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ABOUT COVER

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BRCA mutated pancreatic cancer: A change is coming

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Abstract

Pancreatic cancer remains a leading cause of cancer-related death with few available therapies for advanced disease. Recently, patients with germline *BRCA* mutations have received increased attention due to advances in the management of *BRCA* mutated ovarian and breast tumors. Germline *BRCA* mutations significantly increase risk of developing pancreatic cancer and can be found in up to 8% of patients with sporadic pancreatic cancer. In patients with germline *BRCA* mutations, platinum-based chemotherapies and poly (ADP-ribose) polymerase inhibitors are effective treatment options which may offer survival benefits. This review will focus on the molecular biology, epidemiology, and management of *BRCA*-mutated pancreatic cancer. Further-more, we will discuss future directions for this area of research and promising active areas of research.

Key Words: Pancreatic cancer; Systemic therapy; Platinum chemotherapy; *BRCA*; Deoxyribonucleic acid repair; Poly (ADP-ribose) polymerase inhibitors

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Core Tip: Recent advances in the field of *BRCA*-mutated pancreatic cancer suggest that these patients benefit from platinum-based chemotherapy regimens. In light of new findings from the Pancreas Cancer Olaparib Ongoing trial, patients with germline *BRCA* mutations may benefit from maintenance treatment with olaparib, a Poly (ADP-ribose) polymerase inhibitors following response to platinum-based chemotherapy. Based on these important findings, all pancreatic cancer patients should be offered early access to genetic screening in order to identify patients who will benefit from these therapies.

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INTRODUCTION

Pancreatic cancer (PC) remains one of the most aggressive malignancies, with a 5-year survival rate of 8% [1,2]. Incidence of PC has increased over the past 4 decades, making it a leading cause of cancer-related mortality in North America [1-3]. The vast majority of pancreatic cancers are ductal adenocarcinomas (PDAC) of the exocrine pancreatic glands, occurring most commonly in the head of the pancreas [4]. Most cases of PDAC are considered sporadic, however 5%-10% are estimated to be familial with patients having a family history of PDAC [5]. Several genetic syndromes are known to cause familial PDAC including mutations of deoxyribonucleic acid (DNA) mismatch repair genes (Lynch syndrome), *BRCA1* and *BRCA2* (hereditary breast cancer syndrome); however, in the vast majority of cases a genetic cause cannot be identified [5-7].

Currently, the only potentially curative treatment for PC is surgical resection which is only possible in the early stages of the disease (locoregional) and highly dependent on the degree of invasion of surrounding critical structures such as vessels and bile ducts. Unfortunately, only 15%-20% of PDAC cases are considered resectable, and of these, over 75% will have recurrence within 5 years of their resection [4]. Recent data suggests that in patients with good performance status, treatment with a combination regimen of fluorouracil, oxaliplatin, leucovorin and irinotecan (FOLFIRINOX) is the optimal adjuvant therapy following resection [8]. Because early stage PC is usually asymptomatic, the vast majority of patients present with either locally advanced (involvement of local vasculature) or metastatic disease [4]. In these patients chemotherapy and occasionally radiotherapy form the backbone of treatment and are used to relieve symptoms and modestly prolong life.

In the advanced setting of disease, the two standard of care palliative chemotherapy options include gemcitabine plus albumin-bound paclitaxel (nab-paclitaxel) and FOLFIRINOX. In the first-line setting, both have been shown to prolong overall survival (OS) relative to gemcitabine monotherapy in prospective, randomized clinical trials [9,10]. Even with these treatments, 2-year survival remains at 10% and median OS ranges from 8-11 mo [4].

Recent genomic evidence suggests that PDAC is a genetically heterogeneous disease with different molecular subtypes, potentially explaining the failure of many novel therapies when trialed in unselected populations [11,12]. Currently, efforts are ongoing to identify select PDAC patient populations who would benefit from targeted therapies. A patient group which has garnered much interest are those with mutations of *BRCA1* and *BRCA2*. These genes are important players in the homologous DNA repair (HR) pathway and mutations of both genes are strong risk factors for the development of several cancers including, breast, ovarian, prostate and pancreatic cancer [13,14]. Importantly, *BRCA* mutations also have implications for treatment as they may increase tumor susceptibility to both DNA-damaging chemotherapies such as platinum chemotherapy (PtCh), as well as poly (ADP-ribose) polymerase (PARP) inhibitors in breast and ovarian cancers. More recently, work has been done to determine if these clinical features translate to BRCA-mutated pancreatic cancer. This review will discuss the biology, epidemiology and clinical implications of *BRCA* mutations in PDAC, and will discuss future directions for this area of research.

MOLECULAR BIOLOGY OF HOMOLOGOUS REPAIR

Several reviews have previously described the biology of the HR system and the specific roles of *BRCA1/2* [15,16]. Briefly, DNA damage can occur as either a single-stranded DNA break (SSB) or double-stranded DNA break (DSB). HR along with non-homologous end joining (NHEJ) are the two major pathways that respond to DSB. HR has the highest fidelity and precision of the DSB repair pathways, therefore defects in this pathway (homologous repair deficiency, HRD) lead to error-prone repair and genomic instability, increasing cancer risk. Important proteins in the HR system include *BRCA1*, *BRCA2*, *PALB2*, *ATM* and *RAD51* [15]. Following DSB, *BRCA1*

negatively regulates factors involved in the NHEJ pathway (53BP1) and promotes end resection, an important first step in the HR pathway. BRCA1 directly interacts with PALB2 to bind BRCA2 which facilitates formation of RAD51 filaments later in the pathway[15]. RAD51 filament form along ssDNA created earlier by BRCA1-mediated end resection, allowing formation of homologous DNA and repair of the DSB (Figure 1)[15]. Notably, other proteins involved in the HR pathways such as PALB2 and ATM are also mutated in PC, highlighting the importance of HR pathway integrity in determining PDAC risk[11,17].

