Role of Somatic BRCA Mutation in Solid Tumors

Subjects: Oncology

Contributor: Gyongyver Szentmartoni, Dorottya Mühl, Renata Csanda, Attila Marcell Szasz, Zoltan Herold, Magdolna Dank

Ten percent of patients with breast cancer, and probably somewhat more in patients with ovarian cancer, have inherited germline DNA mutations in the breast and ovarian cancer genes *BRCA1* and *BRCA2*. In the remaining cases, the disease is caused by acquired somatic genetic and epigenetic alterations. Targeted therapeutic agents, such as poly ADP-ribose polymerases (PARP) inhibitors (PARPi), have emerged in treating cancers associated with germline *BRCA* mutations since 2014. The first PARPi was FDA-approved initially for ovarian cancer patients with germline *BRCA* mutations. Deleterious variants in the *BRCA1/BRCA2* genes and homologous recombination deficiency status have been strong predictors of response to PARPi in a few solid tumors since then.

Keywords: somatic BRCA1/2 ; PARP inhibition ; breast neoplasms ; ovarian neoplasms ; pancreatic neoplasms

1. Introduction

The discovery of the BReast CAncer (*BRCA*) genes in the early 1990s, namely *BRCA1* and *BRCA2*, may be considered as one of the most significant achievements in medicine lately. It was found that both genes play a crucial role in the development of hereditary breast cancer (BC). Moreover, it soon became clear that these genes are involved in the pathogenesis of familial ovarian cancer. *BRCA1* and/or *BRCA2* gene mutations have since been shown to play a role in many more tumor types [1][2][3]. *BRCA1* was discovered in 1994, and it is located on chromosome 17q21 containing 22 exons. *BRCA2* was discovered a year later, in 1995, contains 27 exons, and it is located on chromosome 13q12 [2]. Of the two transcriptomes, the BRCA2 protein is the larger, which is mostly involved in homologous recombination (HR). The BRCA1 protein has more active functions, which are carried out through various functional domains of the molecule that can interact with a range of other proteins. Its involvement in DNA repair, checkpoint control of the cell cycle, protein ubiquitination, and chromatin remodeling were previously described [2][4].

The *BRCA1* and *BRCA2* genes are indirect tumor suppressor stability genes [3]. Both germline (g*BRCA*) and somatic (s*BRCA*) mutations of the *BRCA* genes are known (**Figure 1**). A large number of *BRCA* mutation variants are known to significantly increase the risk of developing certain cancers. Most data are available for breast, ovarian, pancreatic, and prostate tumors, but other tumors are also known to be affected [1]. For example, the involvement of *BRCA* genes was reported for cholangiocellular cancer [5][6], melanoma [7], bladder cancer [8], non-small cell lung cancer [9], and gastrointestinal tumors, including esophageal, gastric, and colorectal cancers [10][11][12][13]. The incidence of *BRCA* mutations within the general population is 1:300–800 [14]. Worldwide, 5% to 10% of breast cancers (BCs), 10% to 15% of ovarian cancers, 4% to 7% of pancreatic cancers, 6% of patients with metastatic prostate cancer, and rarely other cancer-type cases originated from those carrying germline *BRCA1/2* (g*BRCA1/2*) mutations [9]. In Hungary, approximately 4–10% of breast cancers, 11% of ovarian cancers, and 33% of male breast cancers are *BRCA* mutant [15][16][17]. The most common *BRCA* mutation variants of European countries are summarized in the article by Dr. Janavičius [18]. The lifetime risk of developing cancer in g*BRCA1/2* carriers is very high, up to 70–80%, compared to that of the much lower risk in the general population [19]. Both *BRCA* genes are autosomal dominant; therefore, the offspring has a 50% probability of inheriting the mutated variant [3]. g*BRCA* is (usually) detected in blood, whereas somatic *BRCA* (s*BRCA*) mutations could be identified from genomic profiling of tumor tissue or by testing the circulating tumor DNA [19].

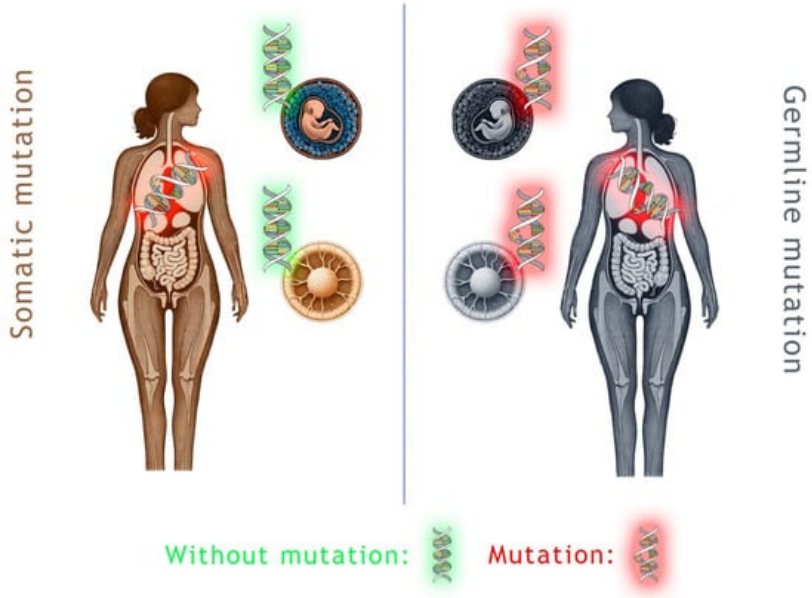

Figure 1. Schematic representation of germline and somatic *BRCA* gene mutations. In the case of germline mutation, all cells of the body contain the mutated gene variant, and it is always passed on from parent to offspring. Somatic mutations occur at a later stage of ontogeny, and the random mutations develop during normal mitotic cell divisions. Note: The schematic human figure, the embryo, and the oocyte were created with the assistance of DALL·E 2; otherwise, the authors did every other aspect of the figure, including the different coloring, arrangement, and labeling. The normal and mutated DNA sequence is courtesy of Wikimedia Commons; the unmodified original was created by NASA/David Herring and distributed under the CC0 1.0 license.

