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REVIEW ARTICLE

Clinical Studies

BRCA-mutant pancreatic ductal adenocarcinoma

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Despite continued research, pancreatic ductal adenocarcinoma (PDAC) remains one of the main causes of cancer death. Interest is growing in the role of the tumour suppressors breast cancer 1 (BRCA1) and BRCA2—typically associated with breast and ovarian cancer—in the pathogenesis of PDAC. Indeed, both germline and sporadic mutations in *BRCA1/2* have been found to play a role in the development of PDAC. However, data regarding *BRCA1/2*-mutant PDAC are lacking. In this review, we aim to outline the specific landscape of *BRCA*-mutant PDAC, focusing on heritability, clinical features, differences between *BRCA1* and *2* mutations and between germline and sporadic alterations, as well as established therapeutic strategies and those that are still under evaluation.

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BACKGROUND

Pancreatic ductal adenocarcinoma (PDAC) represents the most common form of pancreatic cancer. It is the seventh leading cause of cancer death worldwide, with an estimated 9% 5-year survival rate [1, 2]. It usually arises in elderly patients, with a mean age at onset of 71 years for men and 75 years for women [1, 2]. The mainstay of PDAC treatment is chemotherapy; however, this malignancy still has a poor prognosis, and research efforts are thus focused on identifying new therapeutic targets and strategies in addition to investigating the genomic landscape of this genetically and biologically heterogeneous tumour type [2–9]. The vast majority (>80%) of PDAC cases have a sporadic origin, whereas only a small proportion (<10%) result from inherited germline mutations [10–12]. *KRAS* (90%), *CDKN2A* (90%), *TP53* (70%), *SMAD4* (55%), chromatin (20%), DNA repair (17%), cell-cycle regulators (15%), *WNT* (10%), Robo/slit pathway (5%), Notch signalling (5%) have been identified as the main molecular pathways and genes involved in PDAC development [2, 13].

The genes encoding breast cancer 1 and 2—*BRCA1* and *BRCA2*—play a crucial role in the response to DNA damage, by mediating the repair of DNA double-strand breaks (DSBs) via homologous recombination (HR) [14]. *BRCA1/2*-deficient cells that lack HR activity accumulate DSBs, resulting in genomic instability and an increased predisposition to malignant transformation and progression [15, 16]. Germline *BRCA1/2* mutations are found in approximately 5–10% of cases of familial PDAC and approximately 3% of cases of apparently sporadic PDAC [17], and, after breast cancer and ovarian cancer, PDAC has been reported to be the third most common cancer associated with these mutations [2, 18]. Histologically, although the majority of pancreatic cancers associated with germline and somatic *BRCA* mutations comprise PDAC, both mutation types have also been reported in acinar cell carcinomas of the pancreas, which are much rarer [19]. Epidemiology studies and a study examining loss of *BRCA2* heterozygosity in PDAC tissue suggested a reliable link between *BRCA2* carriers and an increased PDAC risk (relative risk in 222 *BRCA2*-mutant families assessed by Moran et al.: 4.1, 95% confidence interval [CI], 1.9–7.8; standardised incidence ratio in 459 *BRCA2*-mutant patients evaluated by Mersch et al.: 21.7, 95% CI, 13.1–34.0; $P < 0.001$); however, this association is not as clearly defined for *BRCA1* carriers [20–25]. Indeed, in *BRCA2*-mutant patients, the relative risk is ~3–4-fold higher (3.51, 95% CI 1.87–6.58) [21]. For *BRCA1* carriers, the relative risk is estimated to be two-fold higher (2.26, 95% CI 1.26–4.06), but some studies have failed to identify any significant association between *BRCA1* mutations and PDAC, suggesting a low penetrance for this malignancy [14, 15, 20].

In this review, we aim to outline the specific landscape of *BRCA*-mutant PDAC, focusing on heritability, clinical features, and differences between *BRCA1* and *BRCA2* mutations and between germline and sporadic alterations. We also discuss established therapeutic strategies based on the increased sensitivity of *BRCA*-mutant cells to platinum-based drugs and PARPi, as well as alternative approaches that are under evaluation.

Mutant *BRCA* versus wild-type *BRCA* in PDAC

PDAC caused by mutations in *BRCA1/2* seems to be different to PDAC occurring in the general population. Generally, PDAC patients belonging to families with known *BRCA1/2* mutations are a decade younger [26]. In *BRCA1*-mutant families, the mean

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age at PDAC diagnosis is 62.9 (standard deviation 12.0) with a median age of 59 (range 45–80) in males and 68 (range 38–87) in females (male:female ratio=2.00), whereas in *BRCA2*-mutant families, the mean age at diagnosis is 62.9 (standard deviation 11.7), with a median age of 67 years (range 39–78) in males and 59 (range 46–81) in females (male:female ratio = 1.11) [27]. Differences in patient survival and molecular landscape between *BRCA*-mutant and wild-type PDAC have also been investigated.

BRCA mutations and patient survival

Most *BRCA* alterations in PDAC are frame-shifting indels, stop-gain mutations and splice-site mutations; single-nucleotide substitutions are rare [28]. *BRCA1/2* mutations can be classified as definitely pathogenic; likely pathogenic; uncertain, likely not pathogenic or of little clinical significance; not pathogenic; or of no clinical significance [29]. The results of genetic tests and the analysis of tumour signatures, which play a key role in the detection of different variants, thus give an important indication of the pathogenicity and the implications of a detected mutation. However, the rarity of the diagnosis of *BRCA1/2*-mutant PDAC, compounded by the infrequent nature of genetic testing, has led to the publication of only a few studies assessing the impact of *BRCA* mutations on the survival of patients, with controversial results [26, 30–33]. A retrospective, single-institution, case-control study demonstrated that the presence of a germline *BRCA1/2* mutation in patients with resected, sporadic PDAC was independently associated with inferior overall survival (OS) and inferior disease-free survival compared with matched *BRCA*-wild-type patients [17]. Takeuchi et al. [34] analysed the presence of mutations in the entire coding region of the *BRCA* pathway genes (*BRCA1*, *BRCA2* and partner and localiser of BRCA2 (*PALB2*) in 42 surgically resected PDAC tumours, and assessed their correlation with clinical-pathological features. Thirteen rare germline mutations were identified in the *BRCA* pathway genes and their functional effect was examined using online prediction programs, including ClinVar. One frameshift mutation (BRCA2S2148fs) was considered to be pathogenic, seven as being of uncertain significance or having conflicting interpretations of pathogenicity, and three as benign; 'no information' on the predicted effect of the other mutations was available. BRCA2R18H and BRCA2G2044V were apparently enriched in tumour cells. However, in contrast with the case-control study outlined above, patients with potentially deleterious mutations (such as pathogenic, conflicting, uncertain) in *BRCA* pathway genes, or those with no information, had a significantly better prognosis than those without mutations or with benign mutations as assessed by ClinVar (5-year OS was 68.6% versus 19.2%, respectively; $P = 0.031$ by log-rank test) [34]. Since *BRCA1/2* has a crucial tumour suppressor role, the better prognosis observed in patients with deleterious mutations of these genes might appear unexpected and it is indeed not exactly understood. Most patients received adjuvant chemotherapy with S-1 and gemcitabine (only some patients were treated with cisplatin) and no significant differences in chemotherapy administration were reported among the cohorts, thus excluding a key prognostic role of chemotherapy in patients with genomic instability. Notably, these data should be considered with caution due to the retrospective nature of this study and the small sample size, which prevent from drawing definitive conclusions. Further prospective and larger studies are needed to explore the prognostic role of *BRCA1/2* deleterious mutations.

The effect of BRCA mutations on the molecular landscape of PDAC

Little is known about the molecular differences that might exist between PDAC patients with mutated *BRCA1/2* and those with wild-type *BRCA1/2*. An immunohistochemistry and next-generation sequencing evaluation of 2818 PDAC samples identified *BRCA1* mutations in 1.3% and *BRCA2* mutations in 3.1% of samples; concomitant mutations in *PALB2* were not reported. The mutational profile of PDAC samples from *BRCA*-mutant patients was significantly different from that of patients with wild-type *BRCA1/2* PDAC. Indeed, mutations in *TP53* and *CDKN2A* were less frequent in *BRCA*-mutant PDAC samples than in *BRCA*-wild-type PDAC samples, whereas mutations in *APC*, *SETD2*, *FLCN*, *ERBB3*, *SUFU*, *WT1* and *KMT2A* were more common. Notably, these differences in the mutational profile might reflect the pathways and mediators involved in carcinogenesis in *BRCA1/2*-mutant and wild-type PDAC, thus suggesting the existence of potential differences in this process between mutant and wild-type tumours. Moreover, 4.8% of *BRCA*-mutant PDAC samples showed microsatellite instability high/deficient mismatch repair (MSI-H/dMMR) status versus 1.2% of wild-type *BRCA1/2* samples; the tumour mutational burden was higher in the *BRCA*-mutant PDAC samples compared with the wild-type *BRCA1/2* samples irrespective of microsatellite status [35]. Further studies are required to assess the real impact of the presence or absence of *BRCA* mutations on the molecular landscape of PDAC, which is likely to impinge on patient prognosis and have implications for treatment.

BRCA mutations and heritability in PDAC

Among the genes that are considered to be involved in PDAC susceptibility, *BRCA1*, *BRCA2*, *PALB2* and *CKDN2A* appear to account for the majority of known genetic causes of hereditary PDAC [18, 36–39].