While BRCA mutations confer increased cancer risk, emerging evidence suggests they also may be important markers for personalized medicine. *In vitro* and *in vivo* evidence suggests that both platinum-based chemotherapies and PARP inhibitors are more effective in patients harboring BRCA mutations[11].

EPIDEMIOLOGY AND DIAGNOSIS OF BRCA-MUTATED PDAC

Incidence of pathogenic BRCA mutations in sporadic and familial PDAC

Mutations of the BRCA1 and BRCA2 genes were first identified as breast and ovarian cancer risk factors in the mid-1990s during studies aimed at characterizing the genes responsible for familial clustering of breast and ovarian cancers[18,19]. Early studies by the Breast Cancer Linkage Consortium identified a 2.3-fold and 3.5-fold increased risk of PC in carriers of BRCA1 and BRCA2 gene mutations, respectively[13,14]. In the general population, germline BRCA mutations occur at a rate between 1/300 and 1/800[20]. However, incidence varies based on population as certain ethnic groups harbor founder mutations, increasing the incidence of BRCA mutations in these subgroups. The strongest example of the founder effect in BRCA is the Ashkenazi Jewish (AJ) population, where the presence of 3 founder mutations have increased rates of BRCA mutation to 1/40[21]. Other groups with founder BRCA mutations who are therefore at increased risk include Dutch, Norwegian and French-Canadian populations[22].

Among unselected PC patient cohorts, multiple studies have aimed to estimate the incidence of germline pathogenic BRCA mutations. Prevalence estimates ranged from 0.7%-5.7% for BRCA2 and 0.3%-2.3% for BRCA1 (Summarized in Table 1)[6,23-26]. Notably, the cohorts in these studies varied widely based on several factors which could influence estimates of prevalence, including, number of AJ PC patients included, the number of patients with family histories of cancer, and median patient age[23]. For example, in AJ PDAC patients, studies have found that up to 19% of patients harbour germline BRCA mutations[23,27,28].

In familial PC, BRCA mutations, especially BRCA2 are also at increased frequency. In the case of BRCA2 mutations, studies have found germline mutations in 3.7%-19% of patients with strong familial histories of PDAC[29-32]. This range in estimates is likely a result of different criteria for familial pancreatic cancer (FPC), and different studies methodologies. Studies finding higher rates of BRCA2 mutation tended to have smaller sample sizes and included patients with three or more first- or second-degree relatives with PC, therefore included higher risk patients. Conversely, more recent studies have included larger sample sizes of patients, who met the more moderate FPC case definition (two first- or second- degree relatives with PC), finding more conservative estimates of prevalence (3.7% and 6%)[31,32]. Therefore, in patients with a stronger family history of PC, BRCA carrier status is more likely. The incidence of BRCA1 mutations in FPC has not been studied as well as BRCA2, however a recent study by Zhen *et al*[31] found that germline BRCA1 mutations were present in 1.2% of patients with FPC.

Diagnosis of BRCA-mutated PDAC and screening guidelines

While the identification of patients carrying BRCA mutations has been important in determining cancer risk, the discovery of personalized medicine options for this population has increased the clinical importance of identifying BRCA carriers. Genetic testing guidelines vary by region however, are primarily based on cancer phenotype which includes family history of breast, ovarian, prostate and pancreatic cancer, AJ ancestry and clinical presentation. Recently, genetic testing guidelines are being increasingly questioned as evidence accumulates to suggest that they would miss a large proportion of patients harboring BRCA mutations who may benefit from PARP inhibitors or platinum chemotherapies. In 2007, a Norwegian study tested breast and ovarian cancer patients for germline mutations in BRCA1 and BRCA2 and identified that 50% of patients with germline BRCA mutations do not have family histories of

Table 1 Summary of studies of incidence of germline BRCA mutations in unselected pancreatic cancer cohorts

| Ref. | Year | Population | Cohort size (Number AJ) | Germline BRCA1 pathogenic mutation incidence (%) | Germline BRCA2 pathogenic mutation incidence (%) | Combined germline BRCA mutation Incidence |
|----------------------------|------|----------------|-------------------------|--------------------------------------------------|--------------------------------------------------|-------------------------------------------|
| Holter <i>et al</i> [23] | 2015 | North American | 306 (33) | 1.0% | 3.6% | 4.6% |
| Brand <i>et al</i> [24] | 2018 | North American | 298 (26) | 1.3% | 1.3% | 2.6% |
| Mizukami <i>et al</i> [25] | 2020 | Japanese | 1005 (-) | 1.7% | 2.5% | 4.2% |
| Grant <i>et al</i> [6] | 2015 | North American | 290 (13) | 0.3% | 0.7% | 1% |
| Lowery <i>et al</i> [26] | 2018 | North American | 615 (111) | 2.3% | 5.7% | 8% |

AJ: Ashkenazi Jewish; BRCA: Breast cancer susceptibility gene.

