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Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers

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Background: The BRCA1/2 proteins are involved in regulation of cellular proliferation by DNA damage repair via homologous recombination. Therefore, *BRCA1/2* mutation carriers with pancreatic cancer may have distinct biologic outcomes.

Methods: Patients with *BRCA1/2*-associated pancreatic ductal adenocarcinoma (PDAC) diagnosed between January 1994 and December 2012 were identified from databases at three participating institutions. Clinical data were collected. Disease-free survival and overall survival (OS) were analysed.

Results: Overall, 71 patients with PDAC and *BRCA1* ($n=21$), *BRCA2* ($n=49$) or both ($n=1$) mutations were identified. Mean age at diagnosis was 60.3 years (range 33–83), 81.7% ($n=58$) had any family history of malignancy; 30% ($n=21$) underwent primary resection. Out of 71 participants, 12 received experimental therapy; one patient had missing data, these 13 cases were excluded from OS analysis. Median OS for 58 patients was 14 months (95% CI 10–23 months). Median OS for patients with stage 1/2 disease has not been reached with 52% still alive at 60 months. Median OS for stage 3/4 was 12 months (95% CI 6–15). Superior OS was observed for patients with stage 3/4 treated with platinum *vs* those treated with non-platinum chemotherapies (22 *vs* 9 months; $P=0.039$).

Conclusion: Superior OS was observed for advanced-disease *BRCA*-associated PDAC with platinum exposure.

Familial clustering is found in ~10% of pancreatic ductal adenocarcinoma (PDAC), often with an apparent autosomal dominant pattern of genetic transmission, suggestive of an inherited cancer syndrome (Shah and Kurtz, 2010). Pancreatic ductal adenocarcinoma is notably over-represented in families with a clustering of breast and ovarian cancers (Easton *et al*, 1996; Lal *et al*, 2000; Hahn *et al*, 2003; Friedenson, 2005). In a subset of these cancer-prone families, germline mutations in either the *BRCA1* or *BRCA2* genes are found, conferring a substantially higher lifetime risk for breast (50%–85% lifetime risk) and ovarian cancer (up to 64% lifetime risk; King *et al*, 2003). The association of mutations in these two genes with increased risk to other cancer types is also well established (Giusti *et al*, 2003; Friedenson, 2005). The Breast Cancer Linkage Consortium reported estimated relative risks for PDAC in *BRCA2* mutation carriers of 3.5 (95% CI 1. 87–6.58; Easton, 1999). Recently, Narod *et al* reported a near doubling of risk for PDAC among *BRCA1* and *BRCA2* mutation carrier (Iqbal *et al*, 2012). Among Ashkenazi Jews, three predominant mutations in *BRCA1* (185delAG, 5382InsC) and *BRCA2* (6174delT) are detected in the majority of high-risk families, and also in 2.5% of

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the general Ashkenazi population (Oddoux *et al*, 1996; Roa *et al*, 1996). The prevalence of the 6174delT *BRCA2* mutation among Ashkenazi Jewish PDAC patients ranges from 5.5% to 13% (Ozcelik *et al*, 1997; Figer *et al*, 2001; Ferrone *et al*, 2009). The prevalence of *BRCA2* mutations in familial PDAC in non-Jewish, ethnically diverse populations has been reported to range from 6% to 17% (Murphy *et al*, 2002; Hahn *et al*, 2003; Couch *et al*, 2007).

The BRCA1 and BRCA2 proteins are involved in the regulation of cell cycle checkpoints in response to DNA damage, including the repair of DNA double-strand breaks via homologous recombination (HR; Venkitaraman, 2002). BRCA1/2-deficient cells that lack HR activity accumulate DNA double-strand breaks, resulting in genomic instability and an increased predisposition to malignant transformation and progression (Tutt and Ashworth, 2002). Somatic, biallelic inactivation of the BRCA1/2 genes confers sensitivity to inhibition of poly(ADP-ribose)-polymerase (PARP), an enzyme involved in base excision repair (Bryant *et al*, 2005) as the loss of both HR and PARP1 pathways leads to synthetic lethality during DNA replication. BRCA-defective cells are also more sensitive to platinums and anthracyclines, as these two agents are selectively lethal in HR-defective cells (Farmer *et al*, 2005; Tutt *et al*, 2005; van der Heijden *et al*, 2005). Thus, it seems plausible to hypothesise that BRCA1 and BRCA2 deficient tumours, particularly in *BRCA1/BRCA2* germline mutation carriers, have a distinct biologic and therapeutic outcome. Indeed, several previous studies suggested that BRCA-associated ovarian cancer patients have a more favourable clinical course than non-carriers, an observation attributable to an improved response to platinum-based chemotherapy (Cass *et al*, 2003; Chetrit *et al*, 2008; Tan *et al*, 2008; Vencken *et al*, 2011). However, a differential therapeutic response to chemotherapy in BRCA mutation carriers was not replicated in all studies (Robson *et al*, 2004; Rennert *et al*, 2007; Lee *et al*, 2011).

