

Personalized Treatment for BRCA Mutated Pancreatic Cancer

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Abstract

Despite advancements in surgical techniques, radiation, and medical therapies, the 5-year survival rate remains below 10%. Recently, the genomic landscape of pancreatic ductal adenocarcinoma (PDAC) has been extensively studied, leading to the identification of BRCA mutations, currently recognized as a target for the development of novel personalized therapies. Alterations in germline BRCA and PALB2 are detected in approximately 5–9% of patients with PDAC and can result in homologous repair deficiency (HRD), and consequently, accumulation of double-stranded breaks. In patients with germline BRCA mutations, platinum-based chemotherapies and poly (ADP-ribose) polymerase inhibitors (PARP inhibitors) are efficacious treatment options that may confer survival benefits. Olaparib is currently indicated for maintenance therapy in metastatic PDAC, BRCA mutated whose disease does not progress after first-line platinum-based chemotherapy. Strategies combining therapies are currently under investigation. This review discusses the rationale for gBRCAm testing in patients with PDAC and its clinical implications. We also summarize recent literature on cisplatin-based chemotherapy and PARP inhibitors in patients with BRCA-mutated PDAC.

Keywords: Pancreatic cancer- germline BRCA mutation- Platinum chemotherapy- Olaparib

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1. Introduction

Pancreatic cancer (PC) remains one of the most lethal and aggressive malignancies, characterized by poor prognosis and low survival rates, with a five-year survival rate of approximately 5-10%. This poor prognosis is mainly due to early systemic spread, local aggressiveness, and the limited efficacy of current therapies [1]. Pancreatic cancer is currently the third leading cause of cancer-related mortality worldwide and is expected to become the second by 2030 [2-4].

Recent epidemiological data show that PC incidence is still rising, reaching 495,773 new cases worldwide in 2020. This translates into the incidence rate of PC around 5.7 cases per 100,000 people in males and 4.1 cases per 100,000 people in female [5]. The most common form of pancreatic cancer is ductal adenocarcinoma (PDAC) [1, 5]. Risk factors are divided into modifiable, including smoking, daily alcohol consumption, chronic pancreatitis,

diet and obesity; and nonmodifiable including age, gender, ethnicity, ABO blood group, diabetes, and family history [6].

Surgical resection remains the only potentially curative therapy; however, only 15-20% of newly diagnosed PC patients are candidates for surgical resection. Among these patients, over 75% will experience recurrence [2, 7]. To reduce the risk of relapse, adjuvant chemotherapy is recommended for all PDAC patients who undergo surgical resection. For fit patients, adjuvant modified FOLFIRINOX regimen (irinotecan, fluorouracil, leucovorin, and oxaliplatin) is the current standard of care. This regimen has demonstrated a significant improvement in median overall survival (OS) compared to gemcitabine monotherapy (OS 54.4 vs. 35 months, HR 0.64; p=0.003). Gemcitabine plus capecitabine or gemcitabine alone are alternatives for patients with contraindications to

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FOLFIRINOX [1].

In the metastatic setting, chemotherapy regimens include gemcitabine plus albumin-bound paclitaxel (nab-paclitaxel) and FOLFIRINOX. Both have shown to prolong OS relative to gemcitabine monotherapy in the first-line setting. However, the five-year OS rate remains under 10%, and median survivals are typically less than one year [2, 3, 7, 8].

The vast majority (>80%) of PDAC cases are sporadic, while a small proportion (<10%) result from inherited germline mutations. Comprehensive analyses have identified four major driver genes in PC: KRAS (90%), CDKN2A (90%), TP53 (70%), and SMAD4 (55%). However, none of these genes are currently clinical targets in therapeutic regimens [9-11]. The genes encoding breast cancer 1 and 2 (BRCA1 and BRCA2) and PALB2 play major roles in DNA damage response by mediating the repair of DNA double-strand breaks (DSBs) via homologous recombination (HR). Germline BRCA1/2 and PALB2 mutations are present in approximately 5-10% of familial PDAC cases and about 3% of apparently sporadic PDAC cases. Mutations in BRCA1 and BRCA2 are strong risk factors for the development of several cancers, including breast, ovarian, prostate, and pancreatic cancer [7, 12].