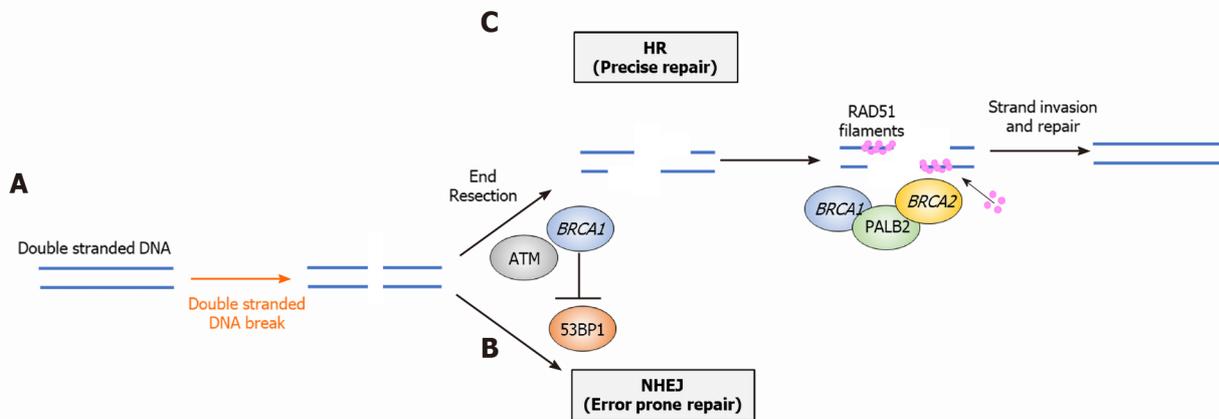


Figure 1 Overview of the homologous repair pathway and roles of key proteins. A: Following double strand break, BRCA 1 binds to the site of damage, mediating end resection and initiating homologous repair. This prevents repair *via* non-homologous end joining; B: BRCA1 binds with PALB2 and BRCA2 which facilitates assembly of RAD51 filaments; and C: RAD51 filaments form along ssDNA, subsequently leading to strand invasion and repair. DSB: Double strand break; HR: Homologous repair; NHEJ: Non-homologous end joining; BRCA: Breast cancer susceptibility gene.

BRCA-associated cancers[33]. Since then, multiple studies in different populations including patients with PDAC have confirmed these findings, showing poor associations between presence of BRCA mutations and expected family histories [23,34-38]. Furthermore, a recent study using data from 23&Me, a direct-to-consumer genetic test identified that 20% of carriers of the AJ founder variants don't identify as AJ, and therefore would be excluded from screening criteria that include AJ ancestry[39]. They also found that of 393 BRCA mutation carriers with available data on family cancer history, 44% had no family history of BRCA-associated cancers, and therefore, given a diagnosis of PDAC, would not meet screening requirements. The recent IMPACT trial by the Memorial Sloan-Kettering Cancer Centre provided strong evidence in favour of increased testing access. Investigators tested 1040 patients (176 PDAC) with advanced cancer and identified germline mutations in 21.5% of the PDAC patients. Notably, they found that across all cancers, 55% of clinically actionable mutations would not have been detected under current phenotype-based screening guidelines[40]. Together, this evidence strongly supports calls for increased access to genetic testing for PC patients. In early 2020, the National Comprehensive Cancer Network updated their recommendations to suggest universal genetic testing for all PC patients as early as possible due to the rapid progression of the disease, and potential for early personalized therapy[41].

CLINICAL FEATURES OF BRCA-MUTATED PDAC AND PROGNOSTIC IMPLICATIONS

While the ability of *BRCA* mutations to increase risk of PDAC is well established, their impact on the clinical features of the disease is less clear. Multiple cohort studies have shown in PDAC patients with germline mutations including *BRCA1*, *BRCA2*, *PALB2*, *CDKN2A* and *ATM*, are diagnosed earlier with PDAC than PDAC patients without germline mutations[31,42]. Conversely, a 2009 study comparing Jewish PDAC patients with and without germline *BRCA* mutations found no significant differences between age at diagnosis or any other clinicopathologic feature studied[28]. From a prognostic perspective, studies have shown mixed results. The largest cohort study to date including 71 *BRCA*-positive PDAC patients found a median OS of 14 mo for the whole cohort and 12 mo for patients with stage 3/4 disease. At time of publication, the median OS for early stage disease had not been reached as 52% of patients were still alive at 60 mo[43]. These findings suggest that *BRCA*-mutated PDAC patients may have a considerably better prognosis than the general PDAC population. On the contrary, more recent case-control studies by Blair *et al*[44] compared PDAC patients with *BRCA1* and *BRCA2* mutations to age-matched controls and showed that both OS and disease-free survival (DFS) were lower in carriers than controls. Another case-control study comparing *BRCA* mutation-positive, early-stage PDAC patients undergoing surgical resection to age-matched *BRCA*-wildtype controls found no significant differences in median OS or DFS between the groups and concluded that *BRCA* mutations were not prognostic in early PDAC[45]. Authors have suggested that early findings of improved prognosis in this population may have been a result of ascertainment bias as patients surviving longer were more likely to receive genetic testing and participate in the study. Another factor that may lead to improved prognosis in this patient population is increased susceptibility to treatments such as PtCh. Most recently, a study using data from the Know Your Tumor program aimed to assess whether mutations of HRD and other DNA-damage response (DDR) genes conferred a survival benefit or whether observed benefits were a result of increased PtCh-sensitivity[46]. The authors found that patients with advanced PDAC and HR/DDR mutations had improved survival but only if treated with PtCh. In PtCh-naïve patients, there was no survival benefit in this patient population[46].

