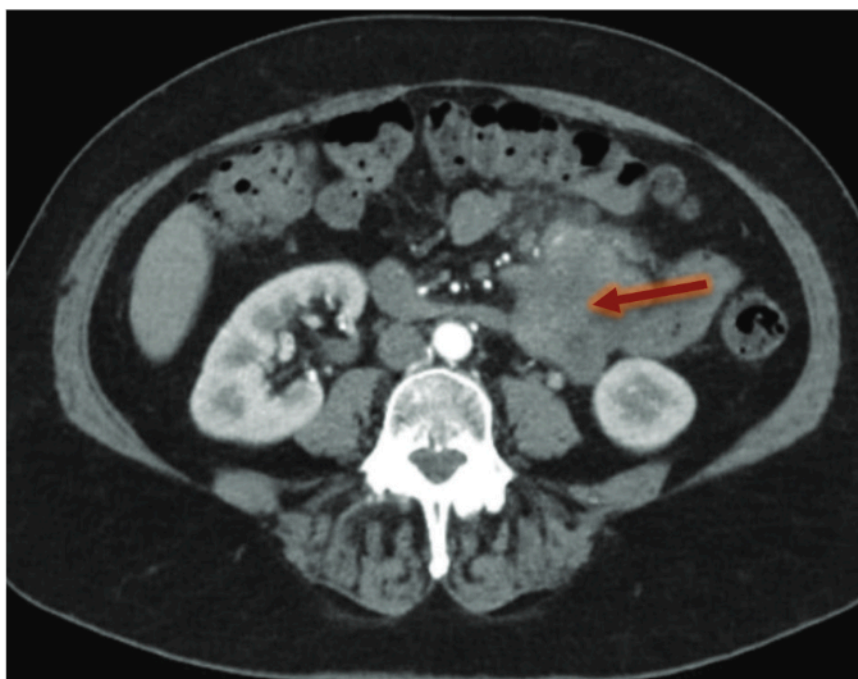


Figure 1. The undifferentiated pleomorphic sarcoma at diagnosis (indicated by an arrow).

cells stained positive for Vimentin but displayed no expression of epithelial markers (Cytokeratin MNF116, Cytokeratin 8/18, Cytokeratin 5, Cytokeratin 7, Cytokeratin 20, and EMA), melanocytic markers (S100 and SOX10), myogenic markers (SMA and Desmin), vascular markers (CD34 and ERG), lymphoid markers (CD45, CD3, CD20, CD5, and CD21), lipogenic markers (MDM2), or 'gastrointestinal stromal tumor' markers (CD117 and DOG1). The tumor cells showed a preserved expression of SMARCB1 (INI1) and SMARCA4. The tumor margins were negative, and the resected lymph nodes had no tumoral invasion. As such, the pathology report was consistent with a high-grade pleomorphic sarcoma, pT2N0M0, FNCLCC grade 3, R0-resection. The patient received no neoadjuvant or adjuvant treatment.

In July 2021, a single tumoral lesion in the left lung was identified (Figure 2) and resected. Histopathological analysis confirmed the hypothesis of a metastasis of the high-grade pleomorphic sarcoma. In January 2022, a left hilar lymphadenopathy (as shown in Figure 3) was visualized and confirmed to be infiltrated by sarcoma cells via endobronchial ultrasound (EBUS) diagnostic function. Stereotactic RT (18 daily fractions of 3 Gy) of this lesion was performed. Unfortunately, in May 2022, multiple asymptomatic metastatic locations were visualized in the right lung, signaling the need for a systemic therapy. In discussion with the patient, no immediate systemic therapy was started, and options for study inclusion were first explored. The patient consented to participate in the Belgian Approach for Local Laboratory Extensive Tumor Testing or BALLETT study (NCT05058937) [9]. The main objective of the BALLETT study was to offer comprehensive genomic profiling (CGP)-guided treatment recommendations fostering precision oncology. For this CGP, the Illumina trusight oncology 500 assay was used. Recommendations were made by the National Molecular Tumor Board established within the Belgian Society of Medical Oncology (BSMO)-PRECISION framework. Treatment recommendations could consist of advice for approved drug use, to participate in a clinical trial or a medical need program, or for off-label drug use and included advices for both molecular guided therapy and/or immunotherapy.

The earlier resected lung metastasis was sent for CGP analysis, which revealed a pathogenic *BRIP1*-mutation (*BRIP1* c.1871C>A p.(Ser624*)) enabling enrollment in the PRECISION-2 olaparib study (NCT03967938). The PRECISION-2 olaparib study [10, 11] intends to evaluate the efficacy of olaparib in advanced cancers of any type occurring in patients with germline or somatic tumor mutations in one of the evaluated homologous recombination repair genes. The results of the performed CGP are depicted in Figure 4. More recently, performed germline testing was also positive for the same *BRIP1*-mutation.

Olaparib at a dose of 300 mg bi-daily (BID) was commenced as a first-line treatment in July 2022. Imaging studies after 2 months on olaparib showed partial regression of the known lung metastases. Follow-up scans were repeated every 2–3 months, and complete oncological response was noted 8 months after olaparib initiation. In Figure 5, radiographic responses of two lung lesions are illustrated. Therapy was well-tolerated with no major side effects and no need for dose reductions.

At present, 36 months after the initiation of olaparib, the patient is still in sustained oncological complete remission with good quality of life in a chemotherapy-free treatment regimen.

Literature review

Homologous recombination deficiency

Human DNA takes the form of a double helix. During replication, both single-strand (ssDNA) and double-strand (dsDNA) DNA breaks can occur [12]. Homologous recombination (HR) ensures error-free repair of dsDNA breaks [13].

Both germline and somatic mutations in genes involved in the HR-cascade can, however, impede a cell's ability to effectively repair these dsDNA breaks [12]. This phenomenon is known as HRD and has proved to be a key player in the development of certain cancer types. In the early 1990s, both *BRCA1* [14] and *BRCA2* [15] were identified as cancer susceptibility genes in patients with early-onset breast and ovarian cancer. Since then,



Figure 2. Single lung metastasis before wedge resection (indicated by an arrow). *Axial liver cross-section showing on CT-scan of thorax; no metastatic lesion.

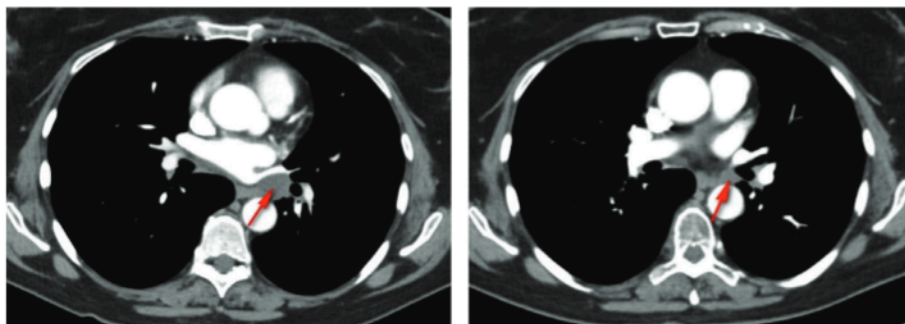


Figure 3. Left hilar lymphadenopathy before and after irradiation (indicated by an arrow).

additional genes involved in the HR-pathway, such as *PALB2*, *ATM*, and *CHECK2* [16], have been identified, and a clear link between HRD and breast, ovarian, prostate, and pancreatic cancer has been established. A somewhat newer entity is *BRIP1*, which exerts its function on a cellular level in conjunction with *BRCA1* and has likewise been identified as a cancer susceptibility gene [13, 17, 18].

An overview of the HR-pathway and the role of *BRIP1* are presented in Figure 6. A more in depth description is presented in Supplementary Appendix 1.