Cancers associated with BRCA mutations exhibit increased sensitivity to platinum agents due to defective DNA repair and demonstrate a synthetically lethal interaction with poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors due to the accumulation of DSBs [12-15]. For a subgroup of PC patients with metastatic disease and a germline BRCA1 or BRCA2 mutation, first-line platinum-based chemotherapy followed by maintenance therapy with the PARP inhibitor olaparib can significantly prolong progression-free survival (PFS) [16]. The POLO phase III trial investigated olaparib as active maintenance therapy for patients with metastatic pancreatic adenocarcinoma and a germline BRCA mutation (gBRCAm) whose disease had not progressed after at least 16 weeks of first-line platinum-based chemotherapy. The POLO study demonstrated a significant PFS benefit for active maintenance olaparib compared to placebo (7.4 months vs. 3.8 months; HR 0.53, $p=0.004$) [2, 3, 7, 9, 12, 14].

Therefore, identifying these mutations at diagnosis is crucial to enabling prompt administration of the most effective treatment [16]. Active maintenance with olaparib in patients with gBRCAm metastatic PC has been approved in multiple countries, including Europe and the United States [7, 16].

In this review, we outline the rationale for gBRCAm testing in patients with PDAC and its clinical implications. We also summarize recent literature on platinum-based chemotherapy and PARP inhibitors in patients with BRCA-mutated PDAC.

2. Methods

A systematic narrative review of the literature was conducted to identify clinical studies and reviews that

had described clinical features and therapeutic outcome of BRCAm PDAC. The review was designed and reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

Eligibility criteria

Prospective and retrospective studies of BRCA mutated pancreatic cancer in adult patients were included in a comparative analysis of any clinical data or BRCA oriented interventions aiming to improve outcome. Abstracts, original articles, clinical trials, short communications were included. Studies were excluded if their outcomes did not include at least response rate, progression free survival or overall survival, or if they were duplicate studies not initially screened out. Furthermore, narrative literature reviews and studies with no patient outcomes were also excluded.

Information sources

A comprehensive literature search was conducted to identify published studies on PubMed, Ovid MEDLINE, and EMBASE platforms. All databases were searched from their inception until June 2024 restricted to French and English language. Used keywords were the following: “pancreatic cancer”, “BRCA”, “precision medicine”.

Search strategy

All studies were screened independently by two authors (SA, NM). Each author collected paper references using the Zotero program. Produced datasets were confronted. Any discrepancies were resolved via discussion and consensus between the reviewers.

Data selection process

Zotero was employed for the deduplication and screening of all the articles retrieved through our online search. After deduplication, two authors independently completed the first phase of screening titles and abstracts adhering to the established inclusion criteria. Data abstraction from the final set of included studies was carried out independently and both authors reviewed all papers for comprehensive analysis.

3. Results

3-1 gBRCA mutation in PDAC: From discovery to therapeutic implications

3.1.1 Discovery of BRCA1 and BRCA2

The identification of BRCA genes provided critical insight into hereditary cancer susceptibility and its therapeutic implications. Initial linkage analyses demonstrated an autosomal-dominant cancer predisposition allele in high-risk families [17], leading to the identification and sequencing of BRCA1 in 1994 and BRCA2 shortly thereafter on chromosome 13q12 [12]. In pancreatic cancer (PC), BRCA2 mutations are detected in approximately 17–19% of patients with two or more affected first-degree relatives [18, 19],

compared with 7.3% in apparently sporadic cases [20]. BRCA1, located on chromosome 17q21, and BRCA2, located on chromosome 13q12–13, encode key proteins involved in the maintenance of genomic stability through homologous recombination-mediated DNA repair and interact functionally via the bridging protein PALB2 [12]. Structural features of BRCA2, including its large exon 11 and RAD51 interaction domain, are essential for effective DNA double-strand break repair. These discoveries established the biological basis for BRCA-associated pancreatic cancer and directly underpin the observed sensitivity of these tumors to platinum-based chemotherapy and PARP inhibition.