Overall, identifying clinical differences between *BRCA*-mutated PDAC and wildtype PDAC has been difficult due to the relative rarity of these patients. Furthermore, the increasing use of personalized therapies (PARP inhibitors and platinum chemotherapy) in this population will make determining the prognostic implications of *BRCA* mutations more challenging.

MANAGEMENT OF BRCA-MUTATED PDAC: SYSTEMIC THERAPY

Platinum chemotherapy

While both FOLFIRINOX and gemcitabine/nab-paclitaxel chemotherapy regimens are more effective than gemcitabine monotherapy, there is yet to be a comparative randomized clinical trial to provide data on which regimen is more effective. In the locally advanced setting, a recent case series of 485 consecutive patients suggested that FOLFIRINOX was associated with a higher response rate (19% *vs* 6%, $P = 0.001$), however OS was not different with either treatment[47]. Retrospective studies in metastatic PDAC are inconclusive, with some studies reporting survival improvement on FOLFIRINOX while others report no difference between the two regimens[47,48]. Given the increased toxicity associated with FOLFIRINOX and potential survival benefits, identifying subsets of patients who are more likely to benefit from this regimen will be an important advancement in PC management.

The HRD phenotype of *BRCA*-mutated cancers appears to render them more sensitive to chemotherapies that induce DNA damage, such as PtCh. Early studies found that cells lacking *BRCA1* are more sensitive to treatment with cisplatin[49]. In the presence of HRD, these cells are unable to appropriately repair the DNA damage, leading to genomic instability and cell death[50]. Clinical studies in breast cancer have found that platinum-chemotherapy improves objective response rates (ORRs) for metastatic breast cancer patients only in *BRCA*-mutated cancers. Based on genomic studies in PDAC, it appears that tumors with *BRCA*-mutations have “unstable” molecular phenotypes and are more likely to be sensitive to genotoxic therapies such as PtCh[11].

In PC, several large retrospective studies have investigated the efficacy of PtCh such as FOLFIRINOX in patients with *BRCA* mutations or other genetic mutations leading to HRD (Table 2). To date, the largest cohort study was conducted by Golan *et al*[43]. This multi-institution cohort study included 71 PC patients with germline *BRCA* mutations and found that among patients with advanced PDAC, OS was significantly longer in patients treated with PtCh (22 *vs* 9 mo). Since this study, several other retrospective cohort studies have reported improved outcomes [ORR, progression free survival (PFS)] in patients with germline mutations to HR-related genes who were treated with PtCh in both resectable and non-resectable PDAC[35,44,51,52]. For example, Blair *et al*[44] showed that median survival was significantly improved in resected PDAC patients with germline *BRCA* mutations who were treated with adjuvant PtCh compared to non-PtCh (31.0 *vs* 17.8 mo). Reiss *et al*[52] showed significant improvement in mOS in patients with unresectable PDAC and mutations in *BRCA1*, *BRCA2* or *PALB2* who were treated with PtCh compared to patients treated with non-PtCh (median follow-up of 20.1 mo *vs* mOS of 15.5 mo). Several studies have also compared the effectiveness of PtCh between patients with and without HRD mutations. In a cohort study of platinum-treated PDAC patients, patients found to have tumor-level mutations to 12 HR-related genes (including *BRCA1*, *BRCA2*, *ATM* and *PALB2*) had significantly improved median PFS compared to platinum-treated patient without HR-related gene mutations[35]. Similarly, two recent case-control studies reported improved PFS and ORR in platinum-treated patients who carried mutations to *BRCA1*, *BRCA2* and *PALB2*[53,54]. Wattenberg *et al*[53] showed an ORR of 58% in mutation carriers treated with PtCh compared to 21% non-mutated PDAC patients. In resected PDAC treated with perioperative PtCh, Yu *et al*[54] reported that mutation carriers had significantly greater survival (mOS not met *vs* 23.1 mo, HR = 0.12).

While these studies are promising, the retrospective nature introduces several limitations. Firstly, outcomes are widely subdivided as PtCh *vs* non-PtCh, however the PtCh groups generally include a variety of regimens such as gemcitabine + cisplatin, gemcitabine + oxaliplatin, FOLFOX and FOLFIRINOX. Seeing as oxaliplatin and cisplatin exert DNA damage through different mechanisms of action, it is unclear how well these findings will translate to modern clinics where patients are typically treated with FOLFIRINOX as a first-line therapy[52]. One study reported that there was no significant difference in survival for mutation-positive patients on different PtCh regimens, however in the mutation-negative group, patients only responded to FOLFIRINOX[53]. This suggests that there is potentially a role for PtCh regimens in *BRCA*-mutated patients that did not show benefit when tested in unselected PDAC populations, in situations when FOLFIRINOX cannot be tolerated. Another limitation is the current practices with respect to treatment selection. Because of the toxicity associated with PtCh such as FOLFIRINOX, these regimens are generally used in younger patients with better performance status. Therefore, in retrospective analyses of *BRCA*-mutated PDAC cohorts, it is unclear whether survival benefits seen are because of increased activity of PtCh in this patient population or because the patients treated with PtCh are younger and have better performance status. Few studies have reported data on patient age in these analyses and none have reported patient performance status. In light of this, these retrospective analyses are difficult to interpret. Lastly, retrospective studies may be affected by survival bias. Most studies compared confirmed mutation carriers to untested cohorts. It is possible that patients who survive longer are more likely to undergo genetic testing and be classified as carriers. In light of these limitations, a recent meta-analysis concluded that the current available evidence suggests PtCh is more effective in *BRCA*-mutated patients, however the quality of evidence is low[55].

