Acta Medica
Okayama

Original Article

Association between *BRCA* Gene Variants and the Response to Modified FOLFIRINOX in Patients with Unresectable Pancreatic Cancer

Shigeru Horiguchi*, Kazuyuki Matsumoto, Kosaku Morimoto, Akihiro Matsumi,
Hiroyuki Terasawa, Yuki Fujii, Tatsuhiro Yamazaki, Koichiro Tsutsumi, and Hironari Kato

Department of Gastroenterology and Hepatology, Okayama University Hospital, Okayama 700-8558, Japan

We investigated the effect of modified FOLFIRINOX (mFFX) in unresectable pancreatic cancer by retrospectively analyzing the cases of 43 patients who underwent *BRCA* testing (germline, n = 11; somatic, n = 26; both germline and somatic, n = 6). The association between *BRCA* mutations and therapeutic effect was clarified. Six patients tested positive for germline pathogenic variants. Familial pancreatic cancer (33% *vs*. 3%, *p* = 0.006) and peritoneal disseminated lesions (66% *vs*. 8%, *p* < 0.001) were significantly more common in patients with germline pathogenic variants. The partial response (PR) rate was 100% in the germline *BRCA*-positive patients, and 27% in the germline *BRCA*-negative patients (*p* < 0.001). The median progression-free survival (PFS) was not reached for any germline *BRCA*-positive patients but was 9.0 months for the germline *BRCA*-negative patients (*p* = 0.042). Patients with stage IV *BRCA*-associated pancreatic cancer had better overall survival than those with non-*BRCA*-associated pancreatic cancer, although the difference was nonsignificant (not reached *vs*. 655 days, *p* = 0.061). Our results demonstrate that a PR and prolonged PFS can be expected in germline *BRCA*-positive patients after treatment with mFFX. Our findings also suggest that germline *BRCA* pathogenic variants may be useful as biomarkers for the therapeutic effect of mFFX in patients with pancreatic cancer.

Key words: *BRCA*, FOLFIRINOX, pancreatic cancer, progression-free survival, pathogenic variant

*B*RCA1 (BReast CAncer gene 1) and *BRCA2* are tumor-suppressor genes that repair both double-stranded DNA breaks and cross-linking damage induced by DNA-damaging drugs, through homologous recombination. *BRCA1* and *BRCA2* are localized in the nucleus in response to DNA damage, leading to the formation of RAD51 foci and the subsequent repair of DNA damage [1]. *BRCA* pathogenic variants have been reported in a large number of Japanese patients with pancreatic cancer, with the rates 0.69-0.90% for *BRCA1* and 2.20-2.50% for *BRCA2* [2,3]. Clinical data from studies of ovarian cancer revealed that patients with *BRCA1* and *BRCA2* mutations had higher response rates and longer progression-free survival (PFS) and overall survival (OS) after treatment with platinum-based and other DNA-damaging agents, resulting in improved outcomes [4-10]. Favorable outcomes have also been reported in patients with breast cancer with respect to the response rate and PFS in *BRCA*-positive patients [11-13].

Similar results have been obtained in studies of patients with pancreatic cancer, suggesting that pancreatic cancer patients who are positive for *BRCA1* and/or *BRCA2* pathogenic variants would achieve better treatment responses to platinum-based drugs compared to those who are negative for these variants [14-16]. A prospective analysis was conducted in patients with

pancreatic cancer with or without germline mutations in *BRCA1* and *BRCA2* who were treated with a combination of folinic acid, 5-fluorouracil (5-FU), irinotecan, and oxaliplatin (*i.e.*, FOLFIRINOX, also referred to as FFX) as neoadjuvant chemotherapy. FOLFIRINOX was shown to have a significant prognostic effect in a phase III study with gemcitabine as the control group [17]. Favorable treatment results have also been reported in phase II trials in Japan [18].

Modified FOLFIRINOX in which the dose of CPT11 (*i.e.*, taxotere, cisplatin and irinotecan) is reduced to 150 mg/m^2 is currently used as the standard treatment due to its safety and efficacy [19]. Another study's results suggested that *BRCA*-positive patients with pancreatic cancer (n = 9) had a better overall response rate (ORR) and disease-free survival than *BRCA*-negative patients (n = 30) [20]. However, there are potential problems with the generalizability of these findings. First, although there have been a large number of studies of patients in Western countries (especially Israel, which included Ashkenazi Jews) who have a genetic predisposition to pancreatic cancer, there have been insufficient studies from Asian countries. Second, some of the previous investigations of *BRCA* mutations were not restricted to pathogenic mutations; rather, they included variants of uncertain significance (VUS) and non-pathogenic *BRCA* mutations. Enrolling patients with VUS or non-pathogenic mutations may result in an underestimation of the role of *BRCA* pathogenic variants in association with the therapeutic effect of anticancer drugs.