3.1.2 Role of BRCA and associated gene mutations in predisposition to Pancreatic Cancer

BRCA1 and BRCA2 are tumor suppressor genes that play a central role in DNA damage repair and the preservation of genomic stability. Loss of function of these genes compromises DNA repair capacity, leading to mutation accumulation and malignant transformation. Oncogenesis arises from either somatic mutations, which are confined to tumor tissue and account for approximately 75–80% of cancers, or germline mutations, which are inherited and present in all cells and contribute to 5–10% of malignancies [12]. In pancreatic cancer (PC), germline pathogenic variants in cancer predisposition genes, including BRCA1, BRCA2, PALB2, and CDKN2A, are identified in approximately 10–20% of patients, even in the absence of extra-pancreatic cancer phenotypes, while 5–8% of patients without a family history harbor germline mutations [21, 22]. In unselected PC cohorts, the prevalence of gBRCAm ranges from 0.7% to 5.7% for BRCA2 and from 0.3% to 2.3% for BRCA1 [23, 24], with higher frequencies reported in specific populations such as Ashkenazi Jews, where up to 19% of PDAC patients carry a gBRCAm [7, 23, 24].

Beyond BRCA genes, additional germline alterations contribute to familial PC susceptibility, including mutations in STK11, PALB2, CDKN2A, ATM, TP53, and mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2, EPCAM), collectively accounting for approximately 10% of cases. These mutations confer variable but clinically significant risk, ranging from a 3.5- to 6.2-fold increase with PALB2 mutations to a 130-fold increase associated with STK11 mutations, while CDKN2A and MMR gene alterations increase PC risk by 13–22-fold and 8.6-fold, respectively [18, 25, 26]. The cumulative lifetime risk of PC in ATM mutation carriers is age-dependent, increasing from 0.08% at age 30 to 9.53% by age 80 [27].

Recognizing the therapeutic and familial implications of these findings, the National Comprehensive Cancer Network (NCCN) recommended universal germline genetic testing for all patients with PC in 2018, encompassing key predisposition genes such as BRCA1, BRCA2, PALB2, CDKN2A, ATM, TP53, STK11, and MMR genes [14, 22]. Germline pathogenic variants affecting DNA double-strand break repair, particularly those associated with homologous recombination

deficiency (HRD), have direct therapeutic relevance, as BRCA1/2 and PALB2 mutations predict enhanced sensitivity to platinum-based chemotherapy and PARP inhibitors [28, 29]. Similarly, germline alterations in MMR genes, associated with microsatellite instability-high (MSI-high) tumors, identify a subset of patients more likely to benefit from immune checkpoint inhibitors [30, 31].

In addition to guiding treatment selection, germline genetic testing has important implications for family members, enabling genetic counseling and the implementation of targeted surveillance and risk-reduction strategies for associated malignancies, including breast, ovarian, prostate, colorectal cancers, and melanoma [14].

3.1.3 BRCA1 and BRCA2 mutations compromise DNA repair mechanisms

DNA damage represents a considerable threat of carcinogenesis if not adequately repaired. The integrity of DNA is particularly jeopardized when DSBs occur [2, 7, 9, 12]. Consequently, it is imperative for cells to possess multiple mechanisms for the repair of DSBs. Two principal pathways are widely acknowledged: homology-directed repair (HDR) and non-homologous end joining (NHEJ) [2, 7, 12]. Inadequacies or defects in HDR result in the accumulation of mutations and, ultimately, genomic instability, thereby elevating the risk of tumorigenesis. Cells that are deficient in either BRCA1 or BRCA2, which are essential for HDR activity, accumulate DSBs, leading to genomic instability and an increased susceptibility to malignant transformation and progression [9, 12].

The BRCA1 and BRCA2 genes encode essential proteins involved in the repair of DSBs via HR. As a result, cancer cells with BRCA mutations have an impaired ability to repair DSBs, which increases their sensitivity to alternative DNA damage repair pathways [32, 33]. As a result, PDAC with gBRCAm demonstrates a heightened sensitivity to both platinum-based chemotherapy and PARP inhibitors. [32, 34].

3.1.4 gBRCA testing in PDAC

Performing germline and somatic sequencing in advanced PC can identify potentially targetable genomic aberrations that impact current standard treatment options. The identification of BRCA mutations, allows family members to benefit from genetic testing and counselling [9]. Germline variants in BRCA genes constitute the most clinically significant molecular abnormalities in PDAC in terms of therapeutic actionability [16]. Approximately 5–8% of unselected patients with PDAC have a gBRCAm [16]. The prevalence of gBRCAm is significantly higher in some populations such as Ashkenazi Jews and African Americans [35, 36]. The most commonly germline BRCA mutation is BRCA2, although additional commonly mutated genes include BRCA1, PALB2, ATM, CDKN2A, and TP53, and MMR genes (MLH1, MSH2, MSH6, and PMS2) [37].