To date, there have been few prospective studies assessing the effectiveness of platinum-chemotherapies in this population. A recent phase II randomized controlled trial investigated cisplatin and gemcitabine with or without Veliparib, a PARP inhibitor in patients with untreated advanced PDAC and a germline mutation of *BRCA* or *PALB2*[56]. While the primary endpoint (response rate) was not significantly different with Veliparib, the authors reported unprecedented survival rates, with a 2-year survival rate of 30.6% and a 3-year survival rate of 17.8%[56]. Response rates were also high for both arms of the study (74% with Veliparib, 65.2% without veliparib)[56]. While this data provides compelling evidence for the use of PtCh in this patient population, the study lacks a control group treated with non-PtCh for comparison. This study adds to the literature as all patients were on the same PtCh regimen (gemcitabine + cisplatin) which showed impressive responses and survival rates. Notably, the patients included in this study all had a good performance status (ECOG 0-1) and therefore these results may not translate as well to real-world PDAC patients

Table 2 Retrospective studies of platinum-chemotherapies in BRCA-mutated pancreatic ductal adenocarcinoma

| Ref. | Year | Study design | Patient population | Findings |
|------------------------------|------|------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Golan <i>et al</i> [43] | 2014 | Multi-institution cohort study | 71 patients with germline BRCA mutations (21 BRCA1, 49 BRCA2, 1 both) | Superior mOS in stage 3/4 patients treated with platinum compared to non-platinum chemotherapy (22 vs 9 mo, $P = 0.039$) |
| Vyas <i>et al</i> [51] | 2015 | Cohort study | 10 patients with BRCA2 mutation and known PDAC | Duration of response on platinum agents ranged from 8-32 wk, mean of 19.3 wk |
| Blair <i>et al</i> [44] | 2018 | Combined case control cohort study | 22 patients with resected sporadic PDAC and germline BRCA mutations (1 BRCA1, 18 BRCA2) | Improved OS in BRCA-mutated patients treated with adjuvant PtCh compared to patients treated with alternative chemotherapies or no adjuvant therapy (31.0 vs 17.8 vs 9.3 mo, $P < 0.001$) |
| Reiss <i>et al</i> [52] | 2018 | Cohort study | 29 patients with unresectable PDAC and germline mutations of BRCA1, BRCA2 or PALB2(12 BRCA1, 15 BRCA2, 2 PALB2) | Superior mOS in platinum-treated patients (undefined mOS (median follow up 21 mo) vs 15.5 mo, $P = 0.02$) |
| Kondo <i>et al</i> [35] | 2018 | Cohort study | 28 patients with advanced PDAC (13 had HR-related gene mutations, 15 without mutations to HR-related genes) | Superior median PFS in HR-mutated PDAC patients treated with platinum chemotherapy compared to PDAC patients without HR mutations treated with platinum therapy (20.8 mo vs 1.7 mo, $P = 0.049$) |
| Yu <i>et al</i> [54] | 2019 | Case control study | 32 resected PC patients with germline BRCA1, BRCA2, or PALB2 mutation, 64 resected PC patient controls without germline mutations | With peri-operative platinum exposure, mOS was longer in mutation-positive group that mutation negative group (mOS not yet met vs 23.1 mo, HR= 0.12) |
| Wattenberg <i>et al</i> [53] | 2020 | Case control study | 26 platinum-treated patients with advanced stage PDAC and mutations of BRCA1, BRCA2 or PALB2, 52 platinum-treated, wildtype, age-matched controls | Improved ORR in patients with mutations compared to controls (58% vs 21%, $P = 0.0022$). Improved real world PFS in mutation carriers (10.1 mo vs 6.9 mo, HR = 0.43, $P = 0.0068$) |

HR: Homologous Repair; mOS: Median overall survival; ORR: Objective response rate; PDAC: Pancreatic adenocarcinoma; PtCh: Platinum chemotherapy; BRCA: Breast cancer susceptibility gene.

where performance status may be lower.

Overall, there is evidence in favour of the use of PtCh as a first-line treatment for BRCA-mutated PDAC, however, most data is retrospective and the quality of the evidence in favour of this treatment is low. There is yet to be a randomized controlled trial confirming the observations that PtCh is preferable to other chemotherapy regimens in this population, however enrollment to such a study may be difficult due to current management practice. Furthermore, it is unclear whether or not FOLFIRINOX or gemcitabine plus cisplatin should be used for this patient population.

PARP inhibitors

The sensitivity of BRCA-deficient cancers to PARP inhibition was first reported in 2005, in which researchers identified that loss of function of both BRCA and PARP is synthetically lethal[57,58]. PARP is an important family of enzymes involved in responding to SSB the other prominent form of DNA damage other than DSB. This combined loss of SSB repair in HRD cells is thought to lead to synthetic lethality (Figure 2). While the exact mechanism of action is still unclear, the earliest theory was that PARP inhibition prevents the repair of single-stranded DNA breaks (SSBs), leading to accumulation of replication-associated DSBs[59]. In HRD cells which have defective DSB repair, DSBs are repaired *via* error-prone NHEJ, leading to genomic instability and cell death. More recent evidence suggests that the biology of BRCA and PARP deficient synthetic lethality is more complex, however the detailed mechanisms are outside the scope of this review[60].