Third, some studies included different treatment regimens, such as FFX, gemcitabine, cisplatin, and 5-FU, leucovorin, and oxaliplatin (FOLFOX; *i.e.*, folinic acid, fluorouracil, and oxaliplatin). Since the therapeutic effects of each of these regimens differ, studies with a uniform regimen should be conducted. To the best of our knowledge, no study has investigated the effect of modified FFX (mFFX) on the prognosis of Japanese patients with unresectable pancreatic cancer with or without germline *BRCA* mutations. Herein we present retrospective, real-world data on 43 Japanese patients with pancreatic cancer who were treated with mFFX, including six *BRCA*-positive patients and 37 *BRCA*-negative patients.

Patients and Methods

Patients. We retrospectively enrolled patients who were treated with mFFX at Okayama University Hospital (Okayama, Japan) and underwent the BRACAnalysis (Myriad, Salt Lake City, UT, USA) or a next-generation sequencing (NGS)-based multiplex assay between August 2019 and September 2021. We obtained the data on the patients' demographics, clinical history, personal and family history of cancer, systemic chemotherapy, and treatment response from their medical records.

Chemotherapy. mFFX was used as the standard of care. Each of the 43 patients was treated with mFFX every 2 weeks as follows: a 2-hr intravenous (IV) infusion of 85 mg/m^2 oxaliplatin and a 2-hr IV infusion of 200 mg/m^2 l-leucovorin. Irinotecan (150 mg/m^2) was intravenously infused over a 90-min period, followed by a continuous 46-hr IV infusion of 2,400 mg/m^2 5-FU (bolus 5-FU was not administered). The patients routinely received palonosetron, aprepitant, and dexamethasone as prophylaxis for emesis. Treatment was continued until the observation of disease progression, unacceptable toxicity, discontinuation at the discretion of the treating physician, or the patient's refusal.

NGS-based multiplex assay. Genomic tests were performed using a somatic test (FoundationOne CDx: Foundation Medicine, Cambridge, MA, USA) and a germline (BRACAnalysis) test. The FoundationOne CDx test uses a NGS platform and hybrid-capture methodology that detects base substitutions, insertions, deletions, and copy-number alterations in up to 324 genes and selected gene rearrangements. Formalin-fixed, paraffin-embedded tumor specimens were sent to a Clinical Laboratory Improvement Amendments-certified and College of American Pathologists-accredited laboratory. Biopsy tissues from distant tumor sites were selected when feasible. DNA extracted from tumor samples was subjected to NGS using the hybrid capture-based FoundationOne CDx assay. Homologous recombination repair (HRR) genes (*ATM*, *BAP1*, *BARD1*, *BRIP1*, *CHEK2*, *FANCA*, *FANCC*, *NBN*, *PALB2*, *RAD51*, *RAD51C*, and *RAD51D*) associated with pancreatic cancer were examined in addition to *BRCA* [21, 22]. The BRACAnalysis test was used to identify carriers of germline loss-of-function (deleterious or suspected deleterious) mutations in *BRCA1* or *BRCA2*.

Response assessment and clinical outcome.
Contrast-enhanced computed tomography was performed every 8-10 weeks. The patients' treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors (ver. 1.1). PFS was defined as the time from the initiation of mFFX therapy to the date of disease progression or death from any cause. Adverse events were compared between *BRCA*-positive and *BRCA*-negative groups. The CTCAE5.0 criteria were used to assess adverse events.

Statistical analyses.   Patient characteristics were compared using the χ^2-test or Fisher's exact test for categorical variables. The *t*-test and an analysis of variance (ANOVA) were used for continuous variables. Time was censored at the date of the last follow-up for patients who were still alive. The Kaplan–Meier method was used to estimate PFS and overall survival, and the log-rank test was used to determine significance. A probability (*p*)-value < 0.05 was considered significant. Statistical analyses were conducted using SAS (ver. 14; SAS, Cary, NC, USA).

Ethical committee approval.   All procedures used herein were in accord with the ethical standards of our institutional research committee and with the 1964 Declaration of Helsinki and its later amendments. This study was approved by the Institutional Review Board of Okayama University (approval no. 2104-010). In light of the study's retrospective design and anonymized data, the requirement for patients' informed consent was waived.

Results

Patients' characteristics.   Between August 2019 and September 2021, 43 patients with unresectable pancreatic cancer were treated with mFFX at Okayama University Hospital and tested for *BRCA* mutations. Germline *BRCA* testing was performed in 11 patients, and somatic *BRCA* testing was performed in 26 patients; six patients underwent both germline and somatic *BRCA* testing. Germline testing was performed in all *BRCA*-positive cases. Six *BRCA*-positive cases were detected by germline testing (n = 2) or germline and somatic testing (n = 4), whereas 37 *BRCA*-negative cases were confirmed by germline testing (n = 9), somatic testing (n = 26), or germline and somatic testing (n = 2). The specific variants are shown in Table 1.