It is well known that BRCA mutations can be germline or somatic [9]. gBRCAm are inherited and present from the time of conception in each cell, as opposed to somatic

BRCA1 or BRCA2 mutations (sBRCAm), which are acquired during life and arise specifically in tumors [16]. Somatic BRCA1/2 mutations are responsible for cases of sporadic PDAC, are detectable only in tumour cells and have been reported in 1-4% of PDAC [9].

In 2018, the NCCN recommended BRCA germline testing (testing blood or skin of non cancer cells) for all individuals with PC. In April 2019, NCCN recommended somatic testing (testing tumor cells) for all patients with advanced PC to evaluate for candidacy for personalized therapies [38].

The accessibility of genetic testing has improved in recent years. As a result, extensive somatic and germline testing in PC has provided a lot of information about the genetic landscape of the disease. Mutations in KRAS, TP53, CDKN2A, and SMAD4 are the major somatic mutations found in PC, with mutations in BRCA1, BRCA2, ATM, and CHEK2 being the most common pathogenic germline variants [39].

It is well established that platinum based chemotherapy is most effective in patients with gBRCAm. In consequence, it is important to identify these patients early at the time of diagnosis. BRCA genetic testing of all patients with PDAC is now recommended by the NCCN and the American Society of Clinical Oncology (ASCO) (Table 1). The value of performing genetic testing in patients with PDAC is well established. Genetic testing not only provides theranostic value through identification of actionable biomarkers, but also diagnostic value, by identifying family members who also carry a gBRCAm.

3.1.5 Therapeutic implications of gBRCAm and associated germline aberrations

Recent data suggest significant therapeutic implications for PDAC patients with germline pathogenic variants in genes regulating DSBs repair, such as homologous recombination deficiency (HRD) and miss-match repair (MMR). Specifically, germline mutations in BRCA1, BRCA2, and increasingly, PALB2 represent the most extensively characterized alterations, which have demonstrated responsiveness to platinum-based chemotherapeutic agents as well as PARP inhibitors. Germline modifications within MMR genes correlated with the microsatellite instability-high (MSI-high) phenotype serve as prognostic indicators for therapeutic response to ICIs. The defect of HR can be useful in increasing the activity of platinum agents or drugs targeting PARP. PARP constitutes a significant family of enzymes that are essential for the cellular response to single-stranded DNA breaks (SSBs), which represent another significant form of DNA damage aside from DSBs. The deficiency of SSB repair in cells with HR deficiencies leads to a state of synthetic lethality. The BRCA1 and BRCA2 genes encode vital proteins that are integral to the repair of DSBs via HR. The inactivation of BRCA1 and BRCA2 genes due to gBRCAm results in a compromised capacity to repair DSBs, thereby escalating reliance on alternative DNA damage response pathways for cellular survival. Consequently, in patients exhibiting gBRCAm, the utilization of platinum-based chemotherapy and PARP

inhibitors enhances the probability of neoplastic cell demise, thereby facilitating tumor control and augmenting overall survival rates. In 2014, Golan et al. reported the results of their retrospective analysis of BRCA1/2-mutant PDAC patients [40]. Among the 58 patients deemed eligible, the OS for individuals with stage I/II disease (n = 15) was not attained after a follow-up of 60 months, whereas it was recorded at 12 months for those with stage III/IV disease (n = 43). Of these 43 patients with stage III/IV disease, twenty-two received platinum-based therapeutic regimens. These patients exhibited a statistically significant enhancement in OS (22 months versus 9 months, respectively; P = 0.039) in comparison to those patients who did not receive platinum-based therapies (n=21).

3-2: Cisplatin-based chemotherapy in treatment of PDAC BRCA mutated:

Commonly used chemotherapeutic regimens for PDAC include FOLFIRINOX, gemcitabine, and nab-paclitaxel, with FOLFIRINOX being the most frequently utilized regimen [41].