Initially, the identification of germline HRD-mutations enabled better cancer screening strategies for patients and their relatives. Moreover, better advice on preventive measures including surgical removal of breasts and ovaries and reproductive genetic counseling could be provided to individuals with a germline HRD-mutation [19]. With a growing understanding of DNA repair pathways, the identification of both germline and somatic loss-of-function mutations in HR-genes also became of therapeutic significance. These mutations can sensitize tumors to cross-linking agents such as platinum-based chemotherapy, causing dsDNA breaks and to PARP-inhibitors, inhibiting ssDNA break repair and hereby inducing synthetic lethality [12, 17]. As of today, the use of four PARP-inhibitors is approved by the *European Medicines Agency*. Indications [20–23] are listed in Supplementary Appendix 2.

BRIP1 as a cancer susceptibility gene

Considering the presumed role of *BRIP1* in the HR-cascade, studies have explored the significance of *BRIP1* as a cancer susceptibility gene. Loss-of-function mutations in *BRIP1* resulting

in reduced helicase activity and/or altered *BRIP1*-*BRCA1* interaction [17] have been linked to an increased risk for breast [17, 19, 24], ovarian [19, 25–27], prostate [28, 29], and pancreatic cancer, [30, 31]. Furthermore, it is noteworthy that bi-allelic inheritance of mutations in *BRIP1*, as well as *BRCA2* and *PALB2*, contributes to the rare disease of Fanconi anemia, with patients being prone to both hematological and solid cancer development [17, 32].

BRIP1-mutations as predictive markers for PARP-inhibitor use in breast, prostate, ovarian, and pancreatic cancers

Limited but growing evidence suggests a potential clinical benefit of PARP-inhibitors in patients with one of the classical HRD-associated cancer types, in whom a *BRIP1*-mutation has been identified.

Trials evaluating the benefit of PARP-inhibitors in breast cancer patients with mutations in HR-pathway genes other than *BRCA1/2* have only included a very limited number of *BRIP1*-mutation patients and have not been able to confirm a PARP-inhibitor benefit for *BRIP1*-carriers [33, 34]. A case presented by Kwapisz et al. [35] of a patient with *BRIP1*-mutated metastatic hormone receptor positive breast cancer demonstrated, however, a resolution of symptoms, significant decrease in CA15.3, and complete metabolic response on positron emission tomography-computed tomography scan after 8 months of olaparib treatment.

In both the TRITON2 [36] and PROfound trial [37] signs of a PFS benefit of PARP-inhibitor use in metastatic castration resistant prostate cancer patients with *BRIP1*-mutations were noted. In the TRITON trial, one of two included patients with a

Variants

Gene	HGVSc	HGVSp	Shortcode	VAF	Biological class	Validation	Clinical class*
BRIP1	c.1871C>A	p.(Ser624*)	S624*	54%	Likely pathogenic	Consensus	TIER IID
TP53	c.774A>T	p.(Glu258Asp)	E258D	22%	Likely pathogenic	Consensus	TIER IID
BCL10	c.181A>G	p.(Ser61Gly)	S61G	62%	VUS	Consensus	TIER III
JAK1	c.1198G>A	p.(Glu400Lys)	E400K	60%	VUS	Consensus	TIER III
CCND3	c.774_775delinsTG	p.(Ser259Ala)	S259A	55%	VUS	Consensus	TIER III
IDH1	c.935T>C	p.(Val312Ala)	V312A	55%	VUS	Consensus	TIER III
PLCG2	c.2837A>G	p.(Asn946Ser)	N946S	40%	VUS	Consensus	TIER III
FAT1	c.7001A>G	p.(His2334Arg)	H2334R	33%	VUS	Consensus	TIER III
PIK3CA	c.1458C>G	p.(Phe486Leu)	F486L	9%	VUS	Consensus	TIER III
GRM3	c.720C>A	p.(Cys240*)	C240*	6%	VUS	Consensus	TIER III

Figure 4. The patient's comprehensive genomic profiling results for the BALLET study.

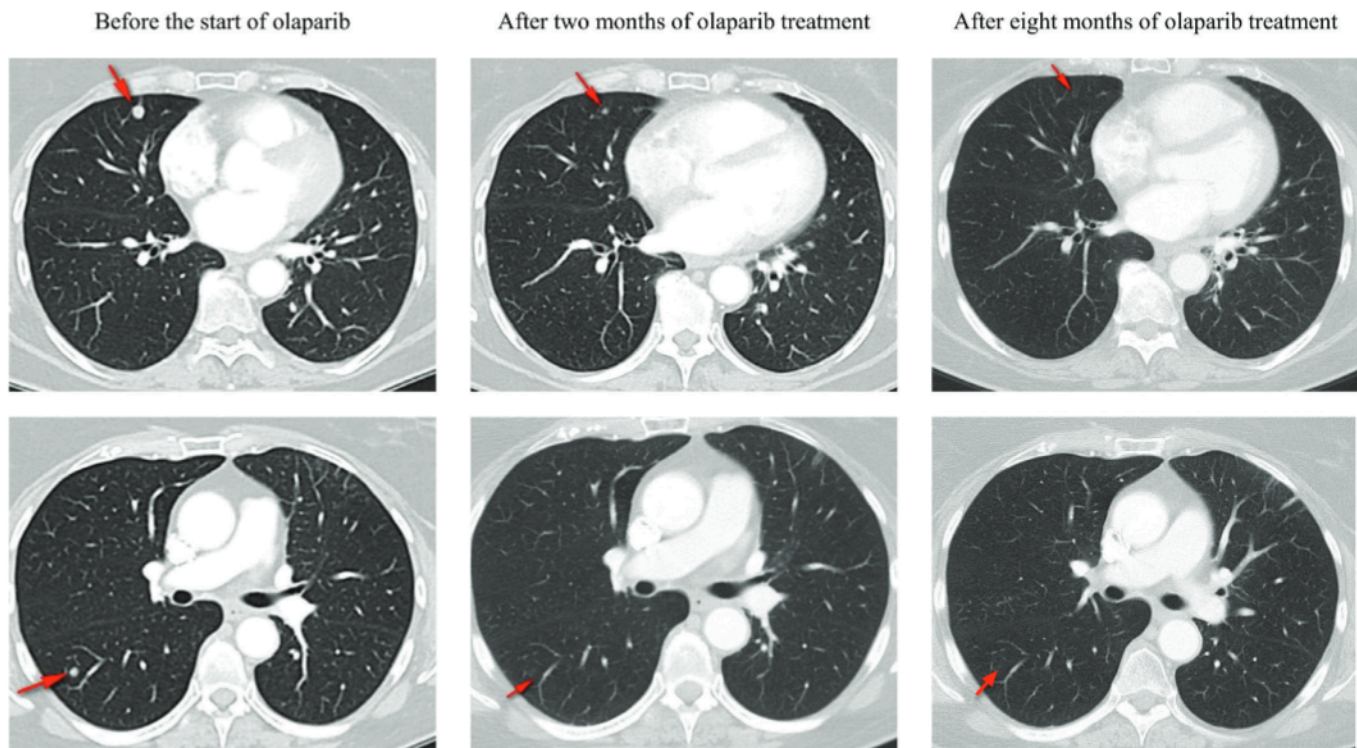


Figure 5. Two examples of complete oncological response of lung metastases after olaparib treatment (indicated by arrows).

BRIP1-mutation had a radiographic and PSA response to rucaparib. The PROfound trial included patients with either a *BRCA1/2*, *ATM*, *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L* mutation in the tumor tissue and compared the use of olaparib versus a control group receiving enzalutamide or abiraterone + prednisone. The median imaging-based PFS was significantly longer in the olaparib group than in the control group (5.8

months versus 3.5 months). No separate outcome data of the 4 enrolled patients with a *BRIP1*-mutation were published [37].