Pathogenic variants, rather than VUS or likely

Table 1   The mutations in the *BRCA*-positive patients

Mutation	Patients
BRCA1 E1214*	1
BRCA2 N2135fs*3	1
BRCA2 I1859fs	2
BRCA2 Q3026*	1
BRCA2 R3128*	1

pathogenic variants, were observed in all six *BRCA*-positive patients. The clinical characteristics of the patients are presented in Table 2. The *BRCA*-positive patients had a significantly higher prevalence of ovarian cancer compared to the *BRCA*-negative patients. The prevalence of peritoneal dissemination and familial pancreatic cancer was also significantly higher in the *BRCA*-positive patients than in the *BRCA*-negative patients. Table 3 lists the patients with a family history of first-degree relatives with cancer. *BRCA*-positive patients were more likely to have a family history of breast cancer. We investigated the presence of other HRR-related genes in all 32 patients who received FoundationOne CDx and identified only one case with *BAP1* variant. HRR-related genes other than *BRCA* were not searched for in the 11 patients who underwent only the BRACAnalysis.

Overall response rate.   The ORR, according to the Response Evaluation Criteria in Solid Tumors (ver. 1.1), was significantly higher in the *BRCA*-positive patients *versus* the *BRCA*-negative patients (100% *vs.* 27%, respectively; $p < 0.001$) (Table 4). It is noteworthy that all six *BRCA*-positive patients had a partial response (n = 6, 100%); no patients in this group had progressive disease or stable disease as the best response. In the *BRCA*-negative group, a partial response was observed in 27% (n = 10) of the patients and stable disease was observed in 51% (n = 19). The disease control rate was 100% (n = 6) in the *BRCA*-positive group and 78% (n = 29) in the *BRCA*-negative group ($p = 0.200$) (Table 4).

We performed a subset analysis to investigate the impact of the mFFX regimen on the patients' ORR. Four of the six *BRCA*-positive patients were treated with mFFX as first-line chemotherapy. Twenty of the 37 *BRCA*-negative patients were treated with mFFX as first-line chemotherapy, and the other 17 were treated with mFFX as second-line chemotherapy.

Table 2 The characteristics of the 43 Japanese patients with pancreatic cancer

Characteristic	*BRCA*-positive (n=6)	*BRCA*-negative (n=37)	*P*-value
Age (years), median	64	60	0.580
Male sex, n (%)	3 (50)	14 (37)	0.570
Primary tumor location, n (%)			
Head/body+tail	1/5	9/28	0.680
Disease status, n (%)			
Locally advanced	0 (0)	12 (32)	0.350
Metastatic	4 (67)	18 (49)	
Recurrent	2 (33)	7 (19)	
Metastases, n (%)			
Liver	4 (66)	20 (54)	0.510
Peritoneal	4 (66)	3 (8)	<0.001
Lung	0 (0)	5 (13)	0.330
Lymph node	0 (0)	4 (11)	0.390
Bone	0 (0)	2 (5)	0.550
Personal history, n (%)			
Breast cancer	1 (16)	1 (3)	0.140
Ovarian cancer	1 (16)	0 (0)	0.014
Prostate cancer	0 (0)	0 (0)	–
Familial pancreatic caner, n (%)	2 (33)	1 (3)	0.006
mFFX, n			
First/second regimen	4/2	20/17	0.560
CA19-9 (U/mL), median	98	56	0.950

CA19-9, carbohydrate antigen 19-9; mFFX, modified FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin).

Table 3 Malignancies in first-degree relatives of the *BRCA*-positive and -negative patients

Malignancy	*BRCA*-positive (n=6)	*BRCA*-negative (n=37)	*P*-value
Breast	4 (67)	2 (5)	<0.001
Ovary	0 (0)	1 (3)	0.680
Pancreas	2 (33)	4 (11)	0.130
Prostate	1 (17)	0 (0)	0.012
Lung	1 (17)	7 (19)	0.890
Stomach	1 (17)	10 (27)	0.580
Bladder	1 (17)	1 (3)	0.130
Skin	1 (17)	0 (0)	0.012
Uterus body	1 (17)	0 (0)	0.012
Uterus cervix	0 (0)	1 (3)	0.680
Thyroid	1 (17)	0 (0)	0.012
Colon	0 (0)	5 (14)	0.330
Esophagus	0 (0)	1 (3)	0.680
Rectum	0 (0)	1 (3)	0.680
Kidney	0 (0)	1 (3)	0.680
Bile duct	0 (0)	2 (5)	0.550
Liver	0 (0)	1 (3)	0.680

The lesion reduction rate on computed tomography in the patients who achieved a partial response was significantly higher in the *BRCA*-positive group than in *BRCA*-negative patients (n=10) (71% *vs.* 44%, respectively; $p=0.044$) (Fig. 1).