In a recent systematic review and meta-analysis [42], authors identified 34 studies of cisplatin efficacy in PDAC, assessing 1599 patients. The majority of the chemotherapy regimens employed involved a combinatory approach incorporating gemcitabine and cisplatin, alongside agents such as 5-fluorouracil, Nab-Paclitaxel, Epirubicin, Capecitabine, and Irinotecan. Regrettably, there was an absence of reported data regarding BRCA status. The OS rate at the one-year mark varied between 38.7% and 41.2%, with an overall response rate (ORR) quantified at 19.2%, and a noteworthy incidence of stable disease reaching 42.3%. The most prevalent toxicities observed included anemia, neutropenia, and abdominal as well as hepatobiliary adverse events, with all-grade incidence rates of 43%, 51%, 55%, and 38%, respectively. In a retrospective study conducted by Fogelman et al. in 2010, treatment with platinum chemotherapy in patients with a family history of breast, ovarian, or pancreatic cancers was associated with a longer survival (22 vs 6 months), whereas platinum use in patients without such a family history of cancer was associated with poor survival. These findings propose that familial history, and potentially BRCA mutations, may function as predictive markers for the application of platinum-based therapies in patients diagnosed with PDAC [37]. Several case series and retrospective studies reported astonishing results in PDAC carrying BRCA mutation who received cisplatin [40, 43-46]. To date, the largest study was reported by Golan et al. [40] showing similar survival differences among BRCA mutant PDAC receiving platinum therapy. In fact, due to the inability to effectively repair DSBs, tumours that harbour a HRD phenotype of BRCA mutation are particularly sensitive to DNA damaging and cross-linking agents such as platinum-based chemotherapy [47]. Wattenberg et al. executed a subset analysis evaluating ORR to each specific regimen administered within the context of BRCA mutant PDAC, revealing that ORR was maximized in patients receiving

cisplatin in conjunction with gemcitabine (66.7%) when contrasted with FOLFIRINOX (60%) and FOLFOX (50%). It is noteworthy that across all regimens, the ORR among BRCA positive patients exceeded the published ORR for FOLFIRINOX. The PFS for BRCA positive patients was recorded at 10.1 months, in contrast to 6.9 months for control patients ($p = 0.0068$), underscoring the enhanced durability of platinum-based therapies and further substantiating the notion that patients with PDAC associated with BRCA or PALB2 mutations exhibit particular sensitivity to platinum treatment [45]. Based on those results, platinum therapy may be particularly desirable for this subset of patients in clinical scenarios marked by high disease burden, symptomatic disease and for patients with locally advanced or borderline resectable tumours where FOLFIRINOX may be poorly tolerated (Table 2). While these studies are promising, the retrospective nature introduces several limitations, preventing them from translating into clinical practice. A limited number of prospective studies addressing this specific inquiry have been conducted. A recent phase II randomized controlled trial explored the efficacy of cisplatin and gemcitabine, with or without Veliparib, a PARP inhibitor, in patients with untreated advanced PDAC and a confirmed germline BRCA mutation or PALB2 [48]. There was no significant difference on the primary endpoint (response rate) with the addition of Veliparib. However, those patients who received cisplatin front line had unprecedented survival rates, with a 2-year survival rate of 30.6% and a 3-year survival rate of 17.8%. No conclusions could be drawn in the absence of a control group.

3-3 PARP inhibitors in treatment of PDAC BRCA mutated

The therapeutic efficacy of PARP inhibitors was initially established in breast and ovarian carcinomas characterized by BRCA mutations. Following the success of these agents in other malignancies associated with BRCA mutations, attention has now transitioned towards applying these insights to PDAC associated with BRCA mutations [2]. Lowery et al. documented in a retrospective analysis three patients with BRCA-mutated PDAC who exhibited a partial radiographic response to treatment with PARP inhibitors, administered either as monotherapy or in conjunction with gemcitabine [2]. A variety of PARP inhibitors have been engineered for clinical use. Olaparib and rucaparib specifically inhibit PARP1, PARP2, and PARP3, whereas Veliparib, niraparib, and talazoparib selectively target PARP1 and PARP3. Currently, multiple phase II clinical trials have investigated PARP inhibitors in patients with PDAC harboring gBRCAm, either as monotherapy, in a maintenance context, or in combination with chemotherapy [9].