The prognostic and predictive marker of germline BRCA-associated PDAC are unknown. The purpose of this study was to investigate the impact of germline *BRCA1* and *BRCA2* mutations on the natural history and therapeutic outcome, with the use of platinum agents, in patients with PDAC.

MATERIALS AND METHODS

Patient identification and data collection. Patients with *BRCA1/2*-associated PDAC diagnosed between January 1994 and December 2012 were identified from clinical databases at three participating institutions: Rambam Medical Institute, Haifa; Princess Margaret Hospital, Toronto, Ontario; and Chaim Sheba Medical Center, Ramat Gan. Data on patient demographics, clinical history, past surgical procedures specifically pertaining to PDAC, systemic chemotherapy and response to treatment were abstracted from patient records. Clinical stage was classified according to the seventh edition of the American Joint Committee on Cancer staging criteria (Edge and Compton, 2010). The institutional review board (IRB) of each participating institute approved this study.

DNA extraction. Genomic DNA was prepared from anticoagulated venous blood, using PUREGene DNA extraction kit (Gentra Systems Inc., Minneapolis, MN, USA) following the manufacturer's recommended protocol or by organic solvent isolation.

Analysis of the founder Jewish mutations in *BRCA1* and *BRCA2*. At the Rambam and Chaim Sheba Medical Centers, mutational analyses for the three predominantly Jewish mutations (185delAG, 5382InsC in *BRCA1* and 6174delT in *BRCA2*) were carried out by restriction enzyme digest of polymerase chain reaction (PCR) products, and analysis of the digested PCR products on agarose gels was carried out, as described previously (Ozcelik *et al*, 1997; Rohlfs *et al*, 1997). For each of these three mutations, a known mutation carrier was used as a positive control in each experiment.

At the Princess Margaret Hospital in Toronto, mutational analysis of exons and flanking regions of the *BRCA1* and *BRCA2* loci was carried out at the Advanced Molecular Diagnostics Laboratory at Mount Sinai Hospital. Polymerase chain reaction was carried out in 12 μl reaction volumes. Polymerase chain reaction primers and conditions are available upon request.

Following PCR clean-up, BigDyeTerminator Cycle Sequencing Version 3.1 (Applied Biosystems, Toronto, ON, Canada) was used for sequencing reactions using 2 μl of the cleaned up PCR products and using the recommended protocol for cycle sequencing, and analysed on an ABI 3730XL Genetic Analyzer (Applied Biosystems, Toronto, ON, Canada). Sequencing files were processed using SequenceAnalysis software (Applied Biosystems, Toronto, ON, Canada) and assembled and analysed using Mutation Surveyor (version 4.0.7, SoftGenetics, LLC, State College, PA, USA). The GenBank reference sequences used for this study were NM_007294.3 for BRCA1 and NM_000059.3 for BRCA2.

Overall survival and disease-free survival. Overall survival (OS) was defined as the time from the date of diagnosis to the date of death from any cause. If a patient is not known to have died, the OS was censored until the date of last follow-up. The OS results for patients exposed to platinum-based treatments during the course of their disease were compared with that of non-platinum chemotherapy-treated carriers. Disease-free survival (DFS) was defined as the time from the date of diagnosis to the date of recurrence in stage 1 and 2 patients. If a patient did not have an event, DFS was censored at the date of last follow-up.

Statistical analysis. Distributions for categorical variables were compared and analysed by the Fisher–Irwin exact test. The Kaplan–Meier (KM) model was used to calculate OS, and DFS as a function of time. The differences between the KM curves were tested for significance with the use of the log-rank test. All statistical tests were analysed to a significance level of 0.05 using the STATA statistical package (StataCorp LP, College Station, TX, USA).