The clinical benefit of PARP-inhibitors in ovarian cancer has been clearly established [38–41]. We identified no studies specifically focusing on the benefit of PARP-inhibitors in *BRIP1*-mutated ovarian cancer. However, aside from *BRCA* status, platinum sensitivity and genomic instability are associated with a better response to PARP-inhibition [42]. As *BRIP1*-mutations

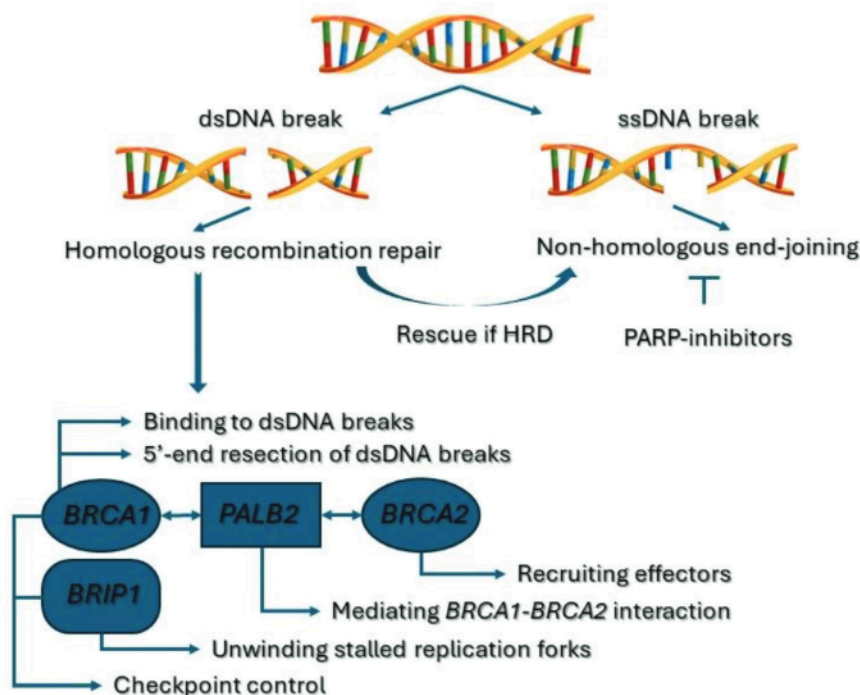


Figure 6. Role of *BRCA1*, *BRCA2*, *PALB2*, and *BRIP1* in the homologous recombination pathway.

are both linked to platinum sensitivity [43, 44] and genomic instability [17], clinical benefit of PARP-inhibitor use is to be expected. Moreover, the presence of a pathogenic *BRIP1*-mutation will often result in a positive HRD-testing, therefore qualifying the patient for olaparib (cfr. Appendix 2) [45]. Consequently, most patients with *BRIP1*-mutated platinum-sensitive stage III or stage IV high-grade ovarian cancer could already receive PARP-inhibitor maintenance therapy.

Finally in pancreatic cancer, trials with niraparib and rucaparib in patients with HRD-mutations other than *BRCA1/2*, including *BRIP1*, are ongoing [46].

Currently, studies are exploring the potential impact of different types of *BRCA1/2* mutations on PARP-inhibitor efficacy. A varying degree of PARP-inhibitor benefit according to the *BRCA1/2* mutation type and site is seen [47, 48]. In *BRIP1*, different loss-of-function mutations may have a potential impact on PARP-inhibitor response as well. Literature on this topic is, however, very limited and inconclusive [49, 50]. The patient in the presented case has a pathogenic *BRIP1* c.1871C>A p.(Ser624*) mutation. This mutation changes the amino acid from a serine to a stop codon within coding exon 12 and is expected to result in loss of function by premature protein truncation (ClinVar version 2025-06-30, RCV000129060). This specific alteration has been reported before in 2 ovarian cancer cases [51, 52] and 2 cases of breast cancer [53].

BRIP1- and other HRD-mutations as predictive markers for the use of PARP-inhibitor in other malignancies

As stated earlier, HR-mutations have been linked to a specific subset of cancers, primarily consisting of breast, ovarian, prostate, and pancreatic cancers. Newer insights are, however, indicative for a broader role of HRD in other cancer types [11, 54, 55].

PARP-inhibitors in HRD-mutated endometrial cancer.

The use of PARP-inhibitors is gaining more interest in endometrial cancer (EC).

Recent studies have shown improvements in disease-free and overall survival in advanced and metastatic EC by adding immunotherapy to chemotherapy [56]. Both the RUBY part 2 [57] and DUO-E [58] trials are investigating whether the addition of, respectively, niraparib and olaparib to the maintenance immunotherapy could further benefit survival. It is important to note that in both trials, no direct head-to-head comparison between the chemotherapy plus immunotherapy arm and the chemotherapy plus immunotherapy plus PARP-inhibitor arm was made; both arms were compared to the chemotherapy only control arm. Therefore, only exploratory subgroup analyses of the added value of PARP-inhibitors can be made. One of these subgroup analyses of the DUO-E trial suggested a further benefit with the addition of olaparib to durvalumab in the pMMR subgroup but not in the dMMR subgroup [58].

The UTOLA trial [59] evaluated the effectiveness of olaparib maintenance in patients with advanced EC, who achieved disease control after first-line platinum-based chemotherapy.

Olaparib did not improve PFS compared to placebo in all participants, but in HRD-tumors, the median PFS was statistically higher with olaparib: 5.4 (90% CI, 3.6–9.6) versus 3.6 (90% CI, 1.8–4.9) months. By reviewing the available literature, we identified, however, multiple case reports of patients with HRD-mutated EC with a more pronounced response to PARP-inhibitors. We identified a case of complete response with olaparib in metastatic high-grade serous EC with a somatic *BRIP1*-mutation [60], a case of complete response with olaparib in metastatic endometrioid, POLE hypermutated EC with somatic *BRIP1*-, *ATM*-, and *RAD51C*-mutation [61], a case of complete remission with olaparib in recurrent metastatic clear cell EC with somatic *BRCA2*-mutation [62], and a case of partial response with niraparib in a patient with high-grade serous EC with brain metastases and a germline *BRCA1*-mutation [63].

Details concerning the prior treatments and extent of response to PARP-inhibitors in the mentioned patients are summarized in Table 1.

PARP-inhibitors in sarcoma patients with HRD-mutations.

As is shown by our case report, HRD might play a role in STS. In the presented case, a complete remission with olaparib was observed for a patient with metastatic high-grade pleomorphic sarcoma with a germline *BRIP1*-mutation. To our knowledge, no previous case of long-term complete remission obtained by the use of PARP-inhibitor in *BRIP1*-mutated sarcomas has been published. The presence of HRD and the use of PARP-inhibitors in sarcomas have, however, been studied before, albeit mostly in a preclinical setting and with variable outcome [64–80].

The most interesting STS subtype in regard of HRD seems to be uterine leiomyosarcoma (uLMS), as growing evidence is supporting the observation that a significant subset of uLMS patients exhibits a HRD phenotype [77–79]. A pan-cancer analysis of germline and somatic *BRCA*-alterations by Jonsson P. et al. [80] even noted that uLMS exhibited the highest rate of homozygous *BRCA2*-deletion, which might indicate a previously unrecognized *BRCA*-dependent cancer type [80]. In both a 2019 case study by Seligson N. et al. [79] and a 2023 case study by Dall G. et al. [81], pathological *BRCA2*-alterations were identified in approximately 10% of the included uLMS cases. In both studies, treatment with off-label olaparib was started if a *BRCA2*-mutation was present with evidence of clinical benefit in all reported cases. Similarly, in a third case study by Pan M. et al. [82], a rapid response to olaparib in a single patient with confirmed *BRCA2*-mutated uLMS was observed. Details concerning the prior treatments and extent of response to olaparib in the mentioned uLMS patients are summarized in Table 2.