Progression-free survival. PFS was used as a surrogate endpoint for mFFX response. The *BRCA*-positive patients had significantly longer PFS compared

Table 4   Efficacy measures: The overall response rate (ORR) and the rates of partial response, stable disease, and disease control

Outcome	*BRCA*-positive (n = 6)	*BRCA*-negative (n = 37)	*P*-value
PFS (months)			
Median	Not reached	9.0	0.042
ORR, n (%)	6 (100)	10 (27)	<0.001
Partial response	6 (100)	10 (27)	
Stable disease	0 (0)	19 (51)	
Progressive disease	0 (0)	8 (22)	
Disease control rate, n (%)	6 (100)	29 (78)	0.200

ORR, overall response rate; PFS, progression-free survival.
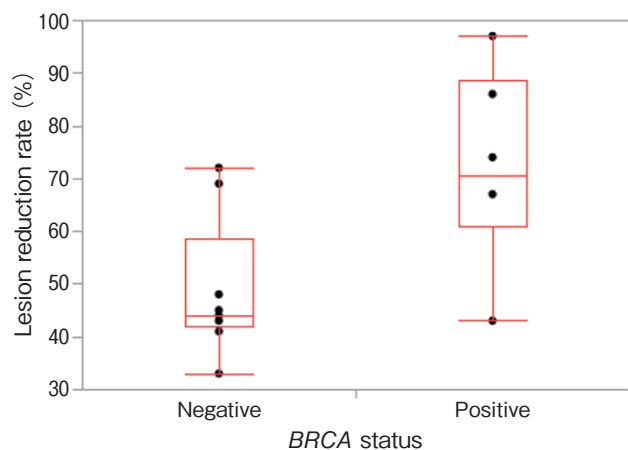
Fig. 1   The lesion reduction rate in the partial responders. The lesion reduction rate was significantly higher in the *BRCA*-positive patients (n = 6) than in the *BRCA*-negative patients (n = 10) (71% *vs.* 44%, respectively; *p* = 0.044).

Fig. 2   Progression-free survival (PFS). The median PFS was significantly longer in the *BRCA*-positive patients (n = 6) than in the *BRCA*-negative patients (n = 37) (not reached *vs.* 274 days, respectively; *p* = 0.047).

to the *BRCA*-negative patients (hazard ratio [HR] 0.24, 95% confidence interval [CI]: 0.039-0.840; *p* = 0.022). The median PFS was not reached in the *BRCA*-positive group and was 9.0 months in the *BRCA*-negative group (Table 4, Fig. 2). As shown in Table 5, the following factors were not significant factors affecting the patients' PFS: patient age, sex, lesion site(s), carbohydrate antigen 19-9 (CA19-9) levels at the start of treatment, and the timing of the administration of mFFX.

Overall survival.   Overall survival was examined in 22 patients (four *BRCA*-positive patients and 18 *BRCA*-negative patients) with stage IV disease at the time of diagnosis. FFX was the initial treatment if all four of the *BRCA*-positive patients and 13 (72%) of the 18 *BRCA*-negative patients. There were no significant differences in age, sex, CA19-9 levels, or treatment
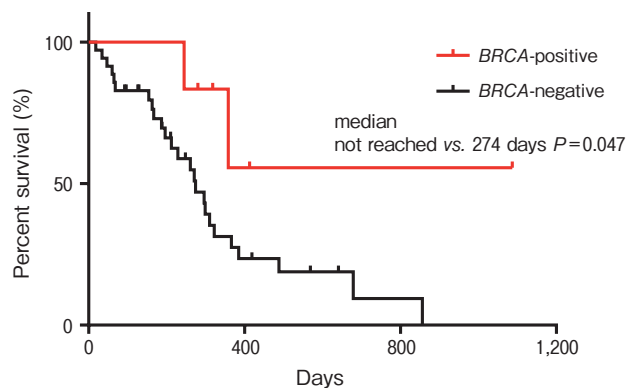
lines between these two groups (Table 6). The germline *BRCA*-positive patients tended to have better overall survival than the germline *BRCA*-negative patients (not reached *vs.* 655 days, respectively; *p* = 0.061) (Fig. 3).

Adverse events.   The incidence of hematotoxicity and that of non-hematologic toxicity were compared between the *BRCA*-positive and -negative groups; no significant between-group difference was detected in the hematologic or non-hematologic toxicity incidence rate. The main adverse events in the *BRCA*-positive and -negative groups were neutropenia (50% *vs.* 57%), febrile neutropenia (0% *vs.* 2.7%), nausea (17% *vs.* 11%), anorexia (33% *vs.* 24%), and peripheral sensory neuropathy (17% *vs.* 8.1%, respectively).

Discussion

The results of our retrospective analyses of 43

Table 5 Univariate analysis of progression-free survival (PFS) in 43 Japanese patients with pancreatic cancer

Variable	HR	95% CI	*P*-value
Age (years) [≥65/<65]	0.45	0.17–1.10	0.080
Sex [male/female]	0.88	0.37–1.90	0.770
Location [head/body+tail]	1.90	0.74–4.60	0.140
CA19-9 (U/mL) [≥40/<40]	1.80	0.72–5.40	0.200
BRCA status [positive/negative]	0.26	0.04–0.91	0.032
mFFX [second/first line]	1.20	0.56–2.70	0.580
Resection [yes/no]	0.85	0.30–2.00	0.750

CA19-9, carbohydrate antigen 19-9; CI, confidence interval; HR, hazard ratio; mFFX, modified FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin); PFS, progression-free survival.