RESULTS

Patient and tumour characteristics. Overall, 71 patients with *BRCA1/2*-associated PDAC diagnosed between January 1994 and December 2012 were identified. Mean age at diagnosis was 60.3 years (range 33–83 years), 58% ($n=41$) were male and 73.2% ($n=52$) were Jewish (Table 1). Stage 1 disease was identified in a single patient (1.4%), whereas stage 2, 3 and 4 disease were observed in 19 (27%), 16 (23%) and 34 (48%) of the patients, respectively (one patient had missing data). A primary resection was performed in 30% ($n=21$) of patients. One patient had metastatic disease at resection and therefore was included in survival data for advanced disease. The clinical characteristics of the subgroup of the 58 patients (excluding the patients treated with PARP inhibitors) is similar to the whole cohort (Table 1).

Of all study participants, 69% ($n=49$) had a *BRCA2* mutation, 30% ($n=21$) a *BRCA1* mutation and 1% ($n=1$) had both a *BRCA1* and a *BRCA2* mutation. Specific mutations are listed in Table 2. In total, 22 patients in the stage 3/4 group received platinum-based treatment. The majority of our platinum-treated patients received gemcitabine and cisplatin, one patient received gemcitabine and oxaliplatin and three patients received FOLFIRINOX (oxaliplatin, irinotecan, folinic acid and fluorouracil).

Family history of cancer. Most of the study participants (58/71, 82%) had a family history of cancer, of which 91% (53/58) had an affected first-degree relative, and 33% (19/58) had a family history of a first or second-degree relative with PDAC. The

Table 1. Patient characteristics in *BRCA1 BRCA2*-associated pancreatic cancer patients

Demographic	All patients (%)	Patients with OS data (%)
Number of patients	71	58
Gender		
Male	41 (57.8)	33 (56.9)
Female	30 (42.2)	25 (43.1)
Age (at diagnosis)		
Mean ± s.d. (years)	60.3 ± 10.0	61.6 ± 9.9
Range (years)	33–83	33–82
Jewish		
Yes	52 (73.2)	41 (70.7)
No	18 (25.4)	17 (29.3)
Missing	1 (1.4)	
Jewish ethnicity	52	
Ashkenazi	47 (90.4)	39 (95.2)
Non-Ashkenazi	2 (3.9)	
Mixed	2 (3.9)	1 (2.4)
Missing	1 (1.8)	1 (2.4)
Not Jewish	18	
Caucasian	13 (72.2)	12 (70.6)
Other	5 (27.8)	5 (29.4)

Abbreviation: OS = overall survival.

family history for one patient was unknown. Thirty-seven percent of patients in our cohort (26/70) also had a personal history of a malignancy including breast ($n = 16$), prostate ($n = 3$), renal cell carcinoma ($n = 2$), malignant melanoma ($n = 1$), ovarian ($n = 1$), endometrial ($n = 1$), thyroid ($n = 1$), bladder ($n = 1$) and colon cancer ($n = 1$). One patient had both breast and endometrial cancer (Table 3).

Disease-free survival and overall survival. In our cohort, 28.2% of patients ($n = 20$) had early-stage disease (stage 1 or 2) and underwent curative intent resection. The median DFS for this group was 13 months (95% CI 6–19 months). The probabilities that a patient remained disease free at 1 and 5 years were 0.54 (95% CI 0.29–0.74) and 0.27 (95% CI 0.09–0.5), respectively.

The median OS (mOS) of patients with a *BRCA1* and *BRCA2* mutations was 15 months (range 4–27 months) and 13 months (range 9–23 months), respectively. This difference was not significant ($P = 0.77$; Figure 1B).