Adding onto these preclinical and isolated case findings, an open-label, phase 1b study from the Italian Sarcoma Group with olaparib and trabectedin in advanced and non-resectable bone and soft-tissue sarcomas (TOMAS) was conducted [83]. Trabectedin chemotherapy causes ssDNA and dsDNA breaks, which theoretically can act synergistically with PARP-inhibitors [83]. The TOMAS trial showed manageable toxicities at active dose levels for both drugs with encouraging preliminary data on

Table 1. Clinical data of four patients with *BRIP1*-, *BRCA2*-, or *BRCA1*-mutated EC treated with PARP-inhibitors.

Case study	HRD-mutation	Pretreatment details	Response
Nakamura K. et al. [60]	Somatic <i>BRIP1</i>	Debulking surgery followed by first-line carboplatin/paclitaxel and second-line doxorubicin/cisplatin chemotherapy.	Because of persistent para-aortic and left lateral iliac enlarged lymph nodes, treatment with off-label olaparib 300 mg BID was started. 3 months after olaparib initiation, disappearance of all residual swollen lymph nodes in the pelvis was noted on CT-scan. At 9 months of treatment, the patient is in continued CR.
Senguttuvan R. et al. [61]	Somatic <i>BRIP1</i> , <i>ATM</i> , and <i>RAD51C</i>	After debulking surgery, adjuvant chemotherapy with carboplatin/paclitaxel was initiated but was paused several times due to poor performance status and complications. After 3 cycles, recurrent disease was seen with new hepatic metastases, peritoneal carcinomatosis and supraclavicular, retroperitoneal, and pelvic nodal metastasis. The patient was switch to liposomal doxorubicin and received one cycle, but this was discontinued due to severe cutaneous toxicity necessitating hospitalization.	Olaparib 200 mg BID in compassionate use was started with a complete clinical response after 1 year. Olaparib treatment was stopped after 3 years with a currently ongoing CR.
Anzellini D. et al. [62]	Somatic <i>BRCA2</i>	Total laparoscopic hysterectomy was performed, and regular follow-up was started. On a follow-up PET-CT, both local recurrence at the vaginal dome and 4 lung metastases were noted. The nodule at the vaginal dome was resected, and systemic therapy with carboplatin/paclitaxel/bevacizumab was started. After 3 cycles, a PET-CT re-evaluation showed that 3 out of 4 lung nodules disappeared, and SBRT of the remaining lung nodule was performed. After the SBRT, bevacizumab maintenance therapy was continued. At the next evaluation, however, further recurrence at the vaginal dome was seen.	Olaparib 300 mg BID was started. After at 5 months of treatment, a PET/CT showed CR. Unfortunately, 3 months later, two cerebral brain metastases in the right fronto-parietal lobe were seen on MRI. Then, stereotactic radiosurgery of the brain metastases was performed while continuing olaparib, at the same dosage as before. 24 months after starting olaparib treatment and 15 months after the end of stereotactic radiotherapy, the patient is in complete remission.
Wang Q. et al. [63]	Germline <i>BRAC1</i>	Debulking surgery followed by adjuvant chemotherapy with liposomal doxorubicin/carboplatin for 6 cycles. The patient later development brain metastases, for which she received whole brain radiotherapy in combination with temozolomide with initial improvement of symptoms but intracranial progression shortly after.	Niraparib 200 mg QD was started because of disease progression on MRI accompanied by progressive neurological symptoms. Two month after the start of niraparib, neurological symptoms disappeared. Cranial MRI after 5 months showed PR. Unfortunately, after 9 months of niraparib, neurological symptoms returned with PD on cranial MRI.

SD: stable disease; PD: progressive disease; CR: complete response; PR: partial response; EC: endometrial cancer; PARP: poly(ADP-ribose) polymerase inhibitors; MRI: magnetic resonance imaging.

anti-tumor activity for STS [83]. The study did not demonstrate a better treatment response in the presence of HRD but was underpowered in this regard. The activity in STS is being further assessed in the ongoing TOMAS2 trial [84]. This is a randomized phase 2 study comparing trabectedin alone versus the combination of trabectedin and olaparib (NCT2018-004497-10). Based on preliminary data [84], the trial failed to meet its primary endpoint. Nevertheless, it should be noted that 20% of patients in the trabectedin + olaparib group were treated for over 1 year. With the available information, it currently remains an unanswered question whether or not these long responders have a higher rate of HRD-mutations.

Discussion and conclusion

We presented a case of metastatic high-grade pleomorphic sarcoma with germline *BRIP1*-mutation who achieved long-term and ongoing complete remission on olaparib. Currently, at 36 months of treatment, the patient remains in oncological remission with an excellent quality of life. Even more so than the extent of the response, the duration of the response to first-line olaparib treatment is noteworthy.

Olaparib and other PARP-inhibitors have already proven their survival benefit and role in clinical practice in the context of metastatic *BRCA*-mutated breast, prostate, and pancreatic cancers and in HRD or platinum-sensitive ovarian cancer [20–23].

In light of the presented case, two important findings were recognized: the significance of *BRIP1* as a potential therapeutic target and the presence of a HRD phenotype in ‘non-traditional’ cancer types.

Similar to *BRCA1/2*, *BRIP1* is believed to be an important player in the HR-pathway, which enables a cell to restore dsDNA breaks and maintain genomic stability. Loss-of-function mutations in *BRIP1* can, therefore, promote cancer development. Indeed, studies have identified *BRIP1* as a cancer susceptibility gene [13, 17, 18]. Moreover, the assumption has been made that patients with *BRIP1*-mutated tumors could benefit from PARP-inhibition, which seems logical from a pathophysiological point of view. Clinical data regarding this topic are scarce because of the low number of patients with a confirmed *BRIP1*-mutation included in studies with PARP-inhibitors in non-*BRCA*-mutated HRD cancer. However, the clinical data, which is available, seem to confirm this hypothesis and support the use of PARP-

Table 2. Clinical data of nine patients with *BRCA2*-mutated uterine leiomyosarcoma treated with olaparib [79, 81, 82].

Case study	Number of prior systemic therapies	Pretreatment details	Response to olaparib
1. Seligson N. et al.	3	Gemcitabine-docetaxel, cisplatin, doxorubicin-ifosfamide and pelvic mass resection and pelvic radiation.	After 3 months of olaparib, diminished FDG-avidity of tumoral lesions on PET-CT was noted, and the patient has exhibited ongoing SD on olaparib for 17 months.
2. Seligson N. et al.	4	Gemcitabine-docetaxel, doxorubicin, pazopanib, and trabectedin	Initial SD followed by a subclinical progression after 5 months of olaparib. At that moment, trabectedin was reinitiated and added to olaparib therapy. This regimen stabilized the patient's disease for 15 months before PD.
3. Seligson N. et al.	2	Intensive chemotherapy was not an option due to comorbidities. The patient was started on pazopanib for 1 year with the addition of everolimus for an additional year because of subclinical tumor progression	After further progression, the patient was initiated on olaparib with ongoing SD after 16 months.
4. Seligson N. et al.	2	Gemcitabine-docetaxel, ifosfamide-etoposide, resection of pulmonary metastases, and radiation of pulmonary, pelvic, adrenal, and pancreatic metastases	Data are still immature. 10 weeks after initiation of olaparib, the largest abdominal mass had decreased by 62%. No new tumors had appeared over this period, and the patient remained stable 16 weeks after initiating olaparib.
5. Dall G. et al.	1	First-line anthracycline-base chemotherapy	Imaging showed SD after 2 months of olaparib and then mixed response at 4 months. The patients received radiation to an enlarging pulmonary metastasis, but despite on-going olaparib developed PD within a further month. Single agent carboplatin was added 7 months after starting PARP-inhibitor with an ongoing PR at 19 months post-initiation of olaparib.
6. Dall G. et al.	4	NA	PR was achieved after 5 months of olaparib, with the addition of localized radiotherapy at 13 months and 19 months of olaparib use because of oligometastatic PD.
7. Dall G. et al.	1	First-line anthracycline-base chemotherapy with mixed response	PR was observed on FDG-PET after 6 weeks of olaparib with continued SD after 3 months.
8. Dall G. et al.	5	Doxorubicin, docetaxel-gemcitabine, pazopanib, ifosfamide, and dacarbazine	The patient achieved PR at 4 months, which was sustained until 12 months, before developing evidence of minor progression in a mediastinal lymph node. Cisplatin was added, and after 3 cycles of cisplatin and olaparib combination therapy, a PR was again observed. After 6 cycles of cisplatin in combination with olaparib, a CR was achieved. Later, upon the development of brain metastases, stereotactic radiosurgery was performed while intermittently continuing on single agent olaparib. At 49 months after starting olaparib, the patient is still in metabolic CR (FDG-PET), outside of the brain.
9. Pan M. et al.	3	Gemcitabine-docetaxel, doxorubicin, and temozolomide regimens	6 weeks after olaparib initiation, major PR was noted on PET-CT with continued SD at 8 months.