BRCA1/2 mutations and family history

Familial pancreatic cancer (FPC) is a term that can be applied to families with at least two first-degree relatives with PDAC who do not fulfil the criteria for other familial cancer syndromes, and is responsible for 10% of cases of PDAC [36–41]. Data on the genetic basis of FPC largely arise from the observed increase in the risk of pancreatic cancer in patients with hereditary cancer syndromes. Many of the studies included only patients with mutated *BRCA2*; in patients with FPC, the prevalence of *BRCA2* mutations was found to be 3–17% in the case of ≥3 relatives with PDAC history, whereas, in unselected patients, the prevalence of *BRCA2* mutations has been reported to be 5–7% [23, 42, 43]. These prevalence data show an increase of detected *BRCA2* mutations when a selection of patients according to PDAC family history is applied.

The PACGENE study [44] found that the 8% of probands who have a first-degree relative with PDAC—unselected for hereditary cancer syndrome patterns or genetic mutational status—harbour a deleterious mutation in one of four genes: *BRCA1*, *BRCA2*, *PALB2* and *CDKN2A*. Probands with relatives other than first-degree relatives with PDAC might also carry a deleterious mutation in the same four genes, although with significantly less probability. The researchers confirmed that these four genes together harbour approximately 5–10% of deleterious mutations in FPC. Overall, any proband with a family history of PDAC has a 6.7% probability of carrying a deleterious mutation in one of these genes. Mutations in *BRCA2* and *CDKN2A* were detected more often than those in *BRCA1* and *PALB2*, consistent with the published literature [42, 43, 45, 46]. Furthermore, the authors also found a younger age of onset of PDAC among probands with a mutation in one of the four genes. A specific age at which to define early-onset pancreatic cancer has not been identified yet, although a cut off of 50 years old has been considered in previous studies of FPC [47, 48]. Having a member of the family with a young-onset pancreatic cancer confers an added risk in FPC kindreds; this finding might help tailoring the clinical/genetic counselling and screening proposal to families with high risk of developing PDAC [48]. Interestingly, the number of family members affected by PDAC did not correlate with the probability of detecting deleterious mutations [44].

BRCA1/2 mutations and ethnicity

It is important to indicate that population ethnicity influences the prevalence rates of *BRCA1/2* mutations and should be taken in consideration when interpreting the literature. In particular, one of the most studied populations is represented by the Ashkenazi Jews (AJs), who have become the subject of many genetic studies of FPC and other related *BRCA*-mutant cancer syndromes. In the AJ population, up to 21% of patients with PDAC harbour a *BRCA1/2* mutation [49, 50]. AJs are known to have founder mutations in *BRCA1* (185_186delAG and 5382insC in 0.4% and 0.1%, respectively, of AJ women) and *BRCA2* (6174delT in 0.6% of Ashkenazi women) that underlie hereditary breast cancer [22, 45, 46]. These founder mutations might also contribute to PDAC predisposition; however, few prospective studies are available and most data derive from clinical database reviews. Ferrone et al. identified that, of 187 Jewish patients who underwent surgery for PDAC, 5.5% of patients with AJ ancestry (unselected for family history of cancer) harboured one of the three common AJ founder mutations (185_186delAG, 5382insC or 6174delT); in AJ families with a history of breast cancer and PDAC, 14.2% were found to carry a mutation in *BRCA1* or *BRCA2*, with nearly equal distribution between the two genes [30, 51]. Salo-Mullen et al. reported that *BRCA2* was the most common gene found to be altered in a series of patients with PDAC who presented for clinical cancer genetics evaluation, accounting for 54% of all identified pathogenic mutations; 85.5% of patients had either a personal history of a second malignancy or at least one first or second degree relative with a history of breast cancer, ovarian cancer, colorectal cancer or PDAC [52]. Overall prevalence of *BRCA1/2* mutations in AJ patients is reported to be 2.5%, that is approximately five times higher than prevalence in the general population [53, 54].

In a large prospective analysis, Holter et al. reported the prevalence of germline *BRCA1/2* mutations in a cohort of unselected patients with incident PDAC diagnosis. Clinical and family histories of these patients were assessed in an attempt to determine predictive factors for genetic testing. Germline *BRCA* mutations were identified in 4.6% of the patients: 1% had a *BRCA1* mutation and 3.6% had a *BRCA2* mutation. Notably, 12.1% of AJ patients were *BRCA*-mutant, compared with 3.7% of non-AJ patients [11]. The absence of a significant family history in the majority of patients with an established deleterious germline mutation might be the result of incomplete penetrance, rather than a de novo germline mutation, which has not been well studied in PDAC [55].

Smith et al. [56] recommend reflex testing for germline mutations in *BRCA1*, *BRCA2*, *PALB2* and *ATM* for patients with French–Canadian/AJ ancestry, and full gene sequencing of patients with incident pancreatic cancer ≤50 years or with family history criteria. Reflex testing is also recommended by the National Comprehensive Cancer Network in the Genetic/Familial High-Risk Assessment [57].

Genetic testing

Regardless of the ethnicity, the identification of *BRCA* mutations allows family members to receive genetic testing and counselling [58]. Genetic counselling is recommended for patients harbouring a pathogenic mutation and for those with a positive family history of cancer, especially PDAC, regardless of mutation status [57, 59, 60]. The American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines recommend germline testing using comprehensive multigene panels for hereditary cancer syndromes that are associated with an increased risk of PDAC for all PDAC patients, irrespective of family history. Indeed, test panels allow individuals to be simultaneously assessed for mutations in multiple genes associated with cancer (generally *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *PALB2*, *STK11*, *MLH1*, *MSH2*, *MSH6* and *PMS2*) [61]. The use of this approach has confirmed the presence of actionable *BRCA1/2* pathogenic, or likely pathogenic, variants (0–3% for *BRCA1* and 1–6% for *BRCA2*, respectively) in unselected PDAC population, thus suggesting potential therapeutic implications [57, 62].

Evidence suggests that screening in high-risk subjects is associated with down-staging of incident tumours, although larger studies are needed to confirm the long-term survival benefit. PDAC screening can be considered for first-degree relatives of individuals with FPC and/or individuals with a family history of PDAC who harbour pathogenic germline variants in genes associated with PDAC susceptibility, after extensive discussion on potential risks/benefits and limitations of surveillance, and should be performed at high-volume centres of expertise. Surveillance could be performed using contrast-enhanced pancreas magnetic resonance imaging/magnetic resonance cholangiopancreatography and/or endoscopic ultrasonography [57, 59, 60]. Furthermore, as many of the germline mutations associated with an increased risk of PDAC are also associated with highly penetrant hereditary cancer syndromes (e.g. Lynch syndrome, hereditary breast cancer and ovarian cancer), and consequently with a higher risk of other cancers, effective strategies for the prevention and screening of these tumours should also be offered [59].

Germline *BRCA* mutations and somatic *BRCA* mutations in PDAC

It is well known that *BRCA* mutations can be germline or somatic [49]. Somatic *BRCA1/2* mutations are responsible for cases of sporadic PDAC, are detectable only in the tumour tissue and have been reported in 1–4% cases of PDAC [35].

'Apparent' sporadic PDAC

Sporadic PDAC that harbours somatic *BRCA* mutations and 'apparently' sporadic PDAC with germline *BRCA* mutations comprise two different entities. Sindo et al. investigated the prevalence of deleterious germline *BRCA1/2* mutations in apparently sporadic PDAC—that is, cases of PDAC with no significant family history of cancer—by sequencing 32 genes, including known pancreatic cancer susceptibility genes, from the DNA of normal (i.e. non-tumour) tissue obtained from 854 patients with PDAC. Thirty-three of these patients presented with a deleterious germline mutation: 12 involved the *BRCA2* gene and three involved the *BRCA1* gene [55]. It has also been reported in different studies that a percentage of non-selected patients with PDAC harboured a germline *BRCA1/2* mutation [11, 23]. Table 1 shows the occurrence of germline *BRCA* mutations in apparently sporadic PDAC [11, 55, 63–66]. Another study revealed a down-regulation of *BRCA1* expression at the RNA level in patients with

Table 1. Prevalence of germline *BRCA1/2* mutations in apparently sporadic pancreatic cancer.

Authors/year	Total no. of PDAC patients	*BRCA1/2* mutations no. patients (%)	Reference
Holter et al., 2015	306	*BRCA1*: 3 (0.98%) *BRCA2*: 11 (3.59%)	[11]
Shindo et al., 2017	854	*BRCA1*: 3 (0.35%) *BRCA2*: 12 (1.4%)	[55]
Grant et al., 2015	290	*BRCA1*: 1 (0.34%) *BRCA2*: 2 (0.68%)	[63]
Hu et al., 2018	2999	*BRCA1*: 18 (0.6%) *BRCA2*: 57 (1.9%)	[64]
Brand et al., 2018	298	*BRCA1*: 4 (1.34%) *BRCA2*: 4 (1.34%)	[65]
Yurgelun et al., 2019	289	*BRCA1*: 3 (1.03%) *BRCA2*: 4 (1.38%)	[66]

PDAC pancreatic ductal adenocarcinoma.

Table 2. Main clinical studies of platinum-based therapy in *BRCA*-mutant pancreatic ductal adenocarcinoma.