Out of 71 participants, 12 received experimental therapy (PARP inhibitors) and 1 patient had missing data; these 13 cases were excluded from OS analysis. Patients treated with PARP inhibitors were excluded from OS analysis since these data that have been acquired in the course of a clinical trial have not yet been published. Median OS for the remaining 58 eligible patients was 14 months (95% CI 10–23 months; Figure 1A). No significant difference in median OS was observed in Jewish patients 13 months (95% CI 5–22 months) in comparison to non-Jewish patients 15 months (95% CI 8–60 months). Among 15 patients with early disease (stage 1/2), the probability that a patient with early-stage disease remained alive at 5 years was 0.52 (CI 0.18–0.78; Figure 2A), and the probability that patients with advanced disease ($n = 43$) remained alive at 5 years was 0.11 with (C.I 0.02–0.28). The mOS in combined stage 3 and 4 disease was 12 months (range 6–15 months; Figure 2B).

Table 2. Specific mutations

Specific mutation	Number of patients	BRCA1/2
185delAG	14	BRCA1
5382insC	4	BRCA1
2318delG	1	BRCA1
4237C>T	1	BRCA1
c.1-?80 + ?dup	1	BRCA1
6174delT	31	BRCA2
4075delGT	1	BRCA2
c3645-3646delinsTAAAAAG p.Phe1216LysfsX14	1	BRCA2
2041insA	1	BRCA2
5996dupT	1	BRCA2
6589delAG	1	BRCA2
c.8332-?-8487 + ?del, exon 19 deleted	1	BRCA2
3393delC	1	BRCA2
8765delAG	1	BRCA2
3967delA	1	BRCA2
IVS7 + 2T>G	1	BRCA2
4003G>T	1	BRCA2
7908T>A	1	BRCA2
9118-1G>C	1	BRCA2
2041delA	1	BRCA2
262_263delCT	1	BRCA2
2957_2958insG	1	BRCA2
5722_5723delCT	1	BRCA2
1736T>G	1	BRCA2
c.2681_2682delAA, p.K894TfsX8/ c.9382C>T, p.R3128X	1	BRCA1 + 2

Table 3. Family history of malignancies

Family history of cancer	Patients (%)
Yes	58 (81.7)
No	12 (16.9)
Missing	1 (1.4)
Family history of PDAC	
Number of patients	58
Yes	19 (32.7)
No	35 (60.3)
Missing	4 (7.0)
First-degree relative with cancer	
Number of patients	58
Yes	53 (91.4)
No	4 (6.9)
Missing	1 (1.7)

Abbreviation: PDAC = pancreatic ductal adenocarcinoma.

Median OS for stage 3 patients ($n = 8$) treated with platinum agents was over 48 months, compared to 10 months for those exposed to only non-platinum agents ($n = 7$, $P = 0.205$;

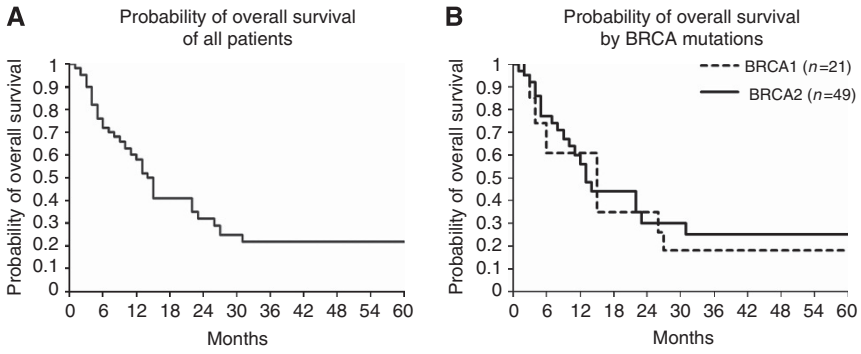

Figure 1. (**A**) Probability of overall survival of all patients. (**B**) Probability of overall survival by BRCA mutations.