SD: stable disease; PD: progressive disease; CR: complete response; PR: partial response; NA: information not available in source article; PARP: poly(ADP-ribose) polymerase inhibitors; FDR: [18 F]Fluorodeoxyglucose.

inhibitors in the context of *BRIP1*-mutated breast, ovarian, and prostate cancers [35–37, 45]. Moreover, the rapid and pronounced response to olaparib in the presented case alludes to a broader field of beneficial PARP-inhibitor use, extending to other tumor types, including STS. This is further illustrated by the germline testing of the presented patient's sister with early-onset breast cancer, which revealed the same *BRIP1* c.1871C>A p.(Ser624*) mutation, suggesting a shared inherited cancer susceptibility gene mutation.

Building onto these findings, we suggest a tumor-agnostic approach for *BRIP1*-mutated cancer, in which the start of a PARP-inhibitor could be considered as a therapeutic option regardless of the tumor type. The identification of a *BRIP1*-mutation can therefore be impactful, especially in cancers with limited treatment options or in patients unable to tolerate more intensive treatment regimens. We see a parallel with

neurotrophic tyrosine receptor kinase (NTRK) inhibitors, which are used to treat patients with advanced solid tumors with a NTRK-gene fusion [85]. Treatment with NTRK-inhibitors is tumor agnostic and dependent on the presence of NTRK-fusions only. A similar approach could be followed for cancers with a *BRIP1*- or other HRD-mutation. Such a tumor-agnostic approach requires a strong emphasis on genomic characterization of patients with (metastatic) cancer.

This article has both strengths and limitations. The diagnosis of metastatic disease was confirmed by resection of a metastatic lesion, and both a central pathology review and central genomic assessment were performed because of clinical trial participation.

To the best of our knowledge, no previous case of long-term complete remission obtained by the use of PARP-inhibitor in *BRIP1*-mutated sarcomas has been published. Nevertheless, the

presence of HRD and the use of PARP-inhibitors in sarcomas have been studied earlier, with some cases of clinical remission on olaparib in *BRCA2*-mutated uLMS [79, 81, 82]. Since the treatment options for metastatic high-grade pleomorphic sarcoma are limited, this new therapeutic route is of great interest and warrants further investigation.

Furthermore, an attempt was made to provide a comprehensive overview of the available literature in order to support our recommendations. As this is a single case, our findings need to be interpreted with caution. For reasons stated in the material and methods section, a narrative review rather than a systematic review was performed, and, therefore, potential relevant information could have been missed.

Furthermore, no conclusion about different loss-of-function mutations in *BRIP1* in relation to potential impact on response to PARP-inhibition could be made. We identified this as a topic for further research.

Finally, the provided insights cannot be directly translated into clinical practice, as a comprehensive genomic assessment is not routinely performed in STS and was, in this case only possible by participation in the BALLETT study. The benefit and feasibility of the clinical implementation of this approach is currently examined within the BSMO-Precision Framework, which results are expected soon [10].

Acknowledgments

This case study has not received any direct funding. The presented patient has been treated in the PRECISION-2 olaparib study. In this PRECISION-2 study, AstraZeneca and Merck were responsible for medication supply and financial contributions. None of these companies took part in the writing of this article.

David Creyten was financially supported by a senior clinical research fellowship from the Research Foundation Flanders (1800725N).

Disclosure statements

The authors report there are no competing interests to declare.

Data availability statement

No dataset was used, and no any statistical analysis was performed. The anonymized patient's data are presented in this article. Additional information may be requested from the corresponding author.

Ethics declarations & trial registry information

The patient previously consented to participate in both the BALLETT (NCT05058937) and PRECISION-2 olaparib clinical trials (NCT03967938). For the publication of this manuscript, we obtained an additional informed consent from the presented patient for the use of her health information and imaging

studies. No additional ethics approval for the publication of this case study was asked.

Author contributions

Conceptualization: S.J., L.L., B.M., and P.A.

Methodology: A.T. and S.J.

Writing: A.T. and S.J. prepared the original draft. D.C. provided the pathology description. S.J. provided insight in the PRECISION-2 olaparib study protocol and B.M. to the BALLETT study.

Review and editing: C.J., S.R., B.M., P.A., and L.L.

Supervision: L.L.

All authors have read and agreed to the published version of the manuscript.

References

- [1] Carbone F, Pizzolorusso A, Di Lorenzo G, Di Marzo M, Cannella L, Barretta ML, et al. Multidisciplinary management of retroperitoneal sarcoma: diagnosis, prognostic factors and treatment. *Cancers* (Basel). 2021;13:4016. <https://doi.org/10.3390/cancers13164016>
- [2] Gronchi A, Miah AB, Dei Tos AP, Abecassis N, Bajpai J, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO–EURACAN–GENTURIS clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32:1348–65. <https://doi.org/10.1016/j.annonc.2021.07.006>
- [3] Graves L, Jeck WR, Grilley-Olson JE. A league of its own? Established and emerging therapies in undifferentiated pleomorphic sarcoma. *Curr Treat Options Oncol*. 2023;24:212–28. <https://doi.org/10.1007/s11864-023-01054-7>
- [4] Lyon AR, Lopez-Fernandez T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS) Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). *Eur Heart J Cardiovasc Imaging*. 2022;23:e333–465.
- [5] van Houdt WJ, Zaidi S, Messiou C, Thway K, Strauss DC, Jones RL. Treatment of retroperitoneal sarcoma: current standards and new developments. *Curr Opin Oncol*. 2017;29:260–7. <https://doi.org/10.1097/CCO.0000000000000377>
- [6] Ferrario T, Karakousis CP. Retroperitoneal sarcomas: grade and survival. *Arch Surg*. 2003;138:248–51. <https://doi.org/10.1001/archsurg.138.3.248>
- [7] Abdelfatah E, Guzzetta AA, Nagarajan N, Wolfgang CL, Pawlik TM, Choti MA, et al. Long-term outcomes in treatment of retroperitoneal sarcomas: a 15 year single-institution evaluation of prognostic features. *J Surg Oncol*. 2016;114:56–64. <https://doi.org/10.1002/jso.24256>
- [8] Dangoor A, Seddon B, Gerrand C, Grimer R, Whelan J, Judson I. UK guidelines for the management of soft tissue sarcomas. *Clin Sarcoma Res*. 2016;6:1–26. <https://doi.org/10.1186/s13569-016-0060-4>
- [9] Maes B, Dedeurwaerdere F, Vanden Bempt I, Van Huysse J, Rottey S, Vermeij J, et al. Comprehensive genomic profiling for precision oncology: the Belgian approach for Local Laboratory Extensive Tumour Testing study (BALLETT). *European Congress of Pathology*. European Congress of Pathology (Dublin, du 10/09/2023 au 13/09/2023).
- [10] Thouvenin J, Van Marcke C, Decoster L, Raicevic G, Punie K, Vandenbulcke M, et al. PRECISION: the Belgian molecular profiling