Table 6 Characteristics of the patients with stage IV pancreatic cancer

Characteristic	*BRCA*-positive (n=4)	*BRCA*-negative (n=18)	*P*-value
Age (years), median	64	59	0.440
Male sex, n (%)	2 (50)	7 (39)	0.680
mFFX, n			
First/second regimen	4/0	13/5	0.230
CA19-9 (U/mL), median	236	206	0.560

CA19-9, carbohydrate antigen 19-9; mFFX, modified FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin).
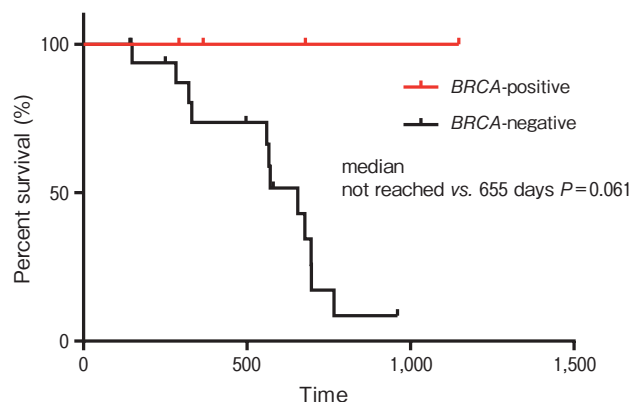

Fig. 3 The overall survival of the patients with stage IV disease. The median overall survival tended to be longer in the *BRCA*-positive patients (n=4) than in the *BRCA*-negative patients (n=18) (not reached *vs.* 655 days, respectively; *p*=0.061).

cancer in real-world clinical settings [14,15,20,23,24]. The progression-free survival after mFFX treatment was also significantly longer in the germline *BRCA*-positive patients compared to the germline *BRCA*-negative patients.

In this patient series, peritoneal dissemination was significantly more common in the *BRCA*-positive group *versus* the *BRCA*-negative group. Although we have found no reports on the relationship between *BRCA* pathogenic variants and the incidence of peritoneal dissemination in patients with pancreatic cancer, a relationship between *BRCA* pathogenic variants and peritoneal metastasis has been reported in patients with ovarian cancer; compared to the *BRCA*-negative patients, the women with ovarian cancer and *BRCA*-positive family members were more likely to have high-grade and extra-ovarian spread [9].

With respect to a family history of malignancies in first-degree relatives, we observed that the present *BRCA*-positive patients had a greater proportion of family members with breast cancer compared to the *BRCA*-negative patients. (67% *vs.* 5%, respectively; *p*<0.001). However, there was no significant between-

Japanese patients with pancreatic cancer demonstrated that the germline *BRCA* mutation carriers with pancreatic cancer responded well to mFFX, with a partial response rate of 100%. This response rate was higher than that of all of the reported patients with pancreatic

group difference in the family history of pancreatic cancer (33% *vs.* 11%, respectively; $p = 0.130$). Golan *et al.* also reported that a greater proportion of the family members of *BRCA*-positive patients had breast cancer compared to *BRCA*-negative patients (33.3% *vs.* 6.6%, respectively; $p = 0.069$), while there was no similar significant difference in patients with pancreatic cancer (22.2% *vs.* 10%, respectively; $p = 0.600$) [20]. Their results suggest that *BRCA* variants may not be uncommon, even in patients without a family history of pancreatic cancer. *BRCA* testing is thus advisable for patients with pancreatic cancer who have first-degree relatives with breast cancer.

Excellent sensitivity to platinum-based chemotherapy has been reported in germline *BRCA*-positive patients with pancreatic cancer [14,15,20,23,25]. FOLFIRINOX is a standard treatment using platinum agents for pancreatic cancer, and FOLFIRINOX has been reported to be useful in *BRCA*-positive pancreatic cancer [20,21]. Based on the results of these reports, we also investigated whether FOLFIRINOX is useful for *BRCA*-pancreatic cancer in Japanese individuals. Our present analyses revealed that the germline *BRCA*-positive patients had a significantly higher ORR than the germline *BRCA*-negative patients (100% *vs.* 27%, respectively; $p < 0.001$). Among the partial responders, the six germline *BRCA*-positive patients had a greater lesion reduction rate than the 10 germline *BRCA*-negative patients (71% *vs.* 44%, respectively; $p = 0.044$).

Golan *et al.* reported that the most striking difference between *BRCA*-positive and -negative patients was the significantly higher pathologic complete response rate to treatment with mFFX for borderline resectable pancreatic cancer (44% *vs.* 10%, respectively; $p = 0.009$) [20]. Wattenberg *et al.* reported that patients with *BRCA*- or *PALB2*-positive pancreatic cancer had better response rates than mutation-negative patients treated with mFFX (60% *vs.* 27%, respectively) [23]. Our present findings also support a favorable response to mFFX and tumor shrinkage in Japanese patients.