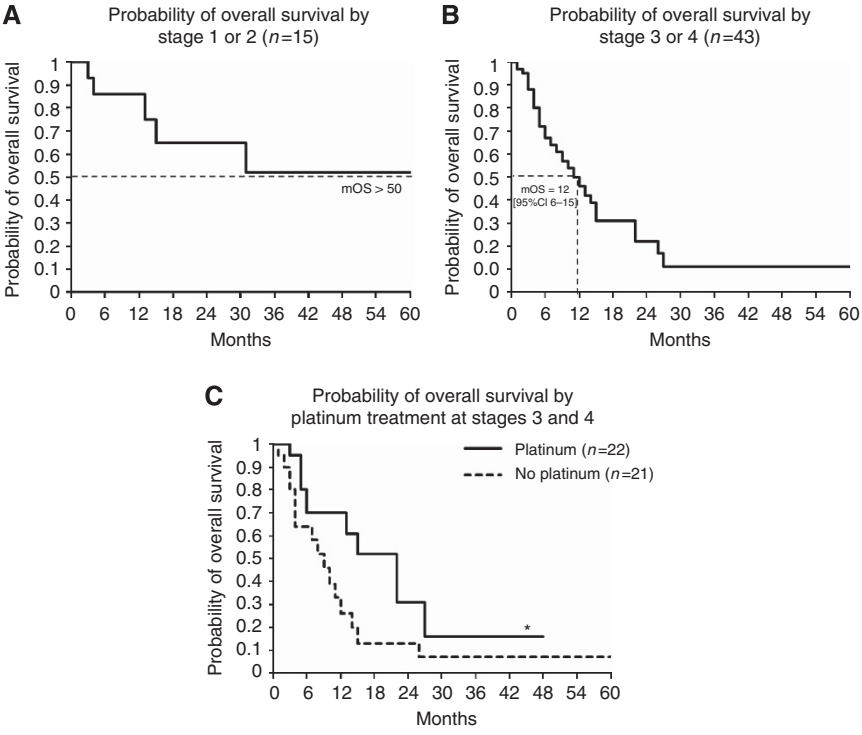

Figure 2. (**A**) Probability of overall survival by stage 1 or 2 ($n=15$). (**B**) Probability of overall survival by stage 3 or 4 ($n=43$). (**C**) Probability of overall survival by platinum treatment at stages 3 and 4.

Table 4. Overall survival in platinum-based chemotherapy *vs* non-platinum based in *BRCA1 BRCA2*-associated pancreatic cancer patients

Stage	Number of patients	Treatment	mOS (months)	Probability of OS at 12, 14–48 and 36 months)			*P*-value
3	15	P—8	>48	0.69 (0.21–0.91)	0.69 (0.21–0.91)	—	0.2059
		NP—7	10 (4–14)	0.21 (0.01–0.6)	0	—	
4	28	P—14	15 (5–22)	0.7 (0.38–0.87)	0.15 (0.01–0.49)	—	0.276
		NP—14	7 (3–15)	0.3 (0.08–0.56)	0.2 (0.03–0.46)	—	
3 and 4	43	P—22	22 (6–27)	0.7 (0.44–0.85)	—	0.16 (0.01–0.46)	**0.0389**
		NP—21	9 (4–12)	0.26 (0.08–0.48)	—	0.07 (0.01–0.26)	

Abbreviations: mOS = median overall survival; NP = no platinum; OS = overall survival; P = platinum. Statistically significant value is in bold.

Table 4). In patients with stage 4 disease, mOS of platinum-treated patients ($n=14$) was 15 months compared with 7 months for those treated with only non-platinum-treated patient ($n=14$, $P=0.276$). When combining data for stages 3 and 4, the mOS was 22 months for the platinum exposed ($n=22$) compared with 9 months for the non-platinum ($n=21$)

treatment groups ($P<0.039$; Figure 2C). Overall survival probabilities are shown in Table 4.

DISCUSSION

Our data suggest that *BRCA* mutation status is an important clinical factor in PDAC and that *BRCA* mutation status may be an important prognostic and predictive biomarker for PDAC.

The median age of diagnosis was a decade younger than an unselected population reported from the Surveillance, Epidemiology, and End Results (Howlader *et al*, 2012). The effect of germline *BRCA1/2* mutations on clinical course and therapeutic outcome compared to sporadic, *BRCA1/2* wild type, subjects has previously been reported in a variety of cancer types. The prognostic significance of *BRCA1* or *BRCA2*-associated PDAC is currently unknown. In ovarian cancer, a significantly longer OS has been reported for *BRCA* mutation carriers compared with non-carriers (53.7 months *vs* 37.9 months, $P=0.002$), with a more pronounced effect for patients with advanced stage, higher grade disease (Chetrit *et al*, 2008). In a study of 1545 consecutive Ashkenazi Jewish breast cancer patients, of whom 10% were *BRCA* carriers, no survival difference was noted between carriers and non-carriers (Rennert *et al*, 2007). In addition, similar outcomes were identified for *BRCA* mutation breast cancer carriers and sporadic cases in a large multivariate analysis (Goodwin *et al*, 2012). In our study, we observed a slightly more favourable outcome in the setting of being a *BRCA1/2* mutation carrier in PDAC patients. Historical controls report an mOS of 4.4 months (Bilimoria *et al*, 2007) yet in the present study, median all-stage OS of 58 PARP inhibitor naive patients was 14 months. Therefore our preliminary data suggest that *BRCA1* or *BRCA2*-associated PDAC has more favourable outcome than non-*BRCA*-associated PDAC.