- program of metastatic cancer for clinical decision and treatment assignment. *ESMO Open*. 2022;7:100524. <https://doi.org/10.1016/j.esmoop.2022.100524>
- [11] Joris S. Efficacy of olaparib in advanced cancers occurring in patients with germline mutations or somatic tumor mutations in homologous recombination genes (1-2018 BSMO [Accessed 2025-08-27]. Available from: <https://classic.clinicaltrials.gov/ct2/show/NCT03967938?term=HRD+olaparib&cntry=BE&draw=2&rank=1>
- [12] Stewart MD, Merino Vega D, Arend RC, Baden JF, Barbash O, Beaubier N, et al. Homologous recombination deficiency: concepts, definitions, and assays. *Oncologist*. 2022;27:167–74. <https://doi.org/10.1093/oncolo/oyab053>
- [13] Roy R, Chun J, Powell SN. BRCA1 and BRCA2: different roles in a common pathway of genome protection. *Nat Rev Cancer*. 2012;12:68–78. <https://doi.org/10.1038/nrc3181>
- [14] Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, et al. Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* (1979). 1990;250:1684–9. <https://doi.org/10.1126/science.2270482>
- [15] Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, et al. Identification of the breast cancer susceptibility gene BRCA2. *Nature*. 1995;378:789–92. <https://doi.org/10.1038/378789a0>
- [16] Sokolova A, Johnstone KJ, McCart Reed AE, Simpson PT, Lakhani SR. Hereditary breast cancer: syndromes, tumour pathology and molecular testing. *Histopathology*. 2023;82:70–82. <https://doi.org/10.1111/his.14808>
- [17] Cantor SB, Guillemette S. Hereditary breast cancer and the BRCA1-associated FANCD1/BACH1/BRIP1. *Fut Oncol*. 2011;7:253–61. <https://doi.org/10.2217/fon.10.191>
- [18] Cantor SB, Bell DW, Ganesan S, Kass EM, Drapkin R, Grossman S, et al. BACH1, a novel helicase-like protein, interacts directly with BRCA1 and contributes to its DNA repair function. *Cell*. 2001;105:149–60. [https://doi.org/10.1016/S0092-8674\(01\)00304-X](https://doi.org/10.1016/S0092-8674(01)00304-X)
- [19] Paluch-Shimon S, Cardoso F, Sessa C, Balmaña J, Cardoso MJ, Gilbert F, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. *Ann Oncol*. 2016;27:v103–10. <https://doi.org/10.1093/annonc/mdw327>
- [20] European Medicines Agency. Lynparza EMA authorisation 2024 [Internet]. [cited 2024 Jan 15]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/lynparza>
- [21] European Medicines Agency. Zejula EMA authorisation 2024 [Internet]. [cited 2024 Jan 15]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/zejula>
- [22] European Medicines Agency. Talzena EMA authorisation 2021 [Internet]. [cited 2024 Jan 15]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/talzena>
- [23] European Medicines Agency. Rubraca EMA authorisation 2023 [Internet]. [cited 2024 Jan 15]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/rubraca>
- [24] Couch FJ, Hart SN, Sharma P, Toland AE, Wang X, Miron P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. *J Clin Oncol*. 2015;33:304. <https://doi.org/10.1200/JCO.2014.57.1414>
- [25] Weber-Lassalle N, Hauke J, Ramser J, Richters L, Groß E, Blümcke B, et al. BRIP1 loss-of-function mutations confer high risk for familial ovarian cancer, but not familial breast cancer. *Breast Cancer Res*. 2018;20:7. <https://doi.org/10.1186/s13058-018-0935-9>
- [26] Ramus SJ, Song H, Dicks E, Tyrer JP, Rosenthal AN, Intermaggio MP, et al. Germline mutations in the BRIP1, BARD1, PALB2, and NBN genes in women with ovarian cancer. *J Natl Cancer Inst*. 2015;107:djv214.
- [27] Suszynska M, Ratajska M, Kozłowski P. BRIP1, RAD51C, and RAD51D mutations are associated with high susceptibility to ovarian cancer: mutation prevalence and precise risk estimates based on a pooled analysis of ~ 30,000 cases. *J Ovarian Res*. 2020;13:1–11. <https://doi.org/10.1186/s13048-020-00654-3>
- [28] Inderjeeth A-J, Topp M, Sanij E, Castro E, Sandhu S. Clinical application of poly (ADP-ribose) polymerase (PARP) inhibitors in prostate cancer. *Cancers (Basel)*. 2022;14:5922. <https://doi.org/10.3390/cancers14235922>
- [29] Kote-Jarai Z, Jugurnauth S, Mulholland S, Leongamornlert DA, Guy M, Edwards S, et al. A recurrent truncating germline mutation in the BRIP1/FANCD1 gene and susceptibility to prostate cancer. *Br J Cancer*. 2009;100:426–30. <https://doi.org/10.1038/sj.bjc.6604847>
- [30] Dudley B, Karloski E, Monzon FA, Singhi AD, Lincoln SE, Bahary N, et al. Germline mutation prevalence in individuals with pancreatic cancer and a history of previous malignancy. *Cancer*. 2018;124:1691–700. <https://doi.org/10.1002/cncr.31242>
- [31] Vietri MT, D'Elia G, Caliendo G, Resse M, Casamassimi A, Passariello L, et al. Hereditary prostate cancer: genes related, target therapy and prevention. *Int J Mol Sci*. 2021;22:3753. <https://doi.org/10.3390/ijms22073753>
- [32] Peake JD, Noguchi E. Fanconi anemia: current insights regarding epidemiology, cancer, and DNA repair. *Hum Genet*. 2022;141:1811–36. <https://doi.org/10.1007/s00439-022-02462-9>
- [33] Gruber JJ, Afghahi A, Timms K, DeWees A, Gross W, Aushev VN, et al. A phase II study of talazoparib monotherapy in patients with wild-type BRCA1 and BRCA2 with a mutation in other homologous recombination genes. *Nat Cancer*. 2022;3:1181–91. <https://doi.org/10.1038/s43018-022-00439-1>
- [34] Tung NM, Robson ME, Ventz S, Santa-Maria CA, Nanda R, Marcom PK, et al. TBCRC 048: phase II study of olaparib for metastatic breast cancer and mutations in homologous recombination-related genes. *J Clin Oncol*. 2020;38:4274–82. <https://doi.org/10.1200/JCO.20.02151>
- [35] Kwapisz D, Verret B, Garcia C, André F. Excellent response to olaparib in metastatic HR-positive, HER2-negative breast cancer with BRIP1 mutation. *Ann Oncol*. 2023;34:315–18. <https://doi.org/10.1016/j.annonc.2023.01.012>
- [36] Abida W, Campbell D, Patnaik A, Shapiro JD, Sautois B, Vogelzang NJ, et al. Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: analysis from the phase II TRITON2 study. *Clin Cancer Res*. 2020;26:2487–96. <https://doi.org/10.1158/1078-0432.CCR-20-0394>
- [37] de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382:2091–102. <https://doi.org/10.1056/NEJMoa1911440>
- [38] Moore K, Colombo N, Scambia G, Kim B-G, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2018;379:2495–505. <https://doi.org/10.1056/NEJMoa1810858>
- [39] Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366:1382–92. <https://doi.org/10.1056/NEJMoa1105535>
- [40] González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2019;381:2391–402. <https://doi.org/10.1056/NEJMoa1910962>
- [41] Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med*. 2016;375:2154–64. <https://doi.org/10.1056/NEJMoa1611310>
- [42] Jiang X, Li X, Li W, Bai H, Zhang Z. PARP inhibitors in ovarian cancer: sensitivity prediction and resistance mechanisms. *J Cell Mol Med*. 2019;23:2303–13. <https://doi.org/10.1111/jcmm.14133>
- [43] Ciccone MA, Adams CL, Bowen C, Thakur T, Ricker C, Culver JO, et al. Inhibition of poly (ADP-ribose) polymerase induces synthetic lethality in BRIP1 deficient ovarian epithelial cells. *Gynecol Oncol*. 2020;159:869–76. <https://doi.org/10.1016/j.ygyno.2020.09.040>
- [44] Pennington KP, Walsh T, Harrell MI, Lee MK, Pennil CC, Rendi MH, et