We observed superior PFS in *BRCA*-positive patients compared to *BRCA*-negative patients (not reached *vs.* 9.0 months, respectively; $p = 0.042$). Wattenberg *et al.* observed that the PFS was 10.1 months in *BRCA*- or *PALB2*-positive patients and 6.9 months in control patients treated with platinum-based chemotherapy ($p = 0.001$) [23]. In a study by Kondo *et al.* reported that the median PFS was significantly longer in patients with HRR gene mutations than in those without HRR gene mutations (20.8 *vs.* 1.7 months, respectively; $p = 0.049$) [24]. However, these studies included inconsistent and variable treatment regimens such as FFX, FOLFOX, gemcitabine + cisplatin, S-1 + oxaliplatin, gemcitabine, and oxaliplatin. In addition, half of the variants were VUS, making it difficult to apply these PFS data in clinical practice. In this context, we believe that our present results are more reliable and reproducible in an actual clinical setting, as all variants were pathogenic, and a uniform chemotherapy regimen (mFFX) was used.

The overall survival of the present patients with stage IV disease (n = 22) was significantly longer in *BRCA*-positive patients (n = 4) than in *BRCA*-negative patients (n = 18). Another study showed that among patients with pancreatic cancer treated with FFX, the group with DNA repair gene mutations had better overall survival than the control group [16]. It has also been reported that *BRCA*-positive patients with stage III/IV pancreatic cancer treated with platinum agents had significantly better survival than those not treated with platinum agents [14]. In the former study [16], over half of the nine patients in the *BRCA*-positive group had VUS, and in the latter study [14] the results of platinum-based treatment in *BRCA*-negative patients were not described. The number of patients in the present investigation (n = 43) is also small, and the question of whether FFX has a significant effect on overall survival depending on the presence or absence of *BRCA* mutations remains a matter of controversy, requiring further research.

No reliable clinical or molecular signatures are currently available for predicting the response to mFFX in patients with pancreatic cancer. Our analyses revealed a high partial response rate and prolonged PFS in the *BRCA*-positive patients. Although none of our *BRCA*-positive patients received chemotherapy other than mFFX as first-line treatment, mFFX may be recommended for germline *BRCA*-positive patients with pancreatic cancer, based on the present excellent response rate. Golan *et al.* also reported favorable results with platinum-based antineoplastic agents for *BRCA*-associated pancreatic cancer [20], but Ashkenazi Jews accounted for > 60% of the study population. The data for other ethnicities, especially Asians, are limited [14,15,20,25]. Our present data can be used as a reference for the clinical utility of mFFX in germline

BRCA-positive non-Ashkenazi Jewish patients with pancreatic cancer, particularly in Asian populations.

Germline *BRCA* testing is expected to be a guide for the selection of neoadjuvant chemotherapy regimens, based on the high lesion-reduction rate in *BRCA*-positive patients. Golan *et al.* described high efficacy of mFFX as neoadjuvant chemotherapy, with a response rate of 66% (complete response, 44%; partial response, 22%) in germline *BRCA* mutation carriers [20]. Our present findings support this high efficacy. Based on these past and present results, the administration of mFFX to germline *BRCA* mutation carriers may pave the way for subsequent conversion surgery for locally advanced unresectable pancreatic cancer.

The main limitations of this study were its single-center, retrospective design and relatively small sample size. The patient series was limited to those with unresectable tumors, and not all of the somatic *BRCA*-negative patients underwent germline testing; the prevalence of *BRCA* pathogenic variants may thus have been underestimated. In addition, we were unable to search for other HRR-related gene mutations in the 11 patients who underwent only the BRACAnalysis.

In conclusion, germline *BRCA* mutation carriers with unresectable pancreatic cancer treated with mFFX showed a superior response and prolonged PFS. Based on the 100% partial response rate, mFFX may be considered as a first-line treatment for germline *BRCA* mutation carriers with unresectable pancreatic cancer.

References

1. Lohse I, Borgida A, Cao P, Cheung M, Pintilie M, Bianco T, Holter S, Ibrahimov E, Kumareswaran R, Bristow RG, Tsao MS, Gallinger S and Hedley DW: *BRCA1* and *BRCA2* mutations sensitize to chemotherapy in patient-derived pancreatic cancer xenografts. Br J Cancer (2015) 113: 425–432.

2. Mizukami K, Iwasaki Y, Kawakami E, Hirata M, Kamatani Y, Matsuda K, Endo M, Sugano K, Yoshida T, Murakami Y, Nakagawa H, Spurdle AB and Momozawa Y: Genetic characterization of pancreatic cancer patients and prediction of carrier status of germline pathogenic variants in cancer-predisposing genes. EBiomedicine (2020) 60: 103033.

3. Momozawa Y, Sasai R, Usui Y, Shiraishi K, Iwasaki Y, Taniyama Y, Parsons MT, Mizukami K, Sekine Y, Hirata M, Kamatani Y, Endo M, Inai C, Takata S, Ito H, Kohno T, Matsuda K, Nakamura S, Sugano K, Yoshida T, Nakagawa H, Matsuo K,

Murakami Y, Spurdle AB and Kubo M: Expansion of cancer risk profile for *BRCA1* and *BRCA2* pathogenic variants. JAMA Oncol (2022) 8: 871–878.