The main finding in our study is an improvement in OS in stage 3 and 4 *BRCA1* or *BRCA2*-associated PDAC patients who were treated with platinum-based agents compared with those who were not treated with these agents. It is worth noting that previous clinical trials have not shown an OS benefit with the combination of platinum agents and gemcitabine in advanced pancreatic cancer(Heinemann *et al*, 2006; Poplin *et al*, 2009). Our results suggested a more favourable outcome with platinum treatment for each individual stage; however, these differences were not statistically significant.

The effect of *BRCA* mutations and response to DNA cross-linking agents in PDAC was evaluated by Lowery *et al* (2011), who reported that 5/6 *BRCA*-associated PDAC patients who received a platinum agent as first-line metastatic therapy demonstrated a partial or complete radiographic response. This favourable response of *BRCA*-associated PDAC to DNA crosslinking agents is also supported by a case report by Sonnenblick (2011). Similarly, a survival advantage with platinum-containing regimens was reported for patients with PDAC and a family history of any malignancy, in whom the status of *BRCA* mutation carrier status was not specified (Oliver *et al*, 2010).

These reports, together with our findings, highlight the potential biological importance of treating tumours with deficient HR pathway with DNA crosslinking agents. Future studies should consider the use of cisplatin, in combination with other agents that selectively kill error-prone, HR-defective cells such as cyclophosphamide, temozalomide and PARP inhibitors (Evers *et al*, 2010). Importantly, these studies should also address differential individual patient sensitivity and *de novo* or acquired resistance to cisplatin using assays that reflect relative genetic instability (low or high copy number alteration, expression of other DNA repair genes, RAD51 nuclear foci as surrogate markers for HR and BRCA1/2-genetic reversion; Bouwman *et al*, 2010; Dent and Bristow, 2011; Vollebergh *et al*, 2012).

The present study is the largest cohort to date that has been reported with *BRCA1/2*-associated PDAC patients. As PARP inhibitors are being introduced to PDAC patients harbouring BRCA mutations, in the context of clinical trials, the assembly and analysis of similar data will be difficult; therefore, our observations may remain unique and difficult to replicate. The majority of our patients in the platinum-based group received gemcitabine and cisplatin, therefore we cannot conclude from our data whether the doublet combination with platinum is sufficient for *BRCA*-associated PDAC or whether the new FOLFIRINOX combination is superior. Previously reported data, combined with data reported herein on the superior therapeutic response to platinum-based chemotherapy in *BRCA*-associated PDAC, needs to be interpreted with caution for several reasons: the non-randomised, retrospective nature of these studies, the limited sample sizes, the comparison to historic controls and the variation in chemotherapy regimens both within and between sites including the use of different platinum agents, dosing schedules, dosing frequency and improvement in chemotherapy drugs over the past decade. In addition, the majority of our patients were of Ashkenazi Jewish descent, and this limits the general applicability of our findings to ethnically diverse PDAC patients with a different spectrum of *BRCA1/2* mutations. Nonetheless, our experiences in non-Israeli cancer centres, suggest similar positive responses to platinum-based therapies for other ethnic groups with *BRCA*-associated PDAC.

In conclusion, the current study suggests that *BRCA* mutation status may be a prognostic and predictive biomarker for PDAC and that *BRCA*-associated PDAC patients may benefit from the addition of platinum agents to standard therapy. Our data have not definitely shown this in all stages and it would be beneficial to further investigate early stage *vs* late stage in a case–control study. A randomised phase II clinical trial evaluating the addition of PARP inhibition to platinum-based therapy in a genetically selected population of *BRCA1*, *BRCA2* or *PALB2* mutation carriers with PDAC is currently underway to further address this clinical issue (NCT01585805).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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