3.3.1- PARPi monotherapy

A single-arm, Phase II multicenter investigation conducted by Kaufman et al. encompassed a cohort of 298 patients possessing germline BRCA1/2 mutations and recurrent cancer, all of whom were administered olaparib as monotherapy [7, 9]. Within this cohort, there

were 23 instances of PDAC that progressed following gemcitabine treatment, with 65% previously subjected to a platinum-based therapeutic regimen. The primary endpoint, which was the ORR, was recorded at 21.7%. Regarding the secondary endpoints, 35% of participants exhibited stable disease for a duration exceeding 8 weeks; the median response duration was documented at 134 days; PFS was noted to be 4.6 months; and overall survival (OS) was determined to be 9.8 months. Lowery et al. conducted a single arm, non-randomized, multicenter Phase II trial assessing the effects of veliparib on patients diagnosed with stage III/IV PDAC and possessing established germline mutations in BRCA1/2 or PALB2, who had undergone 1–2 lines of prior therapy [7, 9]. A total of sixteen patients were enrolled in this study, of which fourteen (88%) had previously received platinum-based treatment. The primary endpoint was the ORR, while secondary endpoints comprised PFS, duration of response, OS, and safety. Veliparib demonstrated a favorable tolerability profile; however, no confirmed responses were recorded, although four (25%) patients remained in the study with stable disease [9]. The RUCAPANC trial, evaluated the safety and efficacy of rucaparib in patients with advanced or metastatic PDAC exhibiting germline or somatic BRCA1/2 mutations. This study included 19 patients, comprising 16 individuals with a gBRCAm and 3 with a somatic BRCA mutation. An objective ORR of 15.8% was observed, with a disease control rate of 31.6% across the entire population and 44.4% among patients who had previously received chemotherapy [8, 9, 49]. In accordance with the protocol, enrollment was terminated due to an inadequate ORR among the initial 15 participants.

3.3.2 PARPi as maintenance therapy

In July of 2019, Golan et al published the results of the POLO trial, a phase III, randomised double-blind trial. In this study, patients with metastatic germline BRCA1/2-mutated PDAC who had achieved at least stable disease after four months of platinum-based chemotherapy were randomized to receive either maintenance olaparib or placebo. Of the 3315 patients who were screened for the study, only 154 patients underwent randomization and efficacy analysis. Patients could not have had disease progression or at least 16 weeks of platinum-based chemotherapy and had to harbor a gBRCAm. The study met its primary endpoint: Maintenance olaparib improved median PFS over placebo (7.4 vs 3.8 months, respectively; HR 0.53; 95% CI 0.35-0.82; $P=0.004$), but it did not extend OS by the time the data was reported (18.9 vs 18.1 months; HR=0.91; 95% CI 0.56-1.46; $P=0.68$) [28, 38, 49]. Only 46% of the participants had met the endpoint at the time of data report [2]. Based on 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 weeks of first line platinum chemotherapy [7, 28, 36, 49]. Reiss et al reported another single arm, phase II clinical trial who assessed the role of the rucaparib as maintenance therapy in patients with

advanced PDAC and germline or somatic pathogenic variant in BRCA1, BRCA2 or PALB2, whose cancer had not progressed following at least 4 months of platinum-based chemotherapy. Patients received after discontinuing chemotherapy rucaparib 600 mg orally twice a day until disease progression. The primary end point was PFS at six months. The study included 46 patients, 42 were evaluable. PFS at six months was 59.5% (95% CI, 44.6 to 74.4), median PFS was 13.1 months (95% CI, 4.4 to 21.8) and OS was 23.5 months (95% CI, 20 to 27). The PFS at 12 months was 54.8%. ORR was 41.7%, and disease control rate was 66.7%. Median duration of response was 17.3 months. The authors conclude that maintenance rucaparib is a safe and effective treatment for platinum-sensitive pancreatic cancer with a pathogenic variant in BRCA1, BRCA2 and PALB2 [4, 8, 26, 48].

3.3.3 PARPi in combination with chemotherapy

A phase II open-label, randomized, multicenter study assessed Veliparib in combination with cisplatin and gemcitabine for germline BRCA/PALB2+ PDAC. The trial included untreated patients with measurable stage III to IV disease. Response rates (RRs) served as the primary endpoint [4, 12, 48]. Among the 50 evaluated patients, ARM1 (gemcitabine, cisplatin, and Veliparib) showed a 74.1% RR, while ARM B (without Veliparib) had a 65.2% RR ($P=0.55$). Disease control rate (DCR) was 100% for ARM A and 78.3% for ARM B ($P=0.02$). Median PFS was 10.1 months in ARM A and 9.7 months in ARM B. OS reached 15.5 months for ARM A and 16.4 months for ARM B. The researchers concluded that cisplatin and gemcitabine effectively treat advanced gBRCA/PALB2 PDAC, but adding Veliparib did not enhance RR [2, 4, 48] (Table 3).