BRCA1/2 mutant tumors respond well to the treatment with poly (ADP-ribose) polymerase (PARP) inhibitor (PARPi) treatments. PARPis are novel drugs acting on the base excision repair pathway. In HR-deficient cells, such as the ones with the *BRCA1/2* mutations, due to the blockage, the DNA double-strand breaks cannot be repaired, which ultimately results in apoptosis [20][21]. The use of PARPi in *BRCA*-related malignancy has largely been limited to g*BRCA* mutations by most guidelines. Targeted treatment of somatic mutations is suggested only in ovarian [22] and prostate [23] cancers, while the precise estimate of the efficacy of PARPi in somatic *BRCA* mutation is still lacking. In other cancer types, the current clinical data is scarce [5], *BRCA* studies are still ongoing [13], or somatic *BRCA* mutations are under-recognized and represent a missed opportunity for PARPi-targeted therapy. It has also to be mentioned that many of the existing clinical trials do not specifically include somatic *BRCA* patients, leading to underrepresentation in the data.

2. Clinical Differences of s*BRCA* and g*BRCA*

Cancers caused by pathogenic g*BRCA* variants are hereditary and can be passed down over generations. These mutations are constant, and there are certain patterns, like positive family history and well-known cancer syndromes. The pathogenic variant is discovered by testing peripheral blood samples for specific, known mutations in the *BRCA* genes. Usually, screening methods are developed for early diagnosis, and the clinical management of family members is highly recommended. In these cases, extensive genetic counseling is necessary, not just the oncological care of the given patient. In contrast, somatic mutations are detected in the tumor tissue or by the analysis of circulating tumor DNA. Cancers caused by s*BRCA* mutation(s) are sporadic. These are not found in every cell in the body, and they cannot be inherited but rather caused by some external noxa (virus, chemical exposure, etc.) or aging.

Germline testing should be considered for patients with ovarian, breast, prostate, and pancreatic cancer if certain risk factors are present, e.g., positive family history, bilateral disease, multiple primary tumors, and/or young age at the onset of tumor diagnosis. In case of positive test results, the testing of the family members should be considered. Nowadays, genetic counseling for affected individuals is recommended by guidelines, involving a genetic expert [24][25].

The use of multigene profiling of the tumor tissue in today's oncology practice is increasingly recommended and enables targeted therapy, mainly in the metastatic setting. However, there are certain differences between germline and somatic testing and findings. The interpretation of the results of multigene tests and the role and importance of variants are not entirely explored [19]. The prognostic and predictive roles of g*BRCA* mutations have been largely demonstrated and shared in the last two decades. It is not entirely clear whether harboring s*BRCA* mutation(s) detected by the analysis of the tumor tissue brings the same prognostic and predictive advantages and whether there is a possible targeted treatment.

Molecular profiling is recommended as a standard care in advanced/metastatic tumors. In addition to current practice and frequency of biopsies in metastatic cancer, s*BRCA* mutations are reported in 2% to 5% and 3% of ovarian and BCs, respectively [26].

PARPis can inhibit the activity of PARP1, PARP2, and PARP3, a group of proteins closely involved in the repair of single-strand DNA breaks. Lately, it has been suggested that PARPis have effects on macrophages and inflammatory makers [27][28]. Several molecules have been developed for inhibition of the PARP function, but to date, five PARP1/2 inhibitors have received marketing authorization for cancer treatment worldwide. The initial clinical trial leading to the U.S. Food and Drug Administration's (FDA) approval for Olaparib in advanced ovarian cancer only examined germline *BRCA* mutations [29].

3. Ovarian Cancer

Carriers of a monoallelic g*BRCA1/2* mutation have a greater risk of cancerous disease in their lifetime [30]. The mean cumulative risk of having ovarian cancer with *BRCA1* pathogenic mutation is 40% [95% confidence interval (CI): 35–46%], and 18% (95% CI: 13–23%) for patients carrying *BRCA2* mutations. The EMBRACE prospective study has shown 59% (95% CI: 43–76%) and 16.5% (95% CI: 7.5–34%) for the same risks, respectively [2][30][31]. It has also been suggested that there are some s/g*BRCA* mutant breast cancer types that share several phenotypic and genomic traits with s/g*BRCA* mutant ovarian cancers [32].

The first PARPi, Olaparib, was FDA-approved in December 2014, initially for metastatic ovarian cancer patients with germline *BRCA* mutations, after multiple cycles of chemotherapy [29][33]. Olaparib is a targeted therapy for DNA damage response and DNA repair pathways. Later, Olaparib was also approved for the treatment of ovarian cancers as a first-line maintenance therapy and in combination with bevacizumab [34][35]. In general, ovarian cancer is often diagnosed in an advanced stage, and despite good sensitivity to taxane– and platinum-based chemotherapy combinations, most patients will relapse in a short time. With the introduction of PARPi, the efficacy of complex treatment approaches has risen [36][37][38]. The updated results of the SOLO1 trial, after 7 years of follow-up, demonstrated a very high percent, nearly 70% survival with Olaparib, and half of the patients did not receive further therapy [37].