- al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. *Clin Cancer Res.* 2014;20:764–75. <https://doi.org/10.1158/1078-0432.CCR-13-2287>
- [45] Guffanti F, Mengoli I, Damia G. Current HRD assays in ovarian cancer: differences, pitfalls, limitations, and novel approaches. *Front Oncol.* 2024;14:1405361. <https://doi.org/10.3389/fonc.2024.1405361>
- [46] Singh HM, Bailey P, Huebschmann D, Berger AK, Neoptolemos JP, Jäger D, et al. Poly (ADP-ribose) polymerase inhibition in pancreatic cancer. *Genes Chromosomes Cancer.* 2021;60:373–84. <https://doi.org/10.1002/gcc.22932>
- [47] Buonaiuto R, Neola G, Caltavuturo A, Longobardi A, Mangiacotti FP, Cefaliello A, et al. Efficacy of PARP inhibitors in advanced high-grade serous ovarian cancer according to BRCA domain mutations and mutation type. *Front Oncol.* 2024;14:1412807. <https://doi.org/10.3389/fonc.2024.1412807>
- [48] Marchetti C, Fagotti A, Fruscio R, Cassani C, Incorvaia L, Perri MT, et al. Benefit from maintenance with PARP inhibitor in newly diagnosed ovarian cancer according to BRCA1/2 mutation type and site: a multicenter real-world study. *ESMO Open.* 2025;10:104533. <https://doi.org/10.1016/j.esmoop.2025.104533>
- [49] Milano L, Alenezi WM, Fierheller CT, Serruya C, Revil T, Oros KK, et al. Genetic and molecular analyses of candidate germline BRIP1/FANCI variants implicated in breast and ovarian cancer. *MedRxiv.* 2023:2023–7. <https://doi.org/10.1101/2023.07.03.23290133>
- [50] Long G, Hu K, Zhang X, Zhou L, Li J. Spectrum of BRCA1 interacting helicase 1 aberrations and potential prognostic and therapeutic implication: a pan cancer analysis. *Sci Rep.* 2023;13:4435. <https://doi.org/10.1038/s41598-023-31109-6>
- [51] Kanchi KL, Johnson KJ, Lu C, McLellan MD, Leiserson MDM, Wendl MC, et al. Integrated analysis of germline and somatic variants in ovarian cancer. *Nat Commun.* 2014;5:3156. <https://doi.org/10.1038/ncomms4156>
- [52] Norquist BM, Harrell MI, Brady MF, Walsh T, Lee MK, Gulsuner S, et al. Inherited mutations in women with ovarian carcinoma. *JAMA Oncol.* 2016;2:482–90. <https://doi.org/10.1001/jamaoncol.2015.5495>
- [53] Thompson ER, Rowley SM, Li N, McInerney S, Devereux L, Wong-Brown MW, et al. Panel testing for familial breast cancer: calibrating the tension between research and clinical care. *J Clin Oncol.* 2016;34:1455–9. <https://doi.org/10.1200/JCO.2015.63.7454>
- [54] Joris S, Denys H, Collignon J, Rasschaert M, de Roodenbeke D, Duhoux FP, et al. Efficacy of olaparib in advanced cancers with germline or somatic mutations in BRCA1, BRCA2, CHEK2 and ATM, a Belgian Precision tumor-agnostic phase II study. *ESMO Open.* 2023;8:102041. <https://doi.org/10.1016/j.esmoop.2023.102041>
- [55] Heeke AL, Pishvaian MJ, Lynce F, Xiu J, Brody JR, Chen W-J, et al. Prevalence of homologous recombination-related gene mutations across multiple cancer types. *JCO Precis Oncol.* 2018;2:1–13. <https://doi.org/10.1200/PO.17.00286>
- [56] Bogani G, Monk BJ, Powell MA, Westin SN, Slomovitz B, Moore KN, et al. Adding immunotherapy to first-line treatment of advanced and metastatic endometrial cancer. *Ann Oncol.* 2024;35:414–28. <https://doi.org/10.1016/j.annonc.2024.02.006>
- [57] Mirza M, Ghamande S, Hanks L, Black D, Raascou-Jensen N, Gilbert L, et al. Dostarlimab plus chemotherapy followed by dostarlimab plus niraparib maintenance therapy among patients with primary advanced or recurrent endometrial cancer in the ENGOT-EN6-NSGO/GOG-3031/RUBY trial. *Gynecol Oncol.* 2024;190:56. <https://doi.org/10.1016/j.ygyno.2024.07.016>
- [58] Westin SN, Moore K, Chon HS, Lee J-Y, Thomes Pepin J, Sundborg M, et al. Durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab with or without olaparib as first-line treatment for advanced endometrial cancer: the phase III DUO-E trial. *J Clin Oncol.* 2024;42:283–99. <https://doi.org/10.1200/JCO.23.02132>
- [59] Lobbedez FJ, Leary A, Ray-Coquard IL, Asselain B, Rodrigues MJ, Gladiéff L, et al. LBA42 Olaparib vs placebo as maintenance therapy after platinum-based chemotherapy in advanced/metastatic endometrial cancer patients: the GINECO randomized phase IIb UTOLA trial. *Ann Oncol.* 2023;34:51283–4. <https://doi.org/10.1016/j.annonc.2023.10.036>
- [60] Nakamura K, Aimono E, Tanishima S, Imai M, Nagatsuma AK, Hayashi H, et al. Olaparib monotherapy for BRIP1-mutated high-grade serous endometrial cancer. *JCO Precis Oncol.* 2020;4:PO-19. <https://doi.org/10.1200/PO.19.00368>
- [61] Senguttuvan RN, Wei C, Raoof M, Dellinger TH, Wang EW. Complete pathologic response to PARP inhibitor olaparib in a patient with stage IVB recurrent endometrioid endometrial adenocarcinoma. *J Clin Med.* 2023;12:3839. <https://doi.org/10.3390/jcm12113839>
- [62] Anzellini D, Arcangeli G, Del Bianco S. Complete response of a mutated BRCA2 metastatic clear cell endometrial adenocarcinoma to the poly (ADP ribose) polymerase (PARP) inhibitor olaparib. *Cancer Diagn Progn.* 2022;2:84. <https://doi.org/10.21873/cdp.10080>
- [63] Wang Q, Zhang F, Gao H, Xu Y. Successful treatment of a patient with brain metastases from endometrial cancer using Niraparib: a case report. *Ann Palliat Med.* 2021;10:18127. <https://doi.org/10.21037/apm-21-113>
- [64] Garnett MJ, Edelman EJ, Heidorn SJ, Greenman CD, Dastur A, Lau KW, et al. Systematic identification of genomic markers of drug sensitivity in cancer cells. *Nature.* 2012;483:570–5. <https://doi.org/10.1038/nature11005>
- [65] Brenner JC, Feng FY, Han S, Patel S, Goyal SV, Bou-Maroun LM, et al. PARP-1 inhibition as a targeted strategy to treat Ewing's sarcoma. *Cancer Res.* 2012;72:1608–13. <https://doi.org/10.1158/0008-5472.CAN-11-3648>
- [66] Smith MA, Hampton OA, Reynolds CP, Kang MH, Maris JM, Gorlick R, et al. Initial testing (stage 1) of the PARP inhibitor BMN 673 by the pediatric preclinical testing program: PALB2 mutation predicts exceptional in vivo response to BMN 673. *Pediatr Blood Cancer.* 2015;62:91–8. <https://doi.org/10.1002/pbc.25201>
- [67] Kovac M, Blattmann C, Ribi S, Smida J, Mueller NS, Engert F, et al. Exome sequencing of osteosarcoma reveals mutation signatures reminiscent of BRCA deficiency. *Nat Commun.* 2015;6:8940. <https://doi.org/10.1038/ncomms9940>
- [68] Norris RE, Adamson PC, Nguyen VT, Fox E. Preclinical evaluation of the PARP inhibitor, olaparib, in combination with cytotoxic chemotherapy in pediatric solid tumors. *Pediatr Blood Cancer.* 2014;61:145–50. <https://doi.org/10.1002/pbc.24697>
- [69] Choy E, Butrynski JE, Harmon DC, Morgan JA, George S, Wagner AJ, et al. Phase II study of olaparib in patients with refractory Ewing sarcoma following failure of standard chemotherapy. *BMC Cancer.* 2014;14:1–6. <https://doi.org/10.1186/1471-2407-14-813>
- [70] Schafer ES, Rau RE, Berg SL, Liu X, Minard CG, Bishop AJR, et al. Phase 1/2 trial of talazoparib in combination with temozolomide in children and adolescents with refractory/recurrent solid tumors including Ewing sarcoma: a Children's Oncology Group Phase 1 Consortium study (ADVL1411). *Pediatr Blood Cancer.* 2020;67:e28073. <https://doi.org/10.1002/pbc.28073>
- [71] Engert F, Kovac M, Baumhoer D, Nathrath M, Fulda S. Osteosarcoma cells with genetic signatures of BRCAness are susceptible to the PARP inhibitor talazoparib alone or in combination with chemotherapeutics. *Oncotarget.* 2017;8:48794. <https://doi.org/10.18632/oncotarget.10720>
- [72] Kivlin CM, Watson KL, Al Sanna GA, Belousov R, Ingram DR, Huang K-L, et al. Poly (ADP) ribose polymerase inhibition: a potential treatment of malignant peripheral nerve sheath tumor. *Cancer Biol Ther.* 2016;17:129–38. <https://doi.org/10.1080/15384047.2015.1108486>
- [73] Mangoni M, Sottili M, Salvatore G, Meattini I, Desideri I, Greto D, et al. Enhancement of soft tissue sarcoma cell radiosensitivity by poly (ADP-ribose) polymerase-1 inhibitors. *Radiat Res.* 2018;190:464–72. <https://doi.org/10.1667/RR15035.1>
- [74] Camero S, Ceccarelli S, De Felice F, Marampon F, Mannarino O, Camicia L, et al. PARP inhibitors affect growth, survival and radiation susceptibility of human alveolar and embryonal rhabdomyosarcoma