3.4 Challenges, Controversies, and Unmet Needs in BRCA-Mutated PDAC

Despite the growing body of evidence supporting platinum-based chemotherapy and PARP inhibitors in BRCA-mutated pancreatic ductal adenocarcinoma (PDAC), several unresolved issues limit the generalizability and clinical impact of current data. Most supporting evidence for platinum sensitivity in BRCA-mutated PDAC derives from retrospective series or small phase II studies, which are inherently subject to selection bias and heterogeneous treatment regimens. Even in the landmark POLO trial, although maintenance olaparib significantly improved progression-free survival, no overall survival benefit was demonstrated at the time of reporting, raising questions about optimal patient selection, treatment sequencing, and crossover effects. Furthermore, the relative clinical relevance of germline versus somatic BRCA mutations remains incompletely defined, as most prospective trials have focused almost exclusively on germline alterations, despite emerging evidence that somatic BRCA and broader homologous recombination deficiency (HRD) phenotypes may confer similar therapeutic vulnerabilities. Additional challenges include the development of acquired resistance to platinum agents and PARP inhibitors through restoration

of homologous recombination, as well as real-world barriers such as limited access to comprehensive genetic testing, cost-effectiveness of long-term PARP inhibition, and disparities in resource-limited settings. Collectively, these considerations underscore the need for refined biomarkers, rational treatment sequencing strategies, and prospective trials incorporating both germline and somatic HRD alterations to optimize personalized therapy in BRCA-mutated PDAC.

Despite the therapeutic advances enabled by BRCA-directed strategies, several limitations and unresolved controversies persist and warrant consideration. The absence of a demonstrated overall survival benefit with PARP inhibitor maintenance in pivotal trials, uncertainties regarding the optimal integration of somatic versus germline BRCA testing, and the emergence of resistance mechanisms to platinum-based chemotherapy and PARP inhibitors remain significant challenges. Moreover, real-world implementation is constrained by unequal access to genetic testing, cost considerations, and variability in healthcare resources, particularly in low- and middle-income settings. Addressing these limitations through prospective trials, improved biomarker stratification, and health system-adapted strategies will be essential to fully realize the promise of precision medicine in BRCA-mutated pancreatic cancer.

4. Perspectives

4.1 Combination PARPi and Immune Checkpoint Inhibitors

Combining ICIs with PARPi represents a novel approach for treating BRCA-mutant cancers [8]. Research indicates that BRCA2-mutant tumors show heightened responsiveness to immune checkpoint blockade, attributed to its impact on the tumor immune microenvironment [50]. In HRD cells, PARPi administration triggers the interferon gene-stimulating factor signaling pathway, leading to DNA accumulation in the cytosol and an inflammatory response. This process enhances lymphocyte infiltration into tumors and increases PDL1 expression [8, 49].

The PARPVAX trial, a randomized phase 1b/2 study, is recruiting patients with platinum-sensitive PDAC to receive niraparib alongside either ipilimumab or nivolumab. Two combination regimens were assessed. Analysis of the BRCA1/2 or PALB2 variant subgroup revealed a median PFS of 3.7 months and median OS of 12.2 months for niraparib plus nivolumab, compared to an extended median PFS of 10.4 months and median OS of 38 months for niraparib plus ipilimumab. These findings suggest that CTLA-4 inhibitors may offer greater benefits when combined with PARPi than PD-1 inhibitors [4].

SWOG S2001, a randomized trial is evaluating pembrolizumab with or without olaparib as maintenance therapy for metastatic PDAC patients with germline BRCA1/2 mutations (NCT04548752) [4, 8]. Multiple studies are investigating PARP inhibitors and immunotherapy combinations, sometimes including additional agents. Examples include trials of PD-1 inhibitor dostarlimab with niraparib in advanced BRCA-

mutated tumors, including PDAC (NCT04673448, NCT04493060), and a closed study of PD-L1 inhibitor avelumab, talazoparib, and MEK inhibitor binimetinib in locally advanced or metastatic RAS-mutated solid tumors (NCT03637491). The MAZEPPA trial is exploring olaparib or kinase inhibitor selumetinib combined with PD-1 inhibitor durvalumab in metastatic PDAC patients with BRCAness, extending beyond BRCA1/2 variants (NCT04348045) [4].