High-grade serous ovarian cancer patients (HGSOC) with *BRCA1/2* alterations are candidates to receive PARPis in second-line therapy since the FDA approval after responding to the first-line platinum-based chemotherapy [39]. Most of the *BRCA* alterations are germline pathogenic mutations, but in 30% of the cases, the alterations can only be seen at the somatic level; therefore, HGSOC patients can benefit from tumor tissue DNA testing for s*BRCA* mutations.

The ORZORA trial further supported the use of maintenance Olaparib in all patients, including s*BRCA*-mutated tumor carriers. This study evaluated the efficacy and safety of maintenance Olaparib in patients with platinum-sensitive relapsed ovarian cancer after ≥ two lines of treatment. Maintenance Olaparib had similar clinical activity in germline and somatic mutations. The activity was also observed in patients with a non-*BRCA* homologous recombination repair (HRR) gene mutation [40]. The OLATRA study aims to scan the efficacy of maintenance Olaparib in relapsed ovarian cancer patients with s/g*BRCA* deleterious mutations after first-line platinum-based chemotherapy, at least a 6-month treatment-free interval since the last platinum and receiving trabectinib and pegylated liposomal doxorubicin [41].

Recently, more options have become available with the approval of the agents niraparib and rucaparib, complicating the therapeutic decision for the best-personalized treatment approach. The Athena-MONO trial demonstrated that rucaparib is an effective treatment, not only in the recurrence setting but in first-line maintenance as well [42][43]. The benefit was demonstrated independently from *BRCA* and homologous recombination deficiency (HRD) status or surgical outcome. Patients with advanced-stage high-grade ovarian cancer undergoing surgical cytoreduction and responding to first-line platinum-doublet chemotherapy were enrolled in this maintenance study. Rucaparib significantly improved progression-free survival (PFS) versus placebo, regardless of *BRCA* or HRD status.

The ENGOT-OV16/NOVA study was a randomized, double-blind, placebo-controlled, phase III trial that enrolled 553 patients with platinum-sensitive, recurrent ovarian cancer for evaluating niraparib. Patients were enrolled into independent germline *BRCA*-mutated and non-germline *BRCA*-mutated cohorts and then randomly assigned in a 2:1 ratio to receive niraparib at 300 mg once daily or placebo after standard platinum therapy. Primary results from the study, released in 2016, indicated a statistically significant PFS benefit for the niraparib maintenance arm, compared to that of placebo in the germline *BRCA*-mutated, non-germline *BRCA*-mutated, homologous repair-deficient and in the homologous repair-proficient populations. Long-term analyses of the second PFS beyond the first disease progression also indicated the benefit of the maintenance niraparib treatment. However, the OS analyses were limited due to missing data [44][45].

4. Breast Cancer

Women with germline pathogenic mutations in *BRCA1* or *BRCA2* have a significantly higher lifetime risk of developing cancers in several organs, especially in the breast and ovaries. Cumulative risk can be up to 57% (95% CI: 47–66%) and 49% (95% CI: 40–57%) for *BRCA1* and *BRCA2* mutations, respectively. Breast cancer cumulative risk is 60% and 55%, respectively. Based on these data, novel therapeutic approaches are eagerly awaited for this subgroup of patients. Additionally, it has to be mentioned that these genetic alterations are usually associated with other cancer types as well. Therefore, *BRCA*-targeted drugs could be used as general tumor-agnostic therapy as well [30][31].

BC is the most common cancer type in women, and below 1% of BC accounts for men. The risk of developing BC is higher if a positive family history is found. BC is a biologically and clinically heterogeneous disease, and patients with similar clinical stages have markedly different outcomes. Around 10% of patients have g*BRCA1/2* mutations, often leading to loss of function in genes implicated in DNA repair and cell cycle checkpoint activation. These patients are diagnosed with BC at a younger age, often with a positive family history of breast and/or ovarian cancer. Besides that, 90% of BC is caused by somatic mutations acquired lifelong; in *BRCA1/2* PV carriers, there is an increased lifetime risk of developing breast cancer. By the age of 80, those patients have up to 70% risk compared to 10% of the general population [46][47]. Extensive analyses have revealed that somatic *BRCA1* mutations are uncommon in unselected patients, but they can be important targetable mutations in metastatic disease [48]. Individuals with a g*BRCA1* mutation are more likely to develop triple-negative BC (TNBC) at a younger age. *BRCA1* mutation carriers develop predominantly but not exclusively estrogen receptor (ER) negative tumors, and there is an observation that patients with g*BRCA2* mutations are likely to develop ER-positive BC. g*BRCA* mutations are found in up to 23% of patients with TNBC and 5% of patients with ER-positive disease [47][49]. These patients are often diagnosed with locally advanced or metastatic disease, and despite aggressive chemotherapeutic regimens, they will relapse in a short time [50]. The lack of hormonal and human epidermal growth factor receptor 2 (HER2 receptor) in TNBC limited the possibility of an effective anticancer treatment.