- cell lines. *J Cancer Res Clin Oncol*. 2019;145:137–52. <https://doi.org/10.1007/s00432-018-2774-6>
- [75] Venneker S, Kruisselbrink AB, Briare-de Bruijn IH, de Jong Y, van Wijnen AJ, Danen EHJ, et al. Inhibition of PARP sensitizes chondrosarcoma cell lines to chemo- and radiotherapy irrespective of the IDH1 or IDH2 mutation status. *Cancers (Basel)*. 2019;11:1918. <https://doi.org/10.3390/cancers11121918>
- [76] Yamasaki H, Miyamoto M, Yamamoto Y, Kondo T, Watanabe T, Ohta T. Synovial sarcoma cell lines showed reduced DNA repair activity and sensitivity to a PARP inhibitor. *Genes Cells*. 2016;21:852–60. <https://doi.org/10.1111/gtc.12387>
- [77] Chudasama P, Mughal SS, Sanders MA, Hübschmann D, Chung I, Deeg KI, et al. Integrative genomic and transcriptomic analysis of leiomyosarcoma. *Nat Commun*. 2018;9:144. <https://doi.org/10.1038/s41467-017-02602-0>
- [78] Rosenbaum E, Jonsson P, Seier K, Chi P, Dickson MA, Gounder MM, et al. DNA damage response pathway alterations and clinical outcome in leiomyosarcoma. *J Clin Oncol*. 2019;37:11048. https://doi.org/10.1200/JCO.2019.37.15_suppl.11048
- [79] Seligson ND, Kautto EA, Passen EN, Stets C, Toland AE, Millis SZ, et al. BRCA1/2 functional loss defines a targetable subset in leiomyosarcoma. *Oncologist*. 2019;24:973–9. <https://doi.org/10.1634/theoncologist.2018-0448>
- [80] Jonsson P, Bandlamudi C, Cheng ML, Srinivasan P, Chavan SS, Friedman ND, et al. Tumour lineage shapes BRCA-mediated phenotypes. *Nature*. 2019;571:576–9. <https://doi.org/10.1038/s41586-019-1382-1>
- [81] Dall G, Vandenberg CJ, Nesic K, Ratnayake G, Zhu W, Vissers JHA, et al. Targeting homologous recombination deficiency in uterine leiomyosarcoma. *J Exp Clin Cancer Res*. 2023;42:1–20. <https://doi.org/10.1186/s13046-023-02687-0>
- [82] Pan M, Ganjoo K, Karam A. Rapid response of a BRCA2/TP53/PTEN-deleted metastatic uterine leiomyosarcoma to olaparib: a case report. *Perm J*. 2021;25:20.251. <https://doi.org/10.7812/TPP/20.251>
- [83] Grignani G, D'Ambrosio L, Pignochino Y, Palmerini E, Zucchetti M, Boccone P, et al. Trabectedin and olaparib in patients with advanced and non-resectable bone and soft-tissue sarcomas (TOMAS): an open-label, phase 1b study from the Italian Sarcoma Group. *Lancet Oncol*. 2018;19:1360–71. [https://doi.org/10.1016/S1470-2045\(18\)30438-8](https://doi.org/10.1016/S1470-2045(18)30438-8)
- [84] D'Ambrosio L, Merlini A, Brunello A, Ferraresi V, Paioli A, Vincenzi B, et al. LBA91 TOMAS2: a randomized phase II study from the Italian Sarcoma Group (ISG) of trabectedin plus olaparib (T+O) or trabectedin (T) in advanced, metastatic, or unresectable soft tissue sarcomas (STS) after failure of standard treatments. *Ann Oncol*. 2023;34:S1332. <https://doi.org/10.1016/j.annonc.2023.10.093>
- [85] Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol*. 2018;15:731–47. <https://doi.org/10.1038/s41571-018-0113-0>
- [86] Symington LS. End resection at double-strand breaks: mechanism and regulation. *Cold Spring Harb Perspect Biol*. 2014;6:a016436. <https://doi.org/10.1101/cshperspect.a016436>
- [87] Brosh RM, Jr, Cantor SB. Molecular and cellular functions of the FANCD1 DNA helicase defective in cancer and in Fanconi anemia. *Front Genet*. 2014;5:372. <https://doi.org/10.3389/fgene.2014.00372>
- [88] Wang W. Emergence of a DNA-damage response network consisting of Fanconi anaemia and BRCA proteins. *Nat Rev Genet*. 2007;8:735–48. <https://doi.org/10.1038/nrg2159>