4.2 Combination PARPi and Anti-Angiogenic agents

Substances that inhibit vascular epidermal growth factor (VEGF) families create a low-oxygen environment [4]. Research indicates that this resulting hypoxic tumor microenvironment causes functional deactivation of RAD51 and BRCA without genetic changes in these genes, resulting in a BRCAness phenotype [51, 52]. Encouraging outcomes have been observed when combining PARP inhibitors and VEGF inhibitors in both ovarian and prostate cancers. For ovarian cancer, the PAOLA-1/ENGOT-ov25 phase 3 trial, which examined olaparib and bevacizumab as post-platinum maintenance therapy, showed a significant PFS benefit in patients with BRCA and non-BRCA HRD mutations [53]. A current phase 2 study (NCT02498613) is investigating the combination of olaparib and the anti-VEGF agent cediranib in advanced solid tumors, including pancreatic ductal adenocarcinoma (PDAC).

4.3 Other approaches

Precision Promise (PrP) and the PRECISION initiative are interconnected in their approach to PC treatment, focusing on novel strategies for therapy and drug advancement. These platforms strive to improve personalized medicine for PDAC through flexible trial designs and biomarker discovery. PrP is a phase 3 Bayesian adaptive platform trial that assesses multiple therapies for metastatic PDAC, allowing for dynamic adjustments based on effectiveness data, [54, 55]. It seeks to broaden patient access to effective treatments by allocating patients to experimental groups or established control treatments, such as gemcitabine and nab-paclitaxel [54].

The PRECISION initiative, working alongside PrP, concentrates on uncovering therapeutic biomarkers to customize treatments according to individual patients' tumor characteristics [56]. This initiative underscores the importance of tailored approaches in oncology, especially in the challenging field of pancreatic cancer [57, 58].

In conclusion, germline mutations in BRCA1, BRCA2, and related genes like PALB2 have profound implications for PDAC, influencing both disease risk and treatment strategies. These mutations disrupt the normal function of tumor suppressor genes, particularly in the context of DNA repair through HR. As a result, cells harboring these mutations exhibit increased genomic instability, leading to the development of cancer, including PDAC.

The presence of BRCA mutations in PDAC patients not only indicates a genetic predisposition to the disease but also has significant therapeutic implications. Notably, tumors with BRCA mutations demonstrate increased

sensitivity to platinum-based chemotherapy and PARP inhibitors. These treatments exploit the defective DNA repair mechanisms in BRCA-mutated cancers, leading to increased efficacy and improved patient outcomes. The therapeutic implications of BRCA mutations in PDAC have led to the inclusion of genetic testing in clinical guidelines by organizations such as the (NCCN) and the American Society of Clinical Oncology (ASCO). These guidelines recommend genetic testing for all PDAC patients to identify those with germline BRCA mutations. For instance, platinum-based chemotherapies have shown enhanced effectiveness in BRCA-mutated PDAC, improving survival rates and offering a more personalized treatment approach. Additionally, PARP inhibitors have emerged as a promising treatment option, particularly in maintenance therapy to prolong PFS. Beyond direct patient care, genetic testing for BRCA mutations also has implications for family members, enabling genetic counseling and the implementation of surveillance strategies for those at increased risk. This proactive approach allows for earlier detection in individuals who may be predisposed to PDAC and other BRCA-associated cancers.

In conclusion, the integration of BRCA genetic testing into the management of PDAC represents a significant advancement in personalized medicine. By identifying patients with gBRCAm, clinicians can tailor treatment strategies that improve outcomes and potentially extend survival. Ongoing research and clinical trials are crucial to refining these approaches and expanding their application to benefit a broader range of patients with PDAC and other BRCA-associated cancers.

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Statement of Transparency and Principles

- The authors declare no conflict of interest.
- The study was approved by the Research Ethics Committee of the authors' affiliated institution.
- All authors contributed to the implementation of this research.

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