TNBCs often harbor somatic mutations or *BRCA* genes that may be silenced. Somatic *BRCA1/2* mutations are detectable in circulating cell-free DNA (cfDNA) in approximately 13.5% of patients with metastatic BC. In pre-clinical models, pathogenic somatic *BRCA1/2* mutations have been shown to respond to PARP inhibition [51]. The COMETA-breast trial was a proof-of-concept study enrolling heavily pretreated TNBC patients with centrally confirmed somatic *BRCA1/2* and no g*BRCA1/2* mutation. Olaparib did not show clinically or statistically significant antitumor activity [52]. In contrast, in the LUCY real-world study, the clinical effectiveness of Olaparib was confirmed for metastatic, HER2-negative BC, regardless of the ER expression level [53].

Olaparib Expanded, a phase II open-label, nonrandomized, investigator-initiated study, assessed Olaparib response in patients with metastatic BC with s*BRCA1/2* mutations or another g/s mutation in homologous recombination-related genes, which are non-*BRCA1/2*. Patients could either have had an s/g pathogenic or likely pathogenic variant of *BRCA1/2* or also germline or somatic alterations in one of DNA repair genes, such as *ATM*, *ATR*, *BAP1*, *BARD1*, *BLM*, *BRIP1*, *CHEK1*, *CHEK2*, *CDK12*, *FANCA*, *FANCC*, *FANCD2*, *FANCF*, *MRE11A*, *NBN*, *PALB2*, *RAD50*, *RAD51C*, *RAD51D*, or *WRN*. If s*BRCA1/2* was present, g*BRCA1/2* had to be excluded via germline testing. The objective response rate [ORR; patients have either partial (PR) or complete response (CR) to the treatment] was the primary endpoint, and there were further secondary endpoints such as clinical benefit rate and PFS. Confirmed responses were seen only with germline *PALB2* and s*BRCA1/2* mutations. With *ATM* or *CHEK2* mutations alone, no responses were observed. With Olaparib, the median ORR and PFS for germline *PALB2* and s*BRCA1/2* PV carriers were 82% and 13.3 months, and 50% and 6.2 months, respectively.

Similar results were reported in a single-institutional, retrospective study. Breast cancer patients with confirmed s*BRCA1/2* or g/s non-*BRCA* HRR mutations were included. Seven patients were treated with Olaparib, off-protocol, off-label for metastatic breast cancer. All s*BRCA1/2* mutation carriers responded to Olaparib, while other HRR-associated mutation carriers did not respond to PARP inhibition. Median PFS was 6.5 months with s*BRCA1/2* mutations, compared to the 3 months of those patients with non-*BRCA* HRR mutations [54]. However, the number of reported cases was low. The results have suggested that patients with tumors harboring s*BRCA1/2* mutations might benefit from the treatment with PARPi, similar to what we have seen in ovarian cancer. The identification of patients beyond g*BRCA1/2* carriers whose cancers may be sensitive to PARP inhibition is clinically meaningful.

5. Pancreatic Cancer

The incidence and mortality rates of pancreatic cancer patients are increasing nowadays. The amount of newly diagnosed cases has doubled since 1990 and is expected to become the second leading cause of cancer-related mortality in the

next few years. About 5–9% of pancreatic cancer patients harbor germline PV of *BRCA* genes. Known g*BRCA* carrier individuals have a higher lifetime risk of developing pancreatic cancer compared to the normal population (with *BRCA1*: 2.2–3.0%; with *BRCA2*: 3.0–7.0%) [55][56][57]. In general, pancreatic cancer is diagnosed in an advanced stage, and despite personalized and modern treatments, it is associated with poor outcomes.

Olaparib is currently the only FDA-approved PARPi to treat pancreatic ductal carcinoma. However, only germline *BRCA*-mutated patients participated in the clinical trials. The POLO trial for pancreatic cancer, which studied Olaparib as maintenance therapy, did not include any somatic *BRCA* patients. This was the first study to show a biomarker-based treatment of pancreatic ductal carcinoma in patients with germline *BRCA* mutation. The study enrolled metastatic pancreatic cancer patients who had not progressed during first-line platinum-based chemotherapy.

Another PARPi, rucaparib was also evaluated in a maintenance setting after platinum treatment in a phase II study. Rucaparib was proven to be a safe and effective therapy for platinum-sensitive, advanced pancreatic cancer with a pathogenic variant in *BRCA1*, *BRCA2*, or *PALB2*. In this study, somatic *BRCA* patients were enrolled too. The findings of efficacy in patients with germline *PALB2* and s*BRCA2* mutations expand the population likely to benefit from PARP inhibition beyond g*BRCA1/2* variant carriers. The median PFS was 13.1 months, the median OS 23.5 months, and the ORR was 41.7% [58]. The RUCAPANC study was terminated early due to a lack of convincing results. Both germline and somatic *BRCA* patients were enrolled in this study, and the difference, compared to the studies above, was that platinum sensitivity was not included in the eligibility criteria [58].

6. Prostate Cancer

Prostate cancer is the second most common cancer in men. Over the last decades, the development of targeted treatments has demonstrated improvement in OS and quality of life, too. Despite novel treatments, the disease remains fatal, and additional treatment approaches are needed. Systemic treatment recommendations, depending on stage, include androgen receptor (AR) signaling targeted therapy and chemotherapy as well [59]. However, germinal and/or somatic alterations of DNA damage response pathway genes are found in a substantial number of patients with advanced prostate cancers.