Authors/year	Study design	No. of patients	Disease stage	Results in *BRCA1/2*-WT patients	Results in *BRCA1/2*-mutant patients	*P*	Reference
Golan et al., 2014	Retrospective analysis	43	III–IV	mOS 13 months	mOS 15 months	0.77	[26]
Reiss et al., 2018	Retrospective Case-control	70	III–IV	mOS 15.5 months	mOS 20.1 months	0.002	[79]
Golan et al., 2017	Retrospective case-control	74	I–II	mOS 43.8 months	mOS 44.4 months	0.775	[32]
Yu et al., 2019	Retrospective case-control	96	I–II	mOS 23.2 months	mOS 46.6 months	0.0156	[80]
Wattenberg et al., 2020	Retrospective case-control	78	III–IV	ORR 21%	ORR 58%	0.0022	[81]
O Reilly et al., 2020	Phase II, randomised	50	III–IV	–	RR 74.1% cisplatin–gemcitabine (arm A) versus 65.2% cisplatin–gemcitabine plus veliparib (arm B)	0.55	[82]

WT wild type, *mOS* median overall survival, *m* months, *ORR* objective response rate, *RR* response rate.

chronic pancreatitis, and downregulation at both the RNA and protein levels in sporadic PDAC, demonstrating a correlation between *BRCA1* expression and PDAC development [67]. These data highlight the importance of extending the criteria used to determine the appropriateness of gene testing beyond the existence of a significant family history in order to avoid missing known deleterious pancreatic cancer susceptibility gene mutations that could potentially be targeted.

BRCA1/2 mutations and treatment potential

The identification of a germline *BRCA1* or *BRCA2* mutation is often used to stratify patients for treatment with platinum-based therapy or poly-ADP ribose polymerase (PARP) inhibitors (PARPi, see below). However, heterogeneous responses are often seen using this approach, prompting Wang et al. to develop a predictive and prognostic model of germline *BRCA*-mutant PDAC in the preclinical setting. In the case of homologous repair deficiency (HRD), tumour polyploidy and a basal-like transcriptomic subtype were independent predictors of poorer survival; HRD genomic hallmarks were crucial for sensitivity to platinum and PARPi, whereas tumour polyploidy predicted resistance [68].

Although no specific data are available regarding somatic *BRCA*-mutant PDAC and platinum-based treatment, a new classification based on whole-genome sequencing indicates that most somatic *BRCA*-mutant and germline *BRCA*-mutant PDACs seem to be part of the unstable subtype, characterised by the presence of genomic instability, with an apparent increased response to platinum-derived therapies both in patients and in patient-derived xenografts, suggesting that no difference in treatment response exists between somatic and germline mutations [69–71]. Different studies have investigated or are still studying the effect of PARPi in *BRCA*-mutant PDAC [72–74]. However, only a few studies have considered both germline and somatic mutations. Among them, a Phase II multicentre study evaluated the efficacy and safety of rucaparib in 19 patients with germline/somatic *BRCA1/2*-mutant locally advanced or metastatic PDAC. Three patients had an objective response; of these, two harboured somatic *BRCA2* mutations [73]. A Phase II open label study will evaluate the effectiveness, safety, and anti-tumour activity of rucaparib in patients with advanced germline/somatic *BRCA1/2*-mutant or *PALB2*-mutant PDAC (NCT03140670) [75]. The prevalence of these mutations and their association with improved clinical outcomes are also the tertiary objectives in a Phase II randomised study in which the primary objective will be the efficacy of modified 5-fluorouracil, irinotecan, levofolinic acid (mFOLFIRI) and veliparib compared to a control arm of FOLFIRI in patients with metastatic PDAC (NCT02890355). Very few studies focus on both germline and somatic mutations, since most consider only germline alterations. Furthermore, no comparative studies between PDAC with germline mutations versus PDAC harbouring somatic mutations assessing potential differences with respect to clinical tumour behaviour, response to treatment and clinical outcomes are available.

BRCA-mutant PDAC and platinum-based therapy

Platinum-based chemotherapies exert their cytotoxic effect by binding directly to DNA, causing crosslinking of DNA strands and inducing DNA DSBs, which cannot be effectively repaired in the presence of *BRCA* mutations [76]. An enhanced sensitivity to platinum-based chemotherapies was first demonstrated in *BRCA1/2*-mutant breast cancer and ovarian cancer [77, 78]. Accordingly, the potential benefit of these has been evaluated in PDAC patients who harbour *BRCA1/2* or *PALB2* germline mutations, both in the early and advanced setting (Table 2).

Focus on stage I–II disease

Golan et al. [32] assessed the predictive and prognostic impact of pathogenic germline *BRCA/PALB2* mutations in patients with

resected PDAC in a retrospective case-control, multi-institution study. Globally, 25 patients with resected *BRCA1/2*-mutant PDAC were matched to 49 wild-type control subjects. No statistically significant differences in median OS (mOS), the primary endpoint (37.06 versus 38.77 months, $P = 0.838$), or median disease-free survival (14.3 versus 12.0 months, $P = 0.303$) were observed between cases and controls. However, when patients who were treated with platinum chemotherapy in the perioperative setting were analysed, a non-significant trend towards improved disease-free survival was observed among *BRCA*-mutant patients ($n = 10$) as compared with controls ($n = 7$) (39.1 versus 12.4 months, $P = 0.255$); no difference in OS was reported (43.8 months for *BRCA*-mutant patients versus 44.4 months for controls; $P = 0.775$) [32].

Another retrospective case-control study [80] analysed 32 patients with germline *BRCA/PALB2* mutations and resected PDAC matched to 64 mutation-negative patients. In each group, 11 patients received perioperative platinum chemotherapy ($n = 13$ 5-fluorouracil, oxaliplatin, irinotecan, levofolinic acid [FOLFIRINOX], $n = 4$ 5-fluorouracil, oxaliplatin, levofolinic acid [FOLFOX], $n = 1$ capecitabine, oxaliplatin, levofolinic acid, $n = 1$ carboplatin/gemcitabine, $n = 2$ cisplatin/gemcitabine, $n = 1$ oxaliplatin/gemcitabine). The mOS (primary endpoint) was 46.6 months in the *BRCA*-mutant group compared to 23.2 months in the *BRCA*-wild-type group (hazard ratio [HR] 0.49; $P = 0.0156$). In this population, a survival advantage in patients with *BRCA*-mutant PDAC compared to those with wild-type PDAC, rather surprisingly since mutation involving tumour suppressors are expected to be related to worse survival. However, due to the retrospective nature of the study, these findings should be considered with caution. The subgroup analysis of patients treated perioperatively with platinum showed that the mOS was not reached in the mutant group, versus 23.1 months in the *BRCA*-wild-type group (HR 0.12; $P = 0.0193$). Finally, when *BRCA*-mutant patients were evaluated by platinum exposure, a trend toward an improvement in mOS was observed among those who received perioperative platinum ($n = 11$) versus patients who did not ($n = 15$) (HR 0.52; $P = 0.0421$) [80].

Focus on stage III–IV disease

In 2011, Lowery et al. [83] reported partial ($n = 4$) or complete ($n = 1$) radiological responses in five out of six *BRCA*-mutant PDAC patients treated with platinum-based first-line chemotherapy. This favourable finding was supported by the publication in the same year of a complete pathological response of a case report treated with cisplatin-based therapy [84]. In 2014, Golan et al. reported the results of their retrospective analysis of *BRCA1/2*-mutant PDAC patients. Among the 58 eligible patients, mOS was not reached for patients with stage I/II disease (n = 15) after 60 months but was 12 months for those with stage III/IV ($n = 43$) disease. Twenty-two out of these 43 patients with stage III/IV disease received platinum-based therapies: 18 were treated with cisplatin/gemcitabine, 3 with FOLFIRINOX and 1 with oxaliplatin/gemcitabine. These patients showed a statistically significant improvement in OS (22 versus 9 months, respectively; $P = 0.039$) compared with those patients who didn't receive platinum ($n = 21$). No statistically significant differences in survival outcomes were found between the *BRCA1*-mutant subgroup and the *BRCA2*-mutant one (mOS 15 versus 13 months, respectively; $P = 0.77$) [26]. Reiss et al. later performed a retrospective case-control study on 29 *BRCA/PALB2*-mutant patients with advanced PDAC patients who were matched to 58 control subjects (non-carriers or untested). A statistically significant benefit in OS (primary endpoint) was observed in the mutation-positive patients compared to the matched controls (mOS: 21.8 versus 8.1 months, respectively. HR 0.35; $P < 0.001$). When patients who received platinum-based chemotherapy were analysed ($n = 18$), a statistically significant benefit in OS was observed in the mutation-positive group compared with control patients (mOS at a median follow-up of 20.1 months: not reached versus 15.5 months, respectively; HR 0.25; $P = 0.002$), whereas no significant survival differences were reported in patients who were not treated with platinum (HR 0.54; $P = 0.12$). Subgroup analysis comparing oxaliplatin to cisplatin did not show any difference between the different regimens administered (i.e. FOLFIRINOX, FOLFOX, cisplatin/gemcitabine, other not specified platinum therapies) [79].