4. Alsop K, Fereday S, Meldrum C, DeFazio A, Emmanuel C, George J, Dobrovic A, Birrer MJ, Webb PM, Stewart C, Friedlander M, Fox S, Bowtell D and Mitchell G: *BRCA* mutation frequency and patterns of treatment response in *BRCA* mutation-positive women with ovarian cancer: A report from the Australian Ovarian Cancer Study Group. J Clin Oncol (2012) 30: 2654–2663.

5. Norquist BM, Brady MF, Harrell MI, Walsh T, Lee MK, Gulsuner S, Bernards SS, Casadei S, Burger RA, Tewari KS, Backes F, Mannel RS, Glaser G, Bailey C, Rubin S, Soper J, Lankes HA, Ramirez NC, King MC, Birrer MJ and Swisher EM: Mutations in homologous recombination genes and outcomes in ovarian carcinoma patients in GOG 218: An NRG Oncology/Gynecologic Oncology Group study. Clin Cancer Res (2018) 24: 777–783.

6. Vencken PMLH, Kriege M, Hoogwerf D, Beugelink S, Van der Burg MEL, Hooning MJ, Berns EM, Jager A, Collée M, Burger CW and Seynaeve C: Chemosensitivity and outcome of *BRCA1*- and *BRCA2*-associated ovarian cancer patients after first-line chemotherapy compared with sporadic ovarian cancer patients. Ann Oncol (2011) 22: 1346–1352.

7. Bolton KL, Chenevix-Trench G, Goh C, Sadetzki S, Ramus SJ, Karlan BY, Lambrechts D, Despierre E, Barrowdale D, McGuffog L, Healey S, Easton DF, Sinilnikova O, Benítez J, García MJ, Neuhausen S, Gail MH, Hartge P, Peock S, Frost D, Evans DG, Eeles R, Godwin AK, Daly MB, Kwong A, Ma ES, Lázaro C, Blanco I, Montagna M, D'Andrea E, Nicoletto MO, Johnatty SE, Kjær SK, Jensen A, Høgdall E, Goode EL, Fridley BL, Loud JT, Greene MH, Mai PL, Chetrit A, Lubin F, Hirsh-Yechezkel G, Glendon G, Andrulis IL, Toland AE, Senter L, Gore ME, Gourley C, Michie CO, Song H, Tyrer J, Whittemore AS, McGuire V, Sieh W, Kristoffersson U, Olsson H, Borg Å, Levine DA, Steele L, Beattie MS, Chan S, Nussbaum RL, Moysich KB, Gross J, Cass I, Walsh C, Li AJ, Leuchter R, Gordon O, Garcia-Closas M, Gayther SA, Chanock SJ, Antoniou AC, Pharoah PD, EMBRACE, kConFab Investigators and Cancer Genome Atlas Research Network: Association between *BRCA1* and *BRCA2* mutations and survival in women with invasive epithelial ovarian cancer. JAMA (2012) 307: 382–390.

8. Singer CF, Tan YY, Muhr D, Rappaport C, Gschwantler-Kaulich D, Grimm C, Polterauer S, Pfeiler G, Berger A and Tea MM: Association between family history, mutation locations, and prevalence of *BRCA1* or *2* mutations in ovarian cancer patients. Cancer Med (2019) 8: 1875–1881.

9. Werness BA, Ramus SJ, DiCioccio RA, Whittemore AS, Garlinghouse-Jones K, Oakley-Girvan I, Tsukada Y, Harrington P, Gayther SA, Ponder BA and Piver MS: Histopathology, FIGO stage, and *BRCA* mutation status of ovarian cancers from the Gilda Radner Familial Ovarian Cancer Registry. Int J Gynecol Pathol (2004) 23: 29–34.

10. Yang D, Khan S, Sun Y, Hess K, Shmulevich I, Sood AK and Zhang W: Association of *BRCA1* and *BRCA2* mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. JAMA (2011) 306: 1557–1565.

11. Tung NM, Boughey JC, Pierce LJ, Robson ME, Bedrosian I, Dietz JR, Dragun A, Gelpi JB, Hofstatter EW, Isaacs CJ, Jatoi I, Kennedy E, Litton JK, Mayr NA, Qamar RD, Trombetta MG, Harvey BE, Somerfield MR and Zakalik D: Management of hereditary breast cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical

Oncology guideline. J Clin Oncol (2020) 38: 2080–2106.

12. Tutt A, Tovey H, Cheang MCU, Kernaghan S, Kilburn L, Gazinska P, Owen J, Abraham J, Barrett S, Barrett-Lee P, Brown R, Chan S, Dowsett M, Flanagan JM, Fox L, Grigoriadis A, Gutin A, Harper-Wynne C, Hatton MQ, Hoadley KA, Parikh J, Parker P, Perou CM, Roylance R, Shah V, Shaw A, Smith IE, Timms KM, Wardley AM, Wilson G, Gillett C, Lanchbury JS, Ashworth A, Rahman N, Harries M, Ellis P, Pinder SE and Bliss JM: Carboplatin in *BRCA1/2*-mutated and triple-negative breast cancer *BRCA*ness subgroups: The TNT trial. Nat Med (2018) 24: 628–637.