In the PROfound phase III trial [60], Olaparib was compared to hormonal therapy after progressing on at least one treatment with enzalutamide or abiraterone, with or without previous taxane chemotherapy, in patients with metastatic castration-resistant prostate cancer (mCRPC). Patients with an alteration in *BRCA1/2* or *ATM* were assigned to cohort A, and patients with other alterations were allocated to cohort B. PFS in the cohort A was longer in the Olaparib group (7.4 months vs. 3.6 months; HR: 0.34; 95% CI: 0.25–0.47; $p < 0.001$) [60]. Post hoc analysis of the subgroup of patients with mCRPC with *BRCA* alterations in the PROfound study has shown a PFS benefit with Olaparib in all zygosity subgroups. Patients with *BRCA2* homozygous deletions experienced prolonged responses to Olaparib (median radiological PFS: 16.6 months). It has to be noted that some evaluations of the study are limited by small patient numbers.

The FDA granted accelerated approval also to rucaparib in May 2020 for the treatment of adult patients with deleterious *BRCA* mutation (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane. This approval was based on data from the multicenter, open-label, single-arm TRITON2 trial [61]. Almost half of the TRITON2 patients with *BRCA*-mutated mCRPC had a complete or partial tumor size reduction with rucaparib. Clinical benefits were also observed with other DNA damage repair gene alterations. Later, the TRITON-3 randomized clinical trial of rucaparib was conducted in the pre-docetaxel setting. TRITON-3 was the second phase III trial to evaluate a PARPi in mCRPC after the PROfound trial of Olaparib and the first to compare a PARPi with docetaxel. The latter is the preferred treatment option for patients with metastatic disease who have progressed after an androgen receptor pathway inhibitor (ARPI). Rucaparib significantly improved radiographic PFS versus docetaxel or a second-generation ARPI in patients with *BRCA1/2*-mutated mCRPC.

There are three known currently recruiting trials in prostatic cancer with *BRCA* alterations. In two of them, the administered drug is a PARPi. In detail: (1) Pamiparib is given in castration-resistant mCRPC patients with s/g*BRCA* mutation or HR-deficiency [62]. (2) In the NePtune trial, Olaparib is given in a neoadjuvant setting with LHRH-agonist for prostatic cancer patients with *BRCA* alterations and high-risk or unfavorable intermediate-risk tumors [63]. (3) There is a study about CX-5461 for patients with s*BRCA2* mutations and/or *PALB2* mutations in the pancreas/prostate/breast or ovary malignancy with the corresponding g*BRCA2*/*PALB2* mutation [64].

References

1. Mersch, J.; Jackson, M.A.; Park, M.; Nebgen, D.; Peterson, S.K.; Singletary, C.; Arun, B.K.; Litton, J.K. Cancers associated with BRCA1 and BRCA2 mutations other than breast and ovarian. Cancer 2015, 121, 269–275.
2. Stoppa-Lyonnet, D. The biological effects and clinical implications of BRCA mutations: Where do we go from here? Eur. J. Hum. Genet. 2016, 24 (Suppl. S1), S3–S9.
3. Olah, E. A BRCA1 és BRCA2 gének. Magy. Tud. 2005, 8, 989–1000.
4. Venkitaraman, A.R. Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell 2002, 108, 171–182.
5. Li, X.Y.; Chen, J.Q.; Aisa, A.; Ding, Y.W.; Zhang, D.; Yuan, Y. Targeting BRCA-mutant biliary tract cancer: Current evidence and future perspectives. J. Dig. Dis. 2023, 24, 85–97.
6. Rizvi, S.; Khan, S.A.; Hallemeier, C.L.; Kelley, R.K.; Gores, G.J. Cholangiocarcinoma—Evolving concepts and therapeutic strategies. Nat. Rev. Clin. Oncol. 2018, 15, 95–111.
7. Gumaste, P.V.; Penn, L.A.; Cymerman, R.M.; Kirchhoff, T.; Polsky, D.; McLellan, B. Skin cancer risk in BRCA1/2 mutation carriers. Br. J. Dermatol. 2015, 172, 1498–1506.
8. Sweis, R.F.; Heiss, B.; Segal, J.; Ritterhouse, L.; Kadri, S.; Churpek, J.E.; Allen, K.; Conway, D.; Marinier, C.; Smith, N.D.; et al. Clinical Activity of Olaparib in Urothelial Bladder Cancer with DNA Damage Response Gene Mutations. JCO Precis. Oncol. 2018, 2, 1–7.
9. Remon, J.; Besse, B.; Leary, A.; Bieche, I.; Job, B.; Lacroix, L.; Auguste, A.; Mauduit, M.; Audigier-Valette, C.; Raimbourg, J.; et al. Somatic and Germline BRCA 1 and 2 Mutations in Advanced NSCLC from the SAFIR02-Lung Trial. JTO Clin. Res. Rep. 2020, 1, 100068.
10. Ueki, A.; Yoshida, R.; Kosaka, T.; Matsubayashi, H. Clinical risk management of breast, ovarian, pancreatic, and prostatic cancers for BRCA1/2 variant carriers in Japan. J. Hum. Genet. 2023, 68, 517–526.
11. Sorscher, S. Helicobacter pylori and gastric cancer risk in BRCA 1/2 pathogenic germline variant carriers. J. Hum. Genet. 2023, 68, 725.
12. Buckley, K.H.; Niccum, B.A.; Maxwell, K.N.; Katona, B.W. Gastric Cancer Risk and Pathogenesis in BRCA1 and BRCA2 Carriers. Cancers 2022, 14, 5953.
13. Maccaroni, E.; Giampieri, R.; Lenci, E.; Scortichini, L.; Bianchi, F.; Belvederesi, L.; Brugiati, C.; Pagliaretta, S.; Ambrosini, E.; Berardi, R. BRCA mutations and gastrointestinal cancers: When to expect the unexpected? World J. Clin. Oncol. 2021, 12, 565–580.
14. Casaubon, J.T.; Kashyap, S.; Regan, J.P. BRCA1 and BRCA2 Mutations. In StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2024.
15. Csokay, B.; Udvarhelyi, N.; Sulyok, Z.; Besznyak, I.; Ramus, S.; Ponder, B.; Olah, E. High frequency of germ-line BRCA2 mutations among Hungarian male breast cancer patients without family history. Cancer Res. 1999, 59, 995–998.
16. Van Der Looij, M.; Szabo, C.; Besznyak, I.; Liszka, G.; Csokay, B.; Pulay, T.; Toth, J.; Devilee, P.; King, M.C.; Olah, E. Prevalence of founder BRCA1 and BRCA2 mutations among breast and ovarian cancer patients in Hungary. Int. J. Cancer 2000, 86, 737–740.
17. Remenyi Kissne, D.; Gede, N.; Szakacs, Z.; Kiss, I. Breast cancer screening knowledge among Hungarian women: A cross-sectional study. BMC Womens' Health 2021, 21, 69.
18. Janavicius, R. Founder BRCA1/2 mutations in the Europe: Implications for hereditary breast-ovarian cancer prevention and control. EPMA J. 2010, 1, 397–412.
19. Roy, R.; Chun, J.; Powell, S.N. BRCA1 and BRCA2: Different roles in a common pathway of genome protection. Nat. Rev. Cancer 2011, 12, 68–78.
20. Peixoto, A.; Pinto, P.; Guerra, J.; Pinheiro, M.; Santos, C.; Pinto, C.; Santos, R.; Escudeiro, C.; Bartosch, C.; Canario, R.; et al. Tumor Testing for Somatic and Germline BRCA1/BRCA2 Variants in Ovarian Cancer Patients in the Context of Strong Founder Effects. Front. Oncol. 2020, 10, 1318.
21. Shi, Y.; Zhou, F.; Jiang, F.; Lu, H.; Wang, J.; Cheng, C. PARP inhibitor reduces proliferation and increases apoptosis in breast cancer cells. Chin. J. Cancer Res. 2014, 26, 142–147.
22. Konstantinopoulos, P.A.; Lacchetti, C.; Annunziata, C.M. Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline Summary. JCO Oncol. Pract. 2020, 16, e835–e838.
23. Tuffaha, H.; Edmunds, K.; Fairbairn, D.; Roberts, M.J.; Chambers, S.; Smith, D.P.; Horvath, L.; Arora, S.; Scuffham, P. Guidelines for genetic testing in prostate cancer: A scoping review. Prostate Cancer Prostatic Dis. 2023, in press.