Wattenberg et al. [81] evaluated the impact of platinum-based therapies in terms of objective response in a 2020 retrospective, case-control analysis. The authors analysed the effect of platinum-based therapies in 26 patients with germline mutations in *BRCA1/2* or *PALB2* and 52 matched control patients with advanced PDAC; FOLFIRINOX was the most commonly used regimen in the control group, whereas a significantly higher number of mutation-positive patients received cisplatin/gemcitabine. The primary endpoints were objective response rate (ORR) and real-world progression-free survival (rwPFS). The ORR was significantly higher in mutation-positive patients treated with platinum-based therapies compared with the control group (58% versus 21%; $P = 0.0022$). No significant difference in ORR was observed among the different platinum-based regimens in the mutant patients ($P = 0.814$). Conversely, all objective responses in the control group occurred in patients treated with FOLFIRINOX. Notably, mutation-positive patients who received first-line platinum therapy had a significantly better ORR than matched control patients (68% versus 29%; $P = 0.007$) and a numerically higher ORR when compared to mutation-positive patients who received platinum in the second-line setting (68% versus 20%; $P = 0.0507$). Moreover, mutation-positive patients had a significantly longer rwPFS than control patients (median rwPFS 10.1 versus 6.9 months, HR 0.43; $P = 0.0068$), and those mutation-positive patients who received first-line platinum had a longer rwPFS (21.1 months) than control patients (7.9 months; $P = 0.0046$) and mutation-positive patients treated with platinum therapy in the second- or later lines (2.5 months; $P = 0.0001$) [81].

Because of their retrospective nature, small sample size, frequent lack of a control group and heterogeneity of platinum therapies, none of these studies was able to demonstrate the superiority of one platinum-based regimen over another in *BRCA/PALB2*-mutant patients. However, despite the limitations of these studies, the results from all of them suggest that patients with germline *BRCA/PALB2*-mutant PDAC represent a small, but clinically significant, subset who might benefit from cytotoxic therapies, such as platinum-based chemotherapy, in the presence of defective HR. To date, unfortunately, no data are available to assume that these observations might be extended to PDAC patients with somatic alterations in these genes.

PARP inhibitors in *BRCA*-mutant PDAC

PARP enzymes, which polymerise ADP-ribose units, play a key role in the repair of single-stranded DNA breaks through the base-excision repair system. PARP-1 is crucial in this process and represents the main target of PARPi in *BRCA1/2*-mutant tumours, on the basis of the mechanism of synthetic lethality [85], a phenomenon in which the combination of two gene perturbations leads to cell death, whilst the perturbation of either of two genes individually has no detrimental effect. In the absence of functional *BRCA1/2*- or *PALB2*-encoded proteins, PARP-1 is over-expressed in order to compensate for their reduced activity [86]. PARPi bind to the catalytic site of PARP enzymes, blocking their activity and simultaneously trapping them inside the DNA, which leads to the collapse of the replication forks. Thus, PARPi leads to a significant accumulation of DSBs, resulting in cell death [85, 87].

Various PARPi have been developed (Fig. 1). Olaparib and rucaparib target PARP-1, PARP-2 and PARP-3, whereas veliparib, niraparib and talazoparib target PARP-1 and PARP-3. Each PARPi shows different catalytic inhibition and PARP trapping potency—the ability to trap PARP–DNA complexes. Notably, the PARP trapping potency, rather than the IC_{50}, seems to be the main

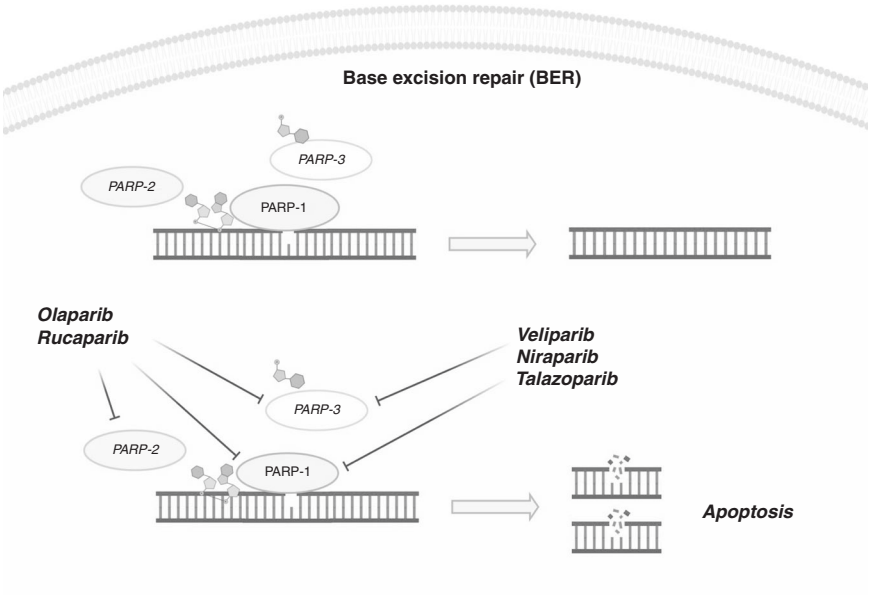

Fig. 1 PARP inhibitors in *BRCA1/2*-mutant pancreatic cancer. The figure shows the PARP inhibitors that have been evaluated in pancreatic ductal adenocarcinoma, together with their mechanism of action. PARP enzymes are crucial in the homologous recombination system, particularly in base-excision repair. By binding to the catalytic site of PARPs, PARP inhibitors block their activity and trap the enzymes inside the DNA. PARPi lead to a significant accumulation of DNA double-strand breaks, resulting in cell death through the phenomenon of synthetic lethality when *BRCA1/2* is deficient. Olaparib and rucaparib target PARP-1, PARP-2 and PARP-3, whereas veliparib, niraparib and talazoparib target PARP-1 and PARP-3. *PARP* poly-ADP ribose polymerase.

driver for cytotoxicity. Therefore, the different PARP trapping capacities of the PARPi might be quite relevant in influencing the capability to induce the cell death [85, 88].

The first preclinical studies that showed the high lethality of PARPi in cancer cells harbouring *BRCA* mutations were published in 2005 [86, 89]. Subsequent Phase I studies investigated the optimal dose of these drugs and demonstrated their efficacy in *BRCA*-mutant solid tumours. These Phase I/Ib studies with PARPi were performed on advanced solid tumours; some focused mainly on breast cancer and ovarian cancer, but all of them showed good results in terms of ORR [90–92]. Further Phase II studies with different PARPi have been conducted on advanced solid tumours with germline *BRCA1/2* mutations, including PDAC. Some trials have focused on PARPi monotherapy, others on PARPi maintenance therapy and on a combination of PARPi and chemotherapy (Table 3).

PARPi monotherapy

A single arm, Phase II study by Kaufman et al. [72] included a cohort of patients with germline *BRCA1/2*-mutant advanced PDAC progressing after gemcitabine (65% pretreated with a prior platinum-based regimen) who received olaparib. The primary endpoint, the ORR, was 22%. In terms of secondary endpoints, 35% reached stable disease at >8 weeks; the median duration of response was 134 days; PFS was 4.6 months; and OS was 9.8 months. The most frequent adverse events of any grade were fatigue (74%), nausea (48%), vomiting and anaemia (40%).

Lowery et al. [93] conducted a Phase II trial of veliparib on patients with stage III/IV PDAC and known germline mutations in *BRCA1/2* or *PALB2* who had been pretreated with 1–2 lines. The primary endpoint was ORR; secondary endpoints included PFS, duration of response, OS and safety. Veliparib showed a good tolerability profile, but no confirmed response was observed, although four (25%) patients remained on the study with stable disease for ≥4 months.

The RUCAPANC trial, by Shrofft et al. [94], assessed the safety and efficacy of rucaparib in advanced or metastatic PDAC patients with germline or somatic *BRCA1/2* mutations. The study enrolled 19 patients, including 16 with a germline *BRCA* mutation and 3 with a somatic *BRCA* mutation. An ORR of 15.8% (3 of 19) was reached, and the disease control rate was 31.6% (6 of 19) in the overall population and 44.4% (4 of 9) in patients who received a previous chemotherapy regimen. As per protocol, enrolment was stopped due to insufficient ORR among the first 15 patients.

PARPi as maintenance treatment

The Phase III, randomised, double-blind study of Golan et al. [74] aimed to evaluate the efficacy of olaparib as maintenance therapy in patients affected by metastatic germline *BRCA1/2*-mutant PDAC not progressing after first-line platinum-based treatment. A total of 154 patients was randomly assigned (3:2 ratio) to receive olaparib tablets (300 mg twice daily; $n = 92$) or placebo ($n = 62$). The primary endpoint was PFS. The study met its primary endpoint: median PFS was higher in the olaparib arm compared to the placebo arm (7.4 months versus 3.8 months; HR 0.53; 95% CI 0.35–0.82; $P = 0.004$). At the interim analysis, no difference between olaparib and placebo groups in mOS, calculated at a data maturity of 46% (18.9 versus 18.1 months; HR 0.91; 95% CI 0.56–1.46; $P = 0.68$), was observed. The incidence of grade 3 or higher adverse events was 40% in the olaparib group compared with 23% in the placebo group. No significant difference in health-related quality of life was reported between the groups.