Therapeutic inhibitors of this pathway were evaluated in a phase I study of olaparib and confirmed activity in several different tumor types harboring BRCA mutations[61]. In ovarian cancer, PARP inhibitors are FDA-approved for use as a maintenance therapy in patients with recurrent ovarian cancer who demonstrated a complete or partial response to PtCh, regardless of HRD biomarker status[62]. This approval came following three phase III trials which demonstrated significant improvements in PFS in patients treated with oral PARP inhibitors as maintenance therapy following chemotherapy[63-65]. More recently, emerging data from several randomized clinical trials reporting efficacy of PARP inhibitors as a front-line treatment for newly diagnosed ovarian cancer[62]. In advanced breast cancer, PARP inhibitors have demonstrated improvements in PFS relative to chemotherapy in patients with HER2-negative, BRCA-mutation positive tumors[66,67]. However, there

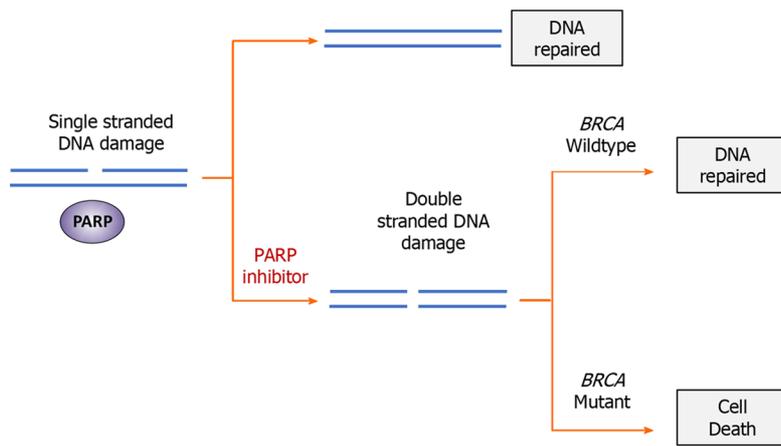


Figure 2 Mechanism of synthetic lethality in *BRCA*-mutated cells treated with poly (ADP-ribose) polymerase inhibitors. While neither a breast cancer susceptibility (*BRCA*) mutation or treatment with Poly (ADP-ribose) polymerase (PARP) inhibitors alone is lethal to cancer cells, dual-inhibition of both systems through mutation and pharmacological inhibition is incompatible with survival. Following PARP inhibition, single-stranded deoxyribonucleic acid (DNA) breaks are unable to be repaired. During replication, replication forks stall at unrepaired DNA damage, resulting in formation of double-stranded DNA break. In cells with defective homologous repair (*BRCA* mutations), double-stranded damage is repaired through non-homologous end joining, resulting in genomic instability and cell death. Poly (ADP-Ribose) Polymerase. PARP: Poly (ADP-ribose) polymerase; *BRCA*: Breast cancer susceptibility gene.

is yet to be a clinical trial demonstrating improvements in OS with PARP inhibitor use in advanced breast cancer[68]. Recently, PARP inhibitors have also demonstrated effectiveness in metastatic prostate cancer[69].

With the success of PARP inhibitors in other *BRCA*-associated cancers, focus has shifted to translating these findings to *BRCA*-associated PDAC. To date multiple phase II studies have evaluated the efficacy of PARP inhibitors in PDAC patients with germline *BRCA* mutations[56,70,71]. In a phase II study by Kaufman *et al*[71], 298 patients with advanced cancer (23 with pancreas cancer) and germline *BRCA1/2* mutations were treated with oral olaparib. The response rate among PC patients was 21.7% in patients who had received two prior lines of chemotherapy[71]. Conversely, another phase II study evaluated the efficacy of Veliparib in 16 advanced PDAC patients with known germline mutations of *BRCA1/2* or *PALB2* who had undergone 1-2 previous lines of treatment, finding no objective responses[70]. Authors suggested potential differences between olaparib and veliparib as a potential explanation for the difference in response rates between the two trials. Furthermore, the high rates of pre-treatment with PtCh (88% of study population) coupled with a high disease progression rate (64% of those on PtCh) may indicate a high-level of platinum-resistance in this study population, which may in turn lead to PARP inhibitor resistance[70]. This is a plausible explanation given the known association between platinum-sensitivity and PARP inhibitor sensitivity seen in ovarian cancer. Due to the tendency of cancers to develop resistance to PARP inhibitors, another approach that has been tried is combination regimens involving chemotherapy and PARP inhibitors. A recent phase II trial compared a combination regimen of gemcitabine plus cisplatin with or without veliparib as first line therapy for advanced PDAC patients with germline mutations of *BRCA1/2* or *PALB2*[56]. Veliparib did not improve response rates over gemcitabine plus cisplatin alone (74.1% vs 65.2%, $P = 0.55$), however as discussed earlier, the response rates in both arms both exceeded pre-study thresholds of efficacy and therefore, the high response rate to gemcitabine plus cisplatin may have obscured any signal of benefit from veliparib.