24. Daly, M.B.; Pal, T.; Maxwell, K.N.; Churpek, J.; Kohlmann, W.; AlHilli, Z.; Arun, B.; Buys, S.S.; Cheng, H.; Domchek, S.M.; et al. NCCN Guidelines(R) Insights: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2024. J. Natl. Compr. Cancer Netw. 2023, 21, 1000–1010.

25. Gradishar, W.J.; Moran, M.S.; Abraham, J.; Abramson, V.; Aft, R.; Agnese, D.; Allison, K.H.; Anderson, B.; Burstein, H.J.; Chew, H.; et al. NCCN Guidelines® Insights: Breast Cancer, Version 4.2023. J. Natl. Compr. Cancer Netw. 2023, 21, 594–608.

26. Toss, A.; Piombino, C.; Tenedini, E.; Bologna, A.; Gasparini, E.; Tarantino, V.; Filieri, M.E.; Cottafavi, L.; Giovanardi, F.; Madrigali, S.; et al. The Prognostic and Predictive Role of Somatic BRCA Mutations in Ovarian Cancer: Results from a Multicenter Cohort Study. Diagnostics 2021, 11, 565.

27. Tricarico, D.; Convertino, A.S.; Mehmeti, I.; Ranieri, G.; Leonetti, F.; Laface, C.; Zizzo, N. Inflammatory Related Reactions in Humans and in Canine Breast Cancers, A Spontaneous Animal Model of Disease. Front. Pharmacol. 2022, 13, 752098.

28. Wang, L.; Wang, D.; Sonzogni, O.; Ke, S.; Wang, Q.; Thavamani, A.; Batalini, F.; Stopka, S.A.; Regan, M.S.; Vandal, S.; et al. PARP-inhibition reprograms macrophages toward an anti-tumor phenotype. Cell Rep. 2022, 41, 111462.

29. Robson, M.; Im, S.A.; Senkus, E.; Xu, B.; Domchek, S.M.; Masuda, N.; Delaloge, S.; Li, W.; Tung, N.; Armstrong, A.; et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N. Engl. J. Med. 2017, 377, 523–533.

30. Chen, S.; Parmigiani, G. Meta-analysis of BRCA1 and BRCA2 penetrance. J. Clin. Oncol. 2007, 25, 1329–1333.

31. Mavaddat, N.; Peock, S.; Frost, D.; Ellis, S.; Platte, R.; Fineberg, E.; Evans, D.G.; Izatt, L.; Eeles, R.A.; Adlard, J.; et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: Results from prospective analysis of EMBRACE. J. Natl. Cancer Inst. 2013, 105, 812–822.