Another single arm, Phase II clinical trial of maintenance rucaparib in patients with advanced PDAC and germline or somatic *BRCA* or *PALB2* mutation, whose cancer had not progressed following at least 4 months of platinum-based chemotherapy (NCT03140670), was conducted by Binder et al. [75]. The primary endpoint was PFS. Globally, 13 patients with a germline *BRCA2* mutation, 3 with a germline *BRCA1* mutation, 2 with a germline *PALB2* mutation, and 1 with a somatic *BRCA2* mutation were enrolled. Median PFS was 9.1 months from the start of rucaparib therapy; ORR was 36.8% (six partial responses; one complete response). The disease control rate was 89.5% for at least 8 weeks. Two patients (10.5%) demonstrated progressive disease at a first follow-up scan 2 months after the start of treatment; eight received rucaparib for >6 months and two

Table 3. Published clinical trials of PARP inhibitors in pancreatic cancer.

Treatment strategy	Drugs	Phase	Setting	No. of patients	Prior platinum	Results	Reference
PARPi monotherapy for advanced disease	Olaparib	II	Recurrent g*BRCA1/2*-mutant PDAC after gemcitabine	25	65%	• Primary endpoint ORR: 22% • Secondary endpoints • SD at 8 weeks: 35% ▪ DOR: 134 days ▪ PFS: 4.6 months ▪ OS: 9.8 months • Safety ▪ Any grade AEs: 74% fatigue, 48% nausea, 40% anaemia ▪ grade ≥3 AEs: 17.4% anaemia, 13% fatigue	[72]
	Veliparib	II	Locally advanced/metastatic g*BRCA1/2* or *PALB2*-mutant PDAC, 1–2 prior lines	16	88%, of which 64.3% platinum resistant	• Primary endpoint ORR: 0% ▪ Secondary endpoints ▪ PFS: 1.7 months ▪ OS: 3.1 months • Safety ▪ grade ≥3 AEs: 25% fatigue, 19% hyperbilirubinemia	[93]
	Rucaparib	II	Locally advanced/metastatic g*BRCA1/2* and s*BRCA1/2*-mutant PDAC, 1–2 prior lines	19	78.9%, of which 42.1% platinum resistant	• Primary endpoint ORR: 15.8% • Safety ▪ any grade AEs: 63.2% nausea, 47.4% anaemia ▪ grade ≥3 AEs: 31.6% anaemia, 15.8% fatigue, 15.8% ascites	[94]
PARPi + chemotherapy	Veliparib+ mFOLFIRI vs FOLFIRI	II	Metastatic PDAC, 1 prior line	123	Not specified	• Primary endpoint OS: 5.1 vs 5.9 months (HR 1.3, 95% CI 0.9–2.0, $P = 0.21$) ▪ Secondary endpoint PFS: 2.1 vs 2.9 months (HR 1.5, 95% CI 1.0–2.2, $P = 0.05$) • Safety ▪ grade ≥3 AEs: neutropenia (33% vs 20%), fatigue (19% vs 4%), nausea (11% vs 4%)	[95]
	Veliparib+ mFOLFOX6	I/II	Metastatic DDR-mutant PDAC and/or family history suggestive of breast or ovarian cancer syndrome; Phase II: 2 cohorts 1) untreated patients; 2) previously treated patients	I: 31; II: 33(15 untreated, 18 pretreated)	24.5%	• Primary endpoint ORR 26% all patients, 58% platinum-naive, FH +, DDR + patients (12) • Secondary endpoints ▪ PFS: 3.7 months ▪ OS: 8.5 months • Safety ▪ grade ≥3 AEs: 16% myelosuppression, 6% nausea/vomiting	[96]
	cisplatin–gemcitabine (arm A) vs cisplatin–gemcitabine + veliparib (arm B)	II	Locally advanced or metastatic g*BRCA/PALB2*-mutant PDAC, untreated patients	50	No previous platinum treatment allowed	• Primary endpoint RR: 74% arm A vs 65.2% arm B $P = 0.55$ • Secondary endpoints ▪ PFS: 10.1 months arm A (95% CI, 6.7–11.5) vs 9.7 months arm B (95% CI, 4.2–13.6), $P = 0.73$) ▪ OS: 15.5 months arm A (95% CI,	[82]

Table 3 continued

Treatment strategy	Drugs	Phase	Setting	No. of patients	Prior platinum	Results	Reference
						12.2–24.3) vs 16.4 months arm B (95% CI, 11.7–23.4 months; $P = 0.6$). • Safety ■ grade ≥3 AEs: neutropenia (48% arm A vs 30% arm B), thrombocytopenia (55% arm A vs 9% arm B), anaemia (52% arm A vs 35% arm B)	
PARPi as maintenance	Olaparib vs placebo	III	Metastatic g*BRCA1/2*-mutant PDAC not progressing during first-line platinum-based chemotherapy	154	Platinum sensitive	• Primary endpoint PFS: 7.4 months olaparib vs 3.8 months; HR 0.53; 95% CI, 0.35–0.82; $P = 0.004$ • Secondary endpoints ■ OS: 18.9 months olaparib vs 18.1 months; HR 0.91; 95% CI, 0.56–1.46; $P = 0.68$ • Safety ■ Any grade AEs: fatigue or asthenia 60% olaparib vs 35% placebo, nausea 45% olaparib vs 23% placebo ■ grade ≥3 AEs: anemia 11% olaparib vs 3% placebo, fatigue or asthenia 5% olaparib vs 2% placebo	[74]
	Rucaparib	II	Metastatic g/s*BRCA1/2*-mutant PDAC not progressing following at least 4 months of first-line platinum-based chemotherapy	24	Platinum sensitive	• Primary endpoint PFS: 9.1 months • Secondary endpoints ■ ORR: 36.8% • Safety ■ Any grade: nausea (grade 1: 41.6%; grade 2: 4.2%), dysgeusia (grade 1: 33.3%), fatigue (grade 1: 25%)	[75]

patients for >1 year (13 months and 15 months, respectively). The seven responding patients included those with germline *BRCA2* mutations ($n = 4$), germline *PALB2* mutations ($n = 2$) and a somatic *BRCA2* mutation ($n = 1$). The authors concluded that rucaparib maintenance shows encouraging disease control with an acceptable safety profile (the most common adverse events being nausea (grade 1, 41.6%; grade 2, 4.2%), dysgeusia (grade 1, 33.3%) and fatigue (grade 1, 25%)).

PARPi plus chemotherapy

Veliparib was evaluated in combination with FOLFIRI versus FOLFIRI alone in a Phase II study of patients with metastatic PDAC, of whom 11 (9%) had HRD, including four germline mutations (in *BRCA1*, *BRCA2*, *ATM*) and seven somatic mutations (in *BRCA2*, *PALB2*, *ATM*, *CDK12*) [95]. An additional 24 patients (20%) had germline mutations ($n = 11$, e.g. in *FANC*, *BLM*, *SLX4*, *CHEK2*) or somatic mutations ($n = 13$, e.g. in *FANC*, *BLM*, *POLD1*, *RIF1*, *MSH2*, *MSH6*) in other DNA repair genes that are not classified as featuring in HRD. A planned interim futility analysis at 35% of expected PFS events showed that the combination of veliparib and FOLFIRI was unlikely to be superior to FOLFIRI; moreover, an increased toxicity was observed (most common grade 3/4 adverse events: neutropenia (33% versus 20%), fatigue (19% versus 4%) and nausea (11% versus 4%)) [92].

In the Phase II trial by Pishvaian et al. [96], patients were preselected to receive veliparib plus modified FOLFOX6 if they had either a pathogenic germline or somatic HRD mutation (in *BRCA1/2*, *PALB2*, *ATM*), and/or a family history suggestive of breast cancer or ovarian cancer syndrome. The primary objective was ORR, whereas key secondary endpoints were PFS and OS. The treatment combination was well tolerated and showed promising efficacy, especially in platinum-naive patients who had a positive family history and/or harboured HRD mutations, for which the ORR was 58%.

A multicentre, randomised, prospective, Phase II trial showed promising activity of the combination of cisplatin and gemcitabine in patients with advanced or metastatic germline *BRCA/PALB2*-mutant PDAC [82]. In this study, 50 patients were treated with cisplatin and gemcitabine plus or minus veliparib (arms A and B, respectively). The response rate, the primary endpoint of the study, was high in both groups (74% arm A versus 65.2% arm B); the addition of veliparib did not improve the response ($P = 0.55$). Interestingly, the 2- and 3-year survival rates of the entire cohort observed in this study are the longest reported in any randomised trial in PDAC (30.6% and 17.8%, respectively). More grade 3–4 haematologic adverse events and dose reductions were observed in arm A than in arm B. However, although the addition of veliparib did not improve the response rate, this study supports the effectiveness of cisplatin plus gemcitabine for the treatment of patients with advanced germline *BRCA/PALB2*-mutant PDAC, thus suggesting this regimen as a standard approach in this patient population [82].

PARPi: overcoming hurdles

Unfortunately, the emergence of PARPi resistance is not uncommon. The mechanisms of resistance so far explored include restoration of HR, stabilisation of the replication forks, alternative mRNA splicing, reduced PARP-1 trapping, P-glycoprotein-mediated drug efflux, cell-cycle control alterations, changes in miRNA expression patterns and dysregulation of signalling pathways [97]. Restoration of HR is the most studied event, and can result from genetic and epigenetic phenomena. The development of secondary, reversion mutations that lead to the restoration of *BRCA* expression seems to be the main underlying mechanism and has been described in various patients with *BRCA2*-mutant PDAC who developed resistance to PARPi with or without platinum [98–100]. The loss of *BRCA1* promoter methylation might also restore the expression of functional *BRCA1* to levels similar to those seen in HR-proficient tumours [98].