With the relative success of combination chemotherapy regimens in PDAC (FOLFIRINOX, Gemcitabine-Abiraterone), focus has been placed on the development of maintenance therapies which can prolong PFS and improve quality of life (QOL) in responders. Most recently, data from the Pancreas Cancer Olaparib Ongoing (POLO) trial has supported the use of PARP inhibitors as a maintenance therapy in this patient population following response to platinum-chemotherapy[72]. The POLO trial was an international phase III, double-blind, placebo-controlled randomized clinical trial investigating oral olaparib maintenance therapy in metastatic PDAC patients with germline *BRCA1/2* mutations who had not progressed during first-line PtCh (minimum of 16 wk of chemotherapy). Patients were randomized to either olaparib or placebo maintenance therapy. PFS was significantly longer in the olaparib group (7.4 vs 3.8 mo). At the time of publication, data on OS was not yet mature but preliminary

results indicated no significant difference in OS between the two groups (18.9 vs 18.1 mo)[72]. 18 patients (20%) in the olaparib and 6 patients (11%) in the placebo group achieved a tumor response, and the median duration of responses were 24.9 mo and 3.7 mo, respectively. Other evidence for maintenance therapy comes from the phase II study by O'Reilly *et al*[56] who reported exploratory analyses for 10 patients with germline *BRCA* or *PALB2* mutations who underwent at least 4 mo of PtCh without progression and subsequently were switched to a PARP inhibitor as maintenance therapy, finding a median PFS of 23.4 mo in this subset of patients.

In the context of maintenance therapy, preservation of quality of life and minimization of adverse effects are important goals of treatment. In the POLO trial, Grade ≥ 3 adverse events occurred in 40% of the olaparib group and 23% of the placebo group[43]. The most frequently reported adverse events in the treatment group were fatigue or anesthesia, nausea and anemia, with the majority of these cases being low grade. Only 15% and 5% of patients on olaparib underwent dose reductions or discontinued treatment because of adverse events, respectively. More recently, secondary outcomes of health-related QOL were reported, showing that olaparib treatment did not lead to a reduction in quality of life scores, a concern in the context of maintenance therapy meant to preserve functioning and QOL[73].

In light of these findings, the FDA has approved olaparib for maintenance therapy in patients with metastatic PDAC patients with germline mutations of *BRCA1/2* who have not progressed on at least 16 wk of first-line PtCh. This approval is not without controversy as there are several criticisms of the POLO trial and unanswered questions in regards to this therapy[74]. For example, the lack of improvement in OS puts the validity of the finding of improved PFS into question[74]. However, this may be because of the high rates of therapy in the placebo group following disease progression, including 15% of the patients who received a PARP inhibitor. In addition, it should be stated that the OS results were from an interim analysis with only 46% data maturity. Furthermore, concern has been raised that the discontinuation of PtCh after 16 wk in patients who were responding is incongruent with clinical practice guidelines for first-line platinum chemotherapy[74]. However, in the POLO trial, the majority of patients received FOLFIRINOX (> 80%) with a median duration of first line PtCh of 5 mo and 33% of patients receiving > 6 mo prior to randomization[72]. In addition, the PRODIGE 4/ACCORD 11 trial recommended a total of 6 mo of palliative chemotherapy[10], therefore, the duration of therapy of 1st line PtCh may not be out of keeping with other clinical trials in this setting of disease. Furthermore, use of placebo alone in the control group has come under criticism as evidence has emerged in favour of the continuation of 5-FU as maintenance therapy in patients who respond to FOLFIRINOX[75]. That being said, the accumulating side effects of > 4 mo of FOLFIRINOX may justify a treatment break, especially if there is no evidence of progression on imaging. Lastly, POLO only included patients with germline mutations of *BRCA1/BRCA2*, therefore it remains unclear if there is a broader population of PDAC patients who would benefit from olaparib as well, such as patients with germline mutations to other components of the HR system (*PALB2*, *ATM*) or patients with other positive biomarkers of HRD.

Immunotherapies

While immunotherapies such as checkpoint inhibitors (anti-PD1/PDL1 and CTLA-4) have revolutionized the management of many cancers, they have had limited efficacy in PDAC. The genomic instability and increased total mutational load of *BRCA*-mutated and other HRD tumors results in neoantigens which may increase efficacy of immunotherapy in these tumors[11]. Recent translational studies have showed that specifically *BRCA2*-mutated tumors show increased sensitivity to immune checkpoint blockade as a result of their effect on the tumor immune microenvironment[76]. This is in line with previous findings of associations between *BRCA* mutations and PD-L1 expression in PDAC, a predictive marker for immunotherapy[77,78].

An emerging strategy for *BRCA*-mutated cancers is combination therapy with immune check point inhibitors and PARP inhibitors[79]. Given that treatment with PARP inhibitors also increases expression of PD-L1 and total mutational burden (potential biomarkers of response), combining these two therapies may act synergistically against HRD tumors[79]. In *BRCA*-mutated ovarian and breast cancers, several clinical trials are currently exploring the clinical efficacy of PARP inhibitor/immune checkpoint blockade combination therapy with early trials showing promising results[80]. In the maintenance setting, the ATHENA trial is currently testing a combination therapy consisting of rucaparib with nivolumab as a therapy for ovarian cancer following response to PtCh (NCT03522246). In PDAC, there are several ongoing Phase II trials investigating combination regimens involving PARP inhibitors

and immune checkpoint inhibitors (Table 3). The PARPVAX study is investigating combination therapy of niraparib + either ipilimumab or nivolumab as maintenance therapy following response to PtCh (NCT03404960). Another phase II study is investigating combination therapy regimens including olaparib plus durvalumab in PDAC with a primary outcomes of changes in genomic and immune markers (NCT03851614). Most recently, a study has been initiated comparing olaparib with and without pembrolizumab as maintenance therapy for *BRCA1/BRCA2* mutated-PDAC patients who responded to first-line PtCh (NCT04548752). Given the recent evidence for PARP inhibitors in PDAC, the use of immune checkpoint blockade for PDAC remains an active field of research.