32. Burgess, M.; Puhalla, S. BRCA 1/2-Mutation Related and Sporadic Breast and Ovarian Cancers: More Alike than Different. Front. Oncol. 2014, 4, 19.

33. Kaufman, B.; Shapira-Frommer, R.; Schmutzler, R.K.; Audeh, M.W.; Friedlander, M.; Balmana, J.; Mitchell, G.; Fried, G.; Stemmer, S.M.; Hubert, A.; et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J. Clin. Oncol. 2015, 33, 244–250.

34. Moore, K.; Colombo, N.; Scambia, G.; Kim, B.G.; Oaknin, A.; Friedlander, M.; Lisyanskaya, A.; Floquet, A.; Leary, A.; Sonke, G.S.; et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N. Engl. J. Med. 2018, 379, 2495–2505.

35. Ray-Coquard, I.; Pautier, P.; Pignata, S.; Perol, D.; Gonzalez-Martin, A.; Berger, R.; Fujiwara, K.; Vergote, I.; Colombo, N.; Maenpaa, J.; et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N. Engl. J. Med. 2019, 381, 2416–2428.

36. Banerjee, S.; Moore, K.N.; Colombo, N.; Scambia, G.; Kim, B.G.; Oaknin, A.; Friedlander, M.; Lisyanskaya, A.; Floquet, A.; Leary, A.; et al. Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2021, 22, 1721–1731.

37. DiSilvestro, P.; Banerjee, S.; Colombo, N.; Scambia, G.; Kim, B.G.; Oaknin, A.; Friedlander, M.; Lisyanskaya, A.; Floquet, A.; Leary, A.; et al. Overall Survival with Maintenance Olaparib at a 7-Year Follow-Up in Patients with Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial. J. Clin. Oncol. 2023, 41, 609–617.

38. Ray-Coquard, I.; Leary, A.; Pignata, S.; Cropet, C.; Gonzalez-Martin, A.; Marth, C.; Nagao, S.; Vergote, I.; Colombo, N.; Maenpaa, J.; et al. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: Final overall survival results from the PAOLA-1/ENGOT-ov25 trial. Ann. Oncol. 2023, 34, 681–692.

39. Ragupathi, A.; Singh, M.; Perez, A.M.; Zhang, D. Targeting the BRCA1/2 deficient cancer with PARP inhibitors: Clinical outcomes and mechanistic insights. Front. Cell Dev. Biol. 2023, 11, 1133472.

40. Pignata, S.; Oza, A.; Hall, G.; Pardo, B.; Madry, R.; Cibula, D.; Klat, J.; Montes, A.; Glasspool, R.; Colombo, N.; et al. Maintenance olaparib in patients with platinum-sensitive relapsed ovarian cancer: Outcomes by somatic and germline BRCA and other homologous recombination repair gene mutation status in the ORZORA trial. Gynecol. Oncol. 2023, 172, 121–129.

41. Redondo, A.; Romero, I. Olaparib after Response to Trabectedin-Pegylated Liposomal Doxorubicin in Recurrent Ovarian Carcinoma. Available online: https://clinicaltrials.gov/study/NCT03470805 (accessed on 15 February 2024).

42. Coleman, R.L.; Oza, A.M.; Lorusso, D.; Aghajanian, C.; Oaknin, A.; Dean, A.; Colombo, N.; Weberpals, J.I.; Clamp, A.; Scambia, G.; et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum

therapy (ARIEL3): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017, 390, 1949–1961.