Table 4. Ongoing clinical trials of PARP inhibitors in pancreatic cancer.

Phase	Treatment arms	Setting	Treatment strategy	NCT number
I	NMS-03305293	Advanced/metastatic, relapsed/refractory solid tumours	Single agent, after progression on standard treatment	NCT04182516
I/II	Nanoliposomal Irinotecan + leucovorin + fluorouracil + rucaparib	Previously treated metastatic pancreatic, colorectal, gastroesophageal, biliary cancer	In combination with chemotherapy (as part of initial treatment)	NCT03337087
II	rucaparib	Solid tumours with deleterious mutations in homologous recombination repair genes	Initial treatment	NCT04171700
II	rucaparib	*BRCA1*-, *BRCA2*- or *PALB2*-mutant pancreatic cancer	Maintenance in *BRCA1*-, *BRCA2*- or *PALB2*-mutant pancreatic cancer without evidence of progression on platinum-based therapy	NCT03140670
II	niraparib	Unresectable and metastatic pancreatic cancer with deficiencies in HR DNA repair	Single agent after ≥2 lines	NCT03601923
II	niraparib	Metastatic pancreatic cancer after previous chemotherapy	Single agent after ≥2 lines	NCT03553004
II	niraparib + nivolumab versus niraparib + ipilimumab	Inoperable PDAC	Maintenance in inoperable PDAC and stability on platinum-based chemotherapy for ≥16 weeks without evidence of progressive disease	NCT 03404960

PDAC pancreatic ductal adenocarcinoma, *HR* homologous repair.

The occurrence of PARPi resistance reflects the complexity and heterogeneity of *BRCA1/2*-mutant PDAC and requires further studies to fully understand the underlying mechanisms and to explore potential therapeutic strategies to overcome this issue.

Current trials are investigating the safety and efficacy of PARPi as a single agent and in combination with other drugs, both in the early and in the metastatic setting (Table 4). In particular, the combination of PARPi and immunotherapy is one of the latest approaches to treatment. PARP inhibition might cause *BRCA*-mutant tumours to become sensitive to immunotherapy not only by enhancing tumour immunogenicity through an increase in tumour antigen burden but also by increasing the expression of the immune checkpoint protein programmed death-ligand 1 in tumour tissue through the *ATM–ATR–CHK1* pathway [101]. Data from these trials will hopefully provide new information on the management of patients with *BRCA*-mutant PDAC.

CONCLUSIONS

BRCA1/2-mutant PDAC represents a type of PC with specific disease features that are still to be fully understood. *BRCA1/2*-mutant PDAC represents the largest molecular subgroup of pancreatic cancer, and *BRCA1/2* genes alterations are the most explored 'targetable' mutations in prospective interventional clinical trials. In the era of precision medicine, this aspect appears crucial in PDAC, where the vast majority of efforts using agents against other molecular targets have provided disappointing results [2]. The discovery of the involvement of *BRCA1/2* in PDAC development should lead to more attention being focused on the family history to identify which patients and relatives should be considered for genetic counselling.

No specific randomised trials have been conducted to investigate potential differences between germline and somatic mutations in *BRCA1/2*; most trials have focused on germline alterations and only a few patients with somatic *BRCA*-mutant PDAC have been enrolled. Owing to the biological rationale of HR mechanisms in which *BRCA1/2* are involved, the *BRCA1/2* PDAC landscape requires further research with traditional cytotoxic agents, especially platinum-based chemotherapy, and at the same time opens a new chapter on innovative therapeutic strategies—namely, PARPi as a single agent and in combination with other drugs. Unfortunately, no gain in OS has been reported with PARPi monotherapy and patients develop resistance [67]. Further research is urgently needed in order to improve PDAC survival outcomes. In this respect, an assessment of the association between PARPi and immunotherapy seems promising. Many questions remain unanswered and the lack of biomarkers to improve the treatment choice and clinical outcomes presents a challenge. Thus, the identification of predictive markers is crucial. The concept of 'BRCAness' has emerged to describe the high-grade genomic instability present in non-*BRCA*-mutated cancers that resembles tumours originating from germline *BRCA*-mutated carriers, and represents a phenotype of defective HR to which somatic mutations in different HR genes, such as *BRCA1/2*, *ATM*, *PALB2*, *CHEK1*, *RAD51*, and *FANCA*, can contribute. BRCAness is under evaluation as a biomarker for DNA-damaging agents and PARPi, but its measures and its predictive role still require further investigation [49, 102]. Germline mutations that are involved with BRCA1/2 and the HR pathway (e.g. *ATM*, *PALB2*, *ATR*, *RAD 51*, *CHEK2*, *FANCA* and BRIP1) have also been considered as potential predictive biomarkers for the same treatment strategies. Currently, clinical trials are assessing PARP inhibitors in patients with PDAC harbouring *PALB2*, *ATM*, *CHEK2* germline mutations. On the other hand, the role of other germline mutations in the HRD pathway remains to be determined [49]. In the era of precision medicine, further studies are needed to identify predictive biomarkers in order to apply a better selection of patients with *BRCA*-mutant PDAC with the aim to offer them a tailored treatment.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
2. Lai E, Puzzoni M, Ziranu P, Pretta A, Impera V, Mariani S, et al. New therapeutic targets in pancreatic cancer. Cancer Treat Rev. 2019;81:101926.
3. Brunetti O, Luchini C, Argentiero A, Tommasi S, Mangia A, Aprile G, et al. The Italian rare pancreatic exocrine cancer initiative. Tumori. 2019;105:353–8.
4. Brunetti O, Aprile G, Marchetti P, Vasile E, Casadei Gardini A, Scartozzi M, et al. Systemic chemotherapy for advanced rare pancreatic histotype tumors: a retrospective multicenter analysis. Pancreas. 2018;47:759–71.
5. Aprile G, Negri FV, Giuliani F, DeCarlo E, Melisi D, Simionato F, et al. Second-line chemotherapy for advanced pancreatic cancer: which is the best option? Crit Rev Oncol Hematol. 2017;115:1–12.
6. Silvestris N, Brunetti O, Vasile E, Cellini F, Cataldo I, Pusceddu V, et al. Multimodal treatment of resectable pancreatic ductal adenocarcinoma. Crit Rev Oncol Hematol. 2017;115:1–12.
7. Pierantoni C, Pagliacci A, Scartozzi M, Berardi R, Bianconi M, Cascinu S. Pancreatic cancer: progress in cancer therapy. Crit Rev Oncol Hematol. 2008;67:27–38.
8. Cascinu S, Scartozzi M, Carbonari G, Pierantoni C, Verdecchia L, Mariani C, et al. COX-2 and NF-KB overexpression is common in pancreatic cancer but does not predict for COX-2 inhibitors activity in combination with gemcitabine and oxaliplatin. Am J Clin Oncol. 2007;30:526–30.
9. Berardi R, Verdecchia L, Scartozzi M, Cascinu S. New frontiers in the neoadjuvant therapy of pancreatic adenocarcinoma: apart from therapeutical protocols. JOP. 2005;13:118–21.
10. Ghiorzo P. Genetic predisposition to pancreatic cancer. World J Gastroenterol. 2014;20:10778–89.
11. Holter S, Borgida A, Dodd A, Grant R, Semotiuk K, Hedley D, et al. Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. J Clin Oncol. 2015;33:3124–9.
12. Friedenson. BBRCA1 and BRCA2 pathways and the risk of cancers other than breast or ovarian. Med Gen Med. 2005;7:60.
13. Cai Y, Li X, Shen P, Zhang D. CCAT2 is an oncogenic long non-coding RNA in pancreatic ductal adenocarcinoma. Biol Res. 2018;51:1–9.
14. Venkitaraman AR. Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell. 2002;108:171–82.
15. Tutt A, Ashworth A. The relationship between the roles of BRCA genes in DNA repair and cancer predisposition. Trends Mol Med. 2002;8:571–6.
16. Walsh CS. Two decades beyond BRCA1/2: homologous recombination, hereditary cancer risk and a target for ovarian cancer therapy. Gynecol Oncol. 2015;137:343–50.
17. Blair AB, Groot VP, Gemenetzis G, Wei J, Cameron JL, Weiss MJ, et al. BRCA1/BRCA2 germline mutation carriers and sporadic pancreatic ductal adenocarcinoma. J Am Coll Surg. 2018;226:630–637.e1.
18. Lal G, Liu G, Schmocker B, Kaurah P, Ozcelik H, Narod SA, et al. Inherited predisposition to pancreatic adenocarcinoma: role of family history and germ-line p16, BRCA1, and BRCA2 mutations. Cancer Res. 2000;60:409–16.
19. Furukawa T, Sakamoto H, Takeuchi S, Ameri M, Kuboki Y, Yamamoto T, et al. Whole exome sequencing reveals recurrent mutations in BRCA2 and FAT genes in acinar cell carcinomas of the pancreas. Sci Rep. 2015;5:8829.
20. Thompson D, Easton DF. Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst. 2002;94:1358–65.
21. The Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst. 1999;91:1310–6.
22. Van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, Hoogerbrugge N, Verhoef S, Vasen HF, et al. Netherlands Collaborative Group on Hereditary Breast Cancer (HEBON). Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet. 2005;42:711–9.
23. Goggins M, Schutte M, Lu J, Moskaluk CA, Weinstein CL, Petersen GM, et al. Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer Res. 1996;56:5360–4.
24. Moran A, O'Hara C, Khan S, Shack L, Woodward E, Maheret ER. Risk of cancer other than breast or ovarian in individuals with BRCA1 and BRCA2 mutations. Fam Cancer. 2012;11:235–42. al.
25. Mersch J, Jackson MA, Park M, Nebgen D, Peterson SK, Singletary C, et al. Cancers associated with BRCA1 and BRCA2 mutations other than breast and ovarian. Cancer. 2015;121:269–75.