13. Zhang J, Lin Y, Sun XJ, Wang BY, Wang ZH, Luo JF, Wang LP, Zhang S, Cao J, Tao ZH, Wu J, Shao ZM, Yang WT and Hu XC: Biomarker assessment of the CBCSG006 trial: A randomized phase III trial of cisplatin plus gemcitabine compared with paclitaxel plus gemcitabine as first-line therapy for patients with metastatic triple-negative breast cancer. Ann Oncol (2018) 29: 1741–1747.

14. Golan T, Kanji ZS, Epelbaum R, Devaud N, Dagan E, Holter S, Aderka D, Paluch-Shimon S, Kaufman B, Gershoni-Baruch R, Hedley D, Moore MJ, Friedman E and Gallinger S: Overall survival and clinical characteristics of pancreatic cancer in *BRCA* mutation carriers. Br J Cancer (2014) 111: 1132–1138.

15. Golan T, Sella T, O'Reilly EM, Katz MH, Epelbaum R, Kelsen DP, Borgida A, Maynard H, Kindler H, Friedmen E, Javle M and Gallinger S: Overall survival and clinical characteristics of *BRCA* mutation carriers with stage I/II pancreatic cancer. Br J Cancer (2017) 116: 697–702.

16. Wattenberg MM, Asch D, Yu S, O'Dwyer PJ, Domchek SM, Nathanson KL, Rosen MA, Beatty GL, Siegelman ES and Reiss KA: Platinum response characteristics of patients with pancreatic ductal adenocarcinoma and a germline *BRCA1*, *BRCA2* or *PALB2* mutation. Br J Cancer (2020) 122: 333–339.

17. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M: Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. N Engl J Med (2011) 364: 1817–1825.

18. Okusaka T, Ikeda M, Fukutomi A, Ioka T, Furuse J, Ohkawa S, Isayama H and Boku N: Phase II study of FOLFIRINOX for chemotherapy-naïve Japanese patients with metastatic pancreatic cancer. Cancer Sci (2014)105: 1321–1326.

19. Ozaka M, Ishii H, Sato T, Ueno M, Ikeda M, Uesugi K, Sata N, Miyashita K, Mizuno N, Tsuji K, Okusaka T and Furuse J: A phase II study of modified FOLFIRINOX for chemotherapy-naïve patients with metastatic pancreatic cancer. Cancer Chemother Pharmacol (2018) 81: 1017–1023.

20. Sehdev A, Gbolahan O, Hancock BA, Stanley M, Shahda S, Wan J, Wu HH, Radovich M and O'Neil BH: Germline and somatic DNA damage repair gene mutations and overall survival in metastatic pancreatic adenocarcinoma patients treated with FOLFIRINOX. Clin Cancer Res (2018) 24: 6204–6211.

21. Golan T, Barenboim A, Lahat G, Nachmany I, Goykhman Y, Shacham-Shmueli E, Halpern N, Brazowski E, Geva R, Wolf I, Goldes Y, Ben-Haim M, Klausner JM and Lubezky N: Increased rate of complete pathologic response after neoadjuvant FOLFIRINOX for *BRCA* mutation carriers with borderline resectable pancreatic cancer. Ann Surg Oncol (2020) 27: 3963–3970.

22. Park W, Chen J, Chou JF, Varghese AM, Yu KH, Wong W, Capanu M, Balachandran V, McIntyre CA, El Dika I, Khalil DN, Harding JJ, Ghalehsari N, McKinnell Z, Chalasani SB, Makarov V, Selenica P, Pei X, Lecomte N, Kelsen DP, Abou-Alfa GK, Robson ME, Zhang L, Berger MF, Schultz N, Chan TA, Powell SN, Reis-Filho JS, Iacobuzio-Donahue CA, Riaz N and O'Reilly EM: Genomic methods identify homologous recombination deficiency in pancreas adenocarcinoma and optimize treatment selection. Clin Cancer Res (2020) 26: 3239–3247.

23. Yadav S, Kasi PM, Bamlet WR, Ho TP, Polley EC, Hu C, Hart SN, Rabe KG, Boddicker NJ, Gnanaolivu RD, Lee KY, Lindstrom TH, Petersen GM, Couch FJ and McWilliams RR: Effect of germline mutations in homologous recombination repair genes on overall survival of patients with pancreatic adenocarcinoma. Clin Cancer Res (2020) 26: 6505–6512.

24. Kondo T, Kanai M, Kou T, Sakuma T, Mochizuki H, Kamada M, Nakatsui M, Uza N, Kodama Y, Masui T, Takaori K, Matsumoto S, Miyake H, Okuno Y and Muto M: Association between homologous recombination repair gene mutations and response to oxaliplatin in pancreatic cancer. Oncotarget (2018) 9: 19817–19825.

25. Golan T and Hammel P: Management of *BRCA* mutation carriers with pancreatic adenocarcinoma. J Natl Compr Canc Netw (2021) 19: 469–473.