43. Monk, B.J.; Parkinson, C.; Lim, M.C.; O'Malley, D.M.; Oaknin, A.; Wilson, M.K.; Coleman, R.L.; Lorusso, D.; Bessette, P.; Ghamande, S.; et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients with Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). J. Clin. Oncol. 2022, 40, 3952–3964.
44. Mirza, M.R.; Monk, B.J.; Herrstedt, J.; Oza, A.M.; Mahner, S.; Redondo, A.; Fabbro, M.; Ledermann, J.A.; Lorusso, D.; Vergote, I.; et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N. Engl. J. Med. 2016, 375, 2154–2164.
45. Del Campo, J.M.; Matulonis, U.A.; Malander, S.; Provencher, D.; Mahner, S.; Follana, P.; Waters, J.; Berek, J.S.; Woie, K.; Oza, A.M.; et al. Niraparib Maintenance Therapy in Patients with Recurrent Ovarian Cancer after a Partial Response to the Last Platinum-Based Chemotherapy in the ENGOT-OV16/NOVA Trial. J. Clin. Oncol. 2019, 37, 2968–2973.
46. Rizzolo, P.; Silvestri, V.; Falchetti, M.; Ottini, L. Inherited and acquired alterations in development of breast cancer. Appl. Clin. Genet. 2011, 4, 145–158.
47. Cortesi, L.; Rugo, H.S.; Jackisch, C. An Overview of PARP Inhibitors for the Treatment of Breast Cancer. Target Oncol. 2021, 16, 255–282.
48. Couch, F.J.; Nathanson, K.L.; Offit, K. Two decades after BRCA: Setting paradigms in personalized cancer care and prevention. Science 2014, 343, 1466–1470.
49. Toss, A.; Molinaro, E.; Venturelli, M.; Domati, F.; Marcheselli, L.; Piana, S.; Barbieri, E.; Grandi, G.; Piombino, C.; Marchi, I.; et al. BRCA Detection Rate in an Italian Cohort of Luminal Early-Onset and Triple-Negative Breast Cancer Patients without Family History: When Biology Overcomes Genealogy. Cancers 2020, 12, 1252.
50. Baretta, Z.; Mocellin, S.; Goldin, E.; Olopade, O.I.; Huo, D. Effect of BRCA germline mutations on breast cancer prognosis: A systematic review and meta-analysis. Medicine 2016, 95, e4975.
51. Vidula, N.; Dubash, T.; Lawrence, M.S.; Simoneau, A.; Niemierko, A.; Blouch, E.; Nagy, B.; Roh, W.; Chirn, B.; Reeves, B.A.; et al. Identification of Somatically Acquired BRCA1/2 Mutations by cfDNA Analysis in Patients with Metastatic Breast Cancer. Clin. Cancer Res. 2020, 26, 4852–4862.
52. De La Haba, J.; Anton, A.; Quiroga, V.; Guerrero, A.; Andrés, R.; Mele, M.; Gonzalez-Santiago, S.; Perez-Fidalgo, J.A.; Ramon y Cajal, T.; Escudero, M.J.; et al. Olaparib (O) in advanced triple negative breast cancer (aTNBC) patients (pts) with BRCA1/2 promoter methylation: GEICAM/2015-06 study (COMETA-Breast). J. Clin. Oncol. 2023, 41, 1093.
53. Balmana, J.; Fasching, P.A.; Couch, F.J.; Delaloge, S.; Labidi-Galy, I.; O'Shaughnessy, J.; Park, Y.H.; Eisen, A.F.; You, B.; Bourgeois, H.; et al. Clinical effectiveness and safety of olaparib in BRCA-mutated, HER2-negative metastatic breast cancer in a real-world setting: Final analysis of LUCY. Breast Cancer Res. Treat. 2023. Online Ahead of Print.
54. Walsh, E.M.; Mangini, N.; Fetting, J.; Armstrong, D.; Chan, I.S.; Connolly, R.M.; Fiallos, K.; Lehman, J.; Nunes, R.; Petry, D.; et al. Olaparib Use in Patients with Metastatic Breast Cancer Harboring Somatic BRCA1/2 Mutations or Mutations in Non-BRCA1/2, DNA Damage Repair Genes. Clin. Breast Cancer 2022, 22, 319–325.
55. Rosen, M.N.; Goodwin, R.A.; Vickers, M.M. BRCA mutated pancreatic cancer: A change is coming. World J. Gastroenterol. 2021, 27, 1943–1958.
56. Wong, W.; Raufi, A.G.; Safyan, R.A.; Bates, S.E.; Manji, G.A. BRCA Mutations in Pancreas Cancer: Spectrum, Current Management, Challenges and Future Prospects. Cancer Manag. Res. 2020, 12, 2731–2742.
57. Klatte, D.C.F.; Wallace, M.B.; Lohr, M.; Bruno, M.J.; van Leerdam, M.E. Hereditary pancreatic cancer. Best Pract. Res. Clin. Gastroenterol. 2022, 58–59, 101783.
58. Reiss, K.A.; Mick, R.; O'Hara, M.H.; Teitelbaum, U.; Karasic, T.B.; Schneider, C.; Cowden, S.; Southwell, T.; Romeo, J.; Izgur, N.; et al. Phase II Study of Maintenance Rucaparib in Patients with Platinum-Sensitive Advanced Pancreatic Cancer and a Pathogenic Germline or Somatic Variant in BRCA1, BRCA2, or PALB2. J. Clin. Oncol. 2021, 39, 2497–2505.
59. Fizazi, K.; Gillessen, S.; ESMO Guidelines Committee. Updated treatment recommendations for prostate cancer from the ESMO Clinical Practice Guideline considering treatment intensification and use of novel systemic agents. Ann. Oncol. 2023, 34, 557–563.
60. de Bono, J.; Mateo, J.; Fizazi, K.; Saad, F.; Shore, N.; Sandhu, S.; Chi, K.N.; Sartor, O.; Agarwal, N.; Olmos, D.; et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N. Engl. J. Med. 2020, 382, 2091–2102.
61. Abida, W.; Campbell, D.; Patnaik, A.; Bryce, A.H.; Shapiro, J.; Bambury, R.M.; Zhang, J.; Burke, J.M.; Castellano, D.; Font, A.; et al. Rucaparib for the Treatment of Metastatic Castration-resistant Prostate Cancer Associated with a DNA Damage Repair Gene Alteration: Final Results from the Phase 2 TRITON2 Study. Eur. Urol. 2023, 84, 321–330.

62. Zhou, F. Pamiparib in mCRPC with HRD or BRCA1/2 Mutation. Available online: https://clinicaltrials.gov/study/NCT05327621 (accessed on 10 February 2024).
63. McKay, R.R. Study of Neoadjuvant PARP Inhibition Followed by Radical Prostatectomy in Patients with Unfavorable Intermediate-Risk or High-Risk Prostate Cancer with BRCA1/2 Gene Alterations (NePtune). Available online: https://clinicaltrials.gov/study/NCT05498272 (accessed on 10 February 2024).
64. Huang, J.-D. Study of CX-5461 in Patients with Solid Tumours and BRCA1/2, PALB2 or Homologous Recombination Deficiency (HRD) Mutation. Available online: https://clinicaltrials.gov/study/NCT04890613 (accessed on 10 February 2024).