26. Golan T, Kanji ZS, Epelbaum R, Devaud N, Dagan E, Holter S, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. Br J Cancer. 2014;111:1132–8.
27. Kim DH, Crawford B, Ziegler J, Beattie MS. Prevalence and characteristics of pancreatic cancer in families with BRCA1 and BRCA2 mutations. Fam Cancer. 2009;8:153–8.
28. Wang D, Guan R, Tao Q, Liu S, Yu M, Li X. A novel somatic BRCA2 point mutation in a metastatic pancreatic cancer patient: a case report. BMC Med Genomics. 2021;14:6.
29. Plon SE, Eccles DM, Easton D, Foulkes WD, Genuardi M, Greenblatt MS. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. Hum Mutat. 2008;29:1282–91.
30. Ferrone CR, Levine DA, Tang LH, Allen PJ, Jarnagin W, Brennan MF, et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol. 2009;27:433–8.
31. Zhu Y, Zhai K, Ke J, Li J, Gong Y, Yang Y, et al. BRCA1 missense polymorphisms are associated with poor prognosis of pancreatic cancer patients in a Chinese population. Oncotarget. 2017;8:36033–9.
32. Golan T, Sella T, O'reilly EM, Katz MH, Epelbaum R, Kelsen DP, et al. Overall survival and clinical characteristics of BRCA mutation carriers with stage I/II pancreatic cancer. Br J Cancer. 2017;116:697–702.
33. Iqbal J, Ragone A, Lubinski J, Lynch HT, Moller P, Ghadirian P, et al. The incidence of pancreatic cancer in BRCA1 and BRCA2 mutation carriers. Br J Cancer. 2012;107:2005–9.
34. Takeuchi S, Doi M, Ikari N, Yamamoto M, Furukawa T. Mutations in BRCA1, BRCA2, and PALB2, and a panel of 50 cancer-associated genes in pancreatic ductal adenocarcinoma. Sci Rep. 2018;8:8105.
35. Seeber A, Zimmer K, Kocher F, Puccini A, Xiu J, Nabhan C, et al. Molecular characteristics of BRCA1/2 and 12 PALB2 mutations in pancreatic ductal adenocarcinoma. ESMO Open. 2020;5:e000942.
36. Shi C, Hruban RH, Klein AP. Familial pancreatic cancer. Arch Pathol Lab Med. 2009;133:365–74.
37. Jones S, Hruban RH, Kamiyama M, Borges M, Zhang X, Parsons DW, et al. Exomic sequencing identifies PALB2 as a pancreatic susceptibility gene. Science. 2009;324:217.
38. McWilliams RR, Wieben ED, Rabe KG, Pedersen KS, Wu Y, Sicotte H, et al. Prevalence of CDKN2A mutations in pancreatic cancer patients: implication for genetic counseling. Eur J Human Genet. 2011;19:472–8.
39. Klein AP. Genetic susceptibility to pancreatic cancer. Mol Carcinog. 2012;51:1–24.
40. Hahn SA, Greenhalf B, Ellis I, Sina-Frey M, Rieder H, Korte B, et al. BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst. 2003;95:214–221.
41. Lowenfels AB, Maisonneuve P. Epidemiologic and etiologic factors of pancreatic cancer. Hematol Oncol Clin North Am. 2002;16:11–16.
42. Murphy KM, Brune KA, Griffin C, Sollenberger JE, Petersen GM, Bansal R, et al. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%. Cancer Res. 2002;62:3789–93.
43. Couch FJ, Johnson MR, Rabe KG, Brune K, De Andrade M, Goggins M, et al. The prevalence of BRCA2 mutations in familial pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2007;16:342–6.
44. Zhen DB, Rabe KG, Gallinger S, Syngal S, Schwartz AG, Goggins MG, et al. BRCA1, BRCA2, PALB2, and CDKN2A mutations in familial pancreatic cancer: a PACGENE study. Genet Med. 2015;17:569–77.
45. Harinck F, Kluijt I, van Mil SE, Waisfisz Q, van Os TA, Aalfs CM, et al. Routine testing for PALB2 mutations in familial pancreatic cancer families and breast cancer families with pancreatic cancer is not indicated. Eur J Hum Genet. 2012;20:577–9.
46. Grant RC, Al-Sukhni W, Borgida AE, Holter S, Kanji ZS, McPherson T, et al. Exome sequencing identifies nonsegregating nonsense ATM and PALB2 variants in familial pancreatic cancer. Hum Genomics. 2013;7:11.
47. Okur V, Chung WK. The impact of hereditary cancer gene panels on clinical care and lessons learned. Cold Spring Harb Mol Case Stud. 2017;3:a002154.
48. Brune KA, Lau B, Palmisano E, Canto M, Goggins MG, Hruban RH, et al. Importance of age of onset in pancreatic cancer kindreds. J Natl Cancer Inst. 2010;102:119–26.
49. Wong W, Raufi AG, Safyan RA, Bates SE, Manji GA. BRCA mutations in pancreas cancer: spectrum, current management, challenges and future prospects. Cancer Manag Res. 2020;12:2731–42.
50. Metcalfe KA, Poll A, Royer R, Llacuachaqui M, Tulman A, Sun P, et al. Screening for founder mutations in BRCA1 and BRCA2 in unselected Jewish women. J Clin Oncol. 2010;28:387–91.
51. Stadler ZK, Salo-Mullen E, Patil SM, Pietanza MC, Vijai J, Saloustros E, et al. Prevalence of BRCA1 and BRCA2 mutations in Ashkenazi Jewish families with breast and pancreatic cancer. Cancer. 2011;118:493–9.
52. Salo-Mullen EE, O'reilly EM, Kelsen DP, Ashraf AM, Lowery MA, Yu KH, et al. Identification of germline genetic mutations in patients with pancreatic cancer. Cancer. 2015;121:4382–8.
53. Kirchhoff T, Satagopan JM, Kauff ND, Huang H, Kolachana P, Palmer C, et al. Frequency of BRCA1 and BRCA2 Mutations in Unselected Ashkenazi Jewish Patients With Colorectal Cancer. J Natl Cancer Inst. 2004;96:68–70.
54. Warner E, Foulkes W, Goodwin P, Meschino W, Blondal J, Paterson C, et al. Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. J Natl Cancer Inst. 1999;91:1241–7.
55. Shindo K, Yu J, Suenaga M, Fesharakizadeh S, Cho C, Macgregor-Das A, et al. Deleterious germline mutations in patients with apparently sporadic pancreatic adenocarcinoma. J Clin Oncol. 2017;35:3382–90.
56. Smith AL, Wong C, Cuggia A, Borgida A, Holter S, Hall A, et al. Reflex testing for germline BRCA1,BRCA2, PALB2, and ATM mutations in pancreatic cancer: mutation prevalence and clinical outcomes from two canadian research registries. JCO Precision Oncol. 2018;2:1–16.
57. Daly MB, Pal T, Berry MP, Buys SS, Dickson P, Domcheck SM, et al. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19:77–102.
58. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW, et al. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110:223–63.
59. Stoffel EM, McKernin SE, Brand R, Canto M, Goggins M, Moravek C, et al. Evaluating susceptibility to pancreatic cancer: ASCO provisional clinical opinion. J Clin Oncol. 2019;37:153–64.
60. Tempero MA, Malafa MP, Al-Hawary M, Behrman SW, Benson AB, Cardin DB, et al. NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 1.2021. December 10, 2020.
61. Abeliovich D, Kaduri L, Lerer I, Weinberg N, Amir G, Sagi M, et al. The founder mutations 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2 appear in 60% of ovarian cancer and 30% of early-onset breast cancer patients among Ashkenazi women. Am J Hum Genet. 1997;60:505–14.
62. Pilarski R. The role of BRCA testing in hereditary pancreatic and prostate cancer families. Am Soc Clin Oncol Educ Book. 2019;39:79–86.
63. Grant RC, Selander I, Connor AA, Selvarajah S, Borgida A, Briollais L, et al. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology. 2015;148:556–64.
64. Hu C, Hart SN, Polley EC, Gnanaolivu R, Shimelis H, Lee KY, et al. Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. J Am Med Assoc. 2018;319:2401–9.
65. Brand R, Borazanci E, Speare V, Dudley B, Karloski E, Peters MLB, et al. Prospective study of germline genetic testing in incident cases of pancreatic adenocarcinoma. Cancer. 2018;124:3520–7.
66. Yurgelun MB, Chittenden AB, Morales-Oyarvide V, Rubinson DA, Dunne RF, Kozak MM, et al. Germline cancer susceptibility gene variants, somatic second hits, and survival outcomes in patients with resected pancreatic cancer. Genet Med. 2019;21:213–23.
67. Beger C, Ramadani M, Meyer S, Leder G, Krüger M, Welte K, et al. Down-regulation of BRCA1 in chronic pancreatitis and sporadic pancreatic adenocarcinoma. Clin Cancer Res. 2004;10:3780–7.
68. Wang Y, Park JYP, Pacis A, Denroche RE, Jang GH, Zhang A. A preclinical trial and molecularly-annotated patient cohort identify predictive biomarkers in homologous recombination deficient pancreatic cancer. Clin Cancer Res. 2020;26:5462–76.
69. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518:495–501.
70. Bailey P, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 2016;531:47–52.
71. Golan T, Stossel C, Atias D, Buzhor E, Halperin S, Cohen K, et al. Recapitulating the clinical scenario of BRCA-associated pancreatic cancer in pre-clinical models. Int J Cancer. 2018;143:179–83.
72. Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmaña J, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015;33:244–50.
73. De-Bono J, Ramanathan RK, Mina L, Chugh R, Glaspy J, Rafii S, et al. Phase I, dose-escalation, two-part trial of the PARP inhibitor talazoparib in patients with advanced germline BRCA1/2 mutations and selected sporadic cancers. Cancer Discov. 2017;7:620–9.