BIOMARKERS OF HRD

In the context of both PtCh and PARP inhibitors, the development of biomarkers for HRD will be an important step in implementing these therapies broadly in clinical practice. While most research to date has focused on germline mutations of *BRCA1/2* and *PALB2*, combined these represent less than 10% of all PDAC cases. While this is an important mechanism of HRD, HRD can also arise through somatic mutations or epigenetic modification of DDR genes potentially resulting in sensitivity to PtCh and PARP inhibitors. Therefore, relying solely on germline mutations of these three genes for treatment selection will likely miss patients who would otherwise benefit from targeted therapy. For example, in advanced pancreatic cancer, tumor-level mutations to HRR genes such as *BRCA1/2*, *ATM*, *PALB2*, *RAD51* were highly predictive of response to PtCh[35]. Recently a meta-analysis compared outcomes (ORR, survival) in PARP inhibitor trials and found that similar outcomes between patients with germline and patients with somatic *BRCA* mutations[81]. Interestingly, out of 99 studies of PARP inhibitors screened, only 18 included patients with somatic mutations, indicating that this is an understudied area of research[81]. Specifically in PDAC, only two studies investigated PARP inhibitors in patients with somatic *BRCA* mutations and both reported a non-significant increase in response rate in patients with somatic mutations, relative to germline[81]. No trials to date have evaluated the efficacy of maintenance olaparib, the only FDA-approved PARP inhibitor indication in PDAC in patients with somatic HR mutations. Two active trials of olaparib in PDAC are including patients with *BRCA*-associated family history or somatic HRD mutations, but explicitly excluding patients with germline *BRCA* mutations (NCT02677038, NCT02511223). However, these trials are not using olaparib in the maintenance setting. Given the efficacy of PARP inhibitors and PtCh in somatic *BRCA*-mutated ovarian cancer[63,82] this is an important area for future investigation in PDAC.

In addition to mutations of *BRCA* and other HR-related genes, genomic signatures of HRD have emerged as a promising biomarker of the HRD phenotype and subsequent treatment response[11]. These biomarkers will allow the identification sub-populations of PDAC patients who would benefit from PtCh or PARP inhibitors, and therefore expand the scope of use for these agents in PDAC. Multiple commercial assays now exist which can assess tumor tissues and assign an HRD score[62]. Examples of these assays include MyChoice CDx Assay (Myriad Genetics) and the FoundationOne CDx (Foundation Medicine) which are both FDA-approved for the evaluation of HRD. These tests combine loss-of heterozygosity scores with other markers of genomic instability (telomeric-allelic imbalance, large-scale transition) in order to quantify HRD and identify patients who would benefit from HRD-targeting therapies. These assays have been used in several clinical trials in breast and ovarian cancer and have been validated as useful biomarkers for response to PARP inhibitors[64,83,84]. Confirmation of HRD by assay is now an FDA-approved biomarker for the use of several treatment regimens including combined olaparib with bevacizumab for ovarian cancer. Furthermore, olaparib was recently approved for metastatic prostate cancer in patients with *BRCA* mutations or HRD. Investigating these biomarkers in PDAC will aid in identifying *BRCA*-wildtype patients who may benefit from PARP inhibitors and PtCh, an important prospect considering the poor prognosis in advanced PC.

CONCLUSION

The field of HRD in PDAC is in its infancy relative to ovarian and breast cancers, however promising advances have been made in recent years. Currently, the available

Table 3 Ongoing phase II clinical trials investigating poly (ADP-ribose) polymerase inhibitor/Immune Checkpoint blockade combination therapy in pancreatic ductal adenocarcinoma

| Study identifier | Patient population | Immunotherapy | PARP inhibitor | Phase and design | Estimated completion date |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|----------------|--------------------------------------------------------------------------------------------|---------------------------|
| NCT03404960 | Advanced PDAC patients who did not progress on PtCh | Nivolumab or Ipilimumab | Niraparib | Phase Ib/II trial evaluating effectiveness of olaparib with either nivolumab or ipilimumab | June 2021 |
| NCT03851614 | Advanced PDAC, leiomyosarcoma or mismatch repair-proficient colorectal cancer | Durvalumab | Olaparib | Phase II trial evaluating impact of combination therapy on genomic and immune biomarkers | March 2022 |
| NCT04493060 | Metastatic PDAC with mutations of <i>BRCA1/2</i> or <i>PALB2</i> , previously treated with 1-2 lines of chemotherapy including a PtCh agent | Dostarlimab | Niraparib | Phase II, evaluating the disease control rate at 12 weeks (DCR12) with combination therapy | December 2022 |
| NCT04548752 | Metastatic PDAC with germline <i>BRCA1</i> or <i>BRCA2</i> mutation treated with first-line PtCh | Pembrolizumab | Olaparib | Phase II trial comparing combination therapy to olaparib alone as maintenance therapy | March 2025 |

PDAC: Pancreatic adenocarcinoma; PtCh: Platinum chemotherapy; BRCA: Breast cancer susceptibility gene.

data from retrospective studies suggests that first-line PtCh is preferred however the PtCh regimen is yet to be defined. Olaparib maintenance therapy is a standard of care option in patients with *BRCA1/2* mutations and offers the benefit of ongoing anti-cancer therapy without traditional cytotoxic therapy toxicities. Important next steps include investigating these PtCh regimens and PARP inhibitors in the neoadjuvant setting, and determining if patients with somatic HR mutations or HRD as detected by genomic assays will also benefit from these treatments.

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