74. Golan T, Hammel P, Reni M, Van-Cutsem E, Macarulla T, Hall MJ, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic. Cancer N Engl J Med. 2019;381:317–27.
75. Binder KAR, Mick R, O'Hara M, Teitelbaum U, Karasic T, Schneider C, et al. A phase II, single arm study of maintenance rucaparib in patients with platinum-sensitive advanced pancreatic cancer and a pathogenic germline or somatic mutation in BRCA1, BRCA2 or PALB2. Cancer Res. 2019;79 (Suppl 13):(abstract CT234).
76. Pihlak R, Valle JW, Mc-Namara MG. Germline mutations in pancreatic cancer and potential new therapeutic options. Oncotarget. 2017;8:73240–57.
77. Tutt A, Tovey H, Cheang MCU, Kernaghan S, Kilburn L, Gazinska P. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. Nat Med. 2018;24:628–37.
78. Bolton KL, Chenevix-Trench G, Goh C, Sadetzki S, Ramus SJ, Karlan BY, et al. EMBRACE; kConFab Investigators; Cancer Genome Atlas Research Network. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. J Am Med Assoc. 2012;307:382–90.
79. Reiss KA, Yu S, Judy R, Symecko H, Nathanson KL, Domchek SM. Retrospective survival analysis of patients with advanced pancreatic ductal adenocarcinoma and germline BRCA or PALB2 mutations. JCO Precision Oncol. 2018;2:1–9.
80. Yu S, Agarwal P, Mamtani R, Symecko H, Spielman K, O'Hara M, et al. Retrospective survival analysis of patients with resected pancreatic ductal adenocarcinoma and a germline BRCA or PALB2 mutation. JCO Precision Oncol. 2019;3:1–11.
81. Wattenberg MM, Asch D, Yu S, O'dwyer PJ, Domchek SM, Nathanson KL, et al. Platinum response characteristics of patients with pancreatic ductal adenocarcinoma and a germline BRCA1, BRCA2 or PALB2 mutation. Br J Cancer. 2020;122:333–9.
82. O'reilly EM, Lee JW, Zalupski M, Capanu M, Park J, Golan T, et al. Randomized, multicenter, phase II trial of gemcitabine and cisplatin with or without veliparib in patients with pancreas adenocarcinoma and a germline BRCA/PALB2 mutation. J Clin Oncol. 2020;38:1378–88.
83. Lowery MA, Kelsen DP, Stadler ZK, Yu KH, Janjigian YY, Ludwig E, et al. An emerging entity: pancreatic adenocarcinoma associated with a known BRCA mutation: clinical descriptors, treatment implications, and future directions. Oncologist. 2011;16:1397–402.
84. Sonnenblick A, Kadouri L, Appelbaum L, Peretz T, Sagi M, Goldberg Y, et al. Complete remission, in BRCA2 mutation carrier with metastatic pancreatic adenocarcinoma, treated with cisplatin based therapy. Cancer Biol Ther. 2011;12:165–8.
85. Gupta M, Iyer R, Fountzilas C. Poly(ADP-ribose) polymerase inhibitors in pancreatic cancer: a new treatment paradigms and future implications. Cancers. 2019;11:1980.
86. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. T: specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005;434:913–917.
87. Lord CJ, Ashworth A. PARP inhibitors: synthetic lethality in the clinic. Science. 2017;355:1152–8.
88. Min A, Im SA. PARP inhibitors as therapeutics: beyond modulation of PARylation. Cancers. 2020;12:394.
89. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005;434:917–21.
90. Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of poly (ADP-ri-bose) polymerase in tumors from BRCA mutation carriers. New Engl J Med. 2009;361:123–34.
91. Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, et al. Oral poly(ADP- ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof of concept trial. Lancet. 2010;376:235–44.
92. Audeh MW, Carmichael J, Penson RT, Friedlander M, Powell B, Bell-McGuinn KM, et al. Oral poly (ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof of-concept trial. Lancet. 2010;376:245–51.
93. Lowery MA, Kelsen DP, Capanu M, Smith SC, Lee JW, Stadler ZK, et al. Phase II trial of veliparib in patients with previously treated BRCA-mutated pancreas ductal adenocarcinoma. Eur J Cancer. 2018;89:19–26.
94. Shroff RT, Hendifar A, McWilliams RR, Geva R, Epelbaum R, Rolfe L, et al. Rucaparib monotherapy in patients with pancreatic cancer and a known deleterious BRCA mutation. JCO Precis Oncol. 2018. https://doi.org/10.1200/PO.17.00316
95. Chiorean EG, Guthrie KA, Philip PA, Swisher EM, Jalikis F, Pishvaian MJ, et al. Randomized phase II study of second-line modified FOLFIRI with PARP inhibitor ABT-888 (Veliparib) (NSC-737664) versus FOLFIRI in metastatic pancreatic cancer (mPC): SWOG S1513. J Clin Oncol. 2019;37:4014.
96. Pishvaian MJ, Wang H, Parenti S, He AR, Hwang JJ, Ley L, et al. Final report of a phase I/II study of veliparib (Vel) in combination with 5-FU and oxaliplatin (FOLFOX) in patients (pts) with metastatic pancreatic cancer (mPDAC). J Clin Oncol. 2019;37:4014.
97. Kim DS, Camacho CV, Kraus WL. Alternate therapeutic pathways for PARP inhibitors and potential mechanisms of resistance. Exp Mol Med. 2021;53:42–51.
98. Pishvaian MJ, Biankin AV, Bailey P, Chang DK, Laheru D, Wolfgang CL, et al. BRCA2 secondary mutation-mediated resistance to platinum and PARP inhibitor-based therapy in pancreatic cancer. Br J Cancer. 2017;116:1021–6.
99. Tao H, Liu S, Huang D, Han X, Wu X, Shao YW, et al. Acquired multiple secondary BRCA2 mutations upon PARPi resistance in a metastatic pancreatic cancer patient harboring a BRCA2 germline mutation. Am J Transl Res. 2020;12:612–7.
100. Tobalina L, Armenia J, Irving E, O'Connor MJ, Forment JV. A meta-analysis of reversion mutations in BRCA genes identifies signatures of DNA end-joining repair mechanisms driving therapy resistance. Ann Oncol. 2020;32:103–12.
101. Kasi A, Al-Jumayli M, Park R, Baranda J, Sun W. Update on the role of poly (ADP-ribose) polymerase inhibitors in the DNA repair-deficient pancreatic cancers: a narrative review. J Pancreat Cancer. 2020;6:107–15.
102. Hu Y, Guo M. Synthetic lethality strategies: beyond BRCA1/2 mutations in pancreatic cancer. Cancer Sci. 2020;111:3111–21.

AUTHOR CONTRIBUTIONS

EL proposed the manuscript topic, conceived, wrote, revised and co-ordinated the manuscript. PZ wrote and co-ordinated the manuscript. DS wrote the introduction, the sections "Mutant *BRCA* versus wild-type *BRCA* in PDAC" and "*BRCA* mutations and heritability in PDAC". MD wrote the section "Germline *BRCA* mutations and somatic *BRCA* mutations in PDAC" and conceived Table 1. AP wrote the section "PARP inhibitors in *BRCA*-mutant PDAC" and conceived Fig. 1 and Tables 3 and 4. ST wrote the section "*BRCA*-mutant PDAC and platinum-based therapy" and conceived Table 2. SC wrote the section "*BRCA*-mutant PDAC and platinum-based therapy". NL helped write the introduction and formatting the manuscript. SM helped write the section "Mutant *BRCA* versus wild-type *BRCA* in PDAC". M. Persano helped write the section "*BRCA* mutations and heritability in PDAC". MM helped write the section "*BRCA*-mutant PDAC and platinum-based therapy". CD helped write the section "PARP inhibitors in *BRCA*-mutant PDAC". LD reviewed the manuscript. VP reviewed the manuscript. M. Puzzoni reviewed the manuscript. MS conceived, reviewed and supervised the manuscript, had full access to the data in the study and final responsibility for the decision to submit for publication. All Authors have conceived and/or designed the work that led to the submission, acquired data, and/or played an important role in interpreting the results, drafted or revised the manuscript, approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Thus, they have all contributed to the work described sufficiently to be named as authors. All authors are aware of the submission of the revised manuscript and agree to it.

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