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Molecular characteristics of *BRCA1/2* and *PALB2* mutations in pancreatic ductal adenocarcinoma

Andreas Seeber ,[1] Kai Zimmer,[1] Florian Kocher,[1] Alberto Puccini ,[2] Joanne Xiu,[3] Chadi Nabhan,[3] Andrew Elliott,[3] Richard M Goldberg,[4] Axel Grothey,[5] Anthony F Shields,[6] Francesca Battaglin,[7] Wafik S El-Deiry,[8] Philip A Philip,[6] John L Marshall,[9] Michael Hall,[10] W Michael Korn,[3] Heinz-Josef Lenz,[7] Dominik Wolf,[1] Clemens Feistritzer,[1] Gilbert Spizzo [1,11]

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AS and KZ contributed equally.
CF and GS contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Professor Gilbert Spizzo; gilbert.spizzo@i-med.ac.at

ABSTRACT

Introduction Poly-(ADP)-ribose polymerase (PARP) inhibitors are successfully used for treatment of *BRCA*-mutated (mut) breast cancers and are under extensive evaluation for *BRCA*- and *PALB2*-mutated pancreatic ductal adenocarcinoma (PDAC). However, the optimal treatment regimen for *BRCA/PALB2*-mutated PDCA has yet to be established. Moreover, limited data are available on the association of *BRCA/PALB2* gene alterations with other comutations and immunological biomarkers.

Material and methods Tumour samples of 2818 patients with PDAC were analysed for *BRCA*1/2 *PALB2* mutations and other genes by next-generation sequencing (NGS) (MiSeq on 47 genes, NextSeq on 592 genes). TMB was calculated based on somatic non-synonymous missense mutations. MSI-H/dMMR was evaluated by NGS, and PD-L1 expression was determined using immunohistochemistry.

Results In 4.2% (n=124) of all PDAC samples *BRCA* mutations have been detected. *BRCA2* mutations were more commonly observed than *BRCA1* mutations (3.1%(n=89) vs 1.1% [n=35], p<0.0001). *BRCA2* mutation was associated with an older age (64 vs 61 years for wild-type (wt), p=0.002) and *PALB2* mutation was observed more frequently in female than in male patients. *BRCA* and *PALB2* mutations were associated with MSI-H/dMMR compared with wt (*BRCA*: 4.8% vs 1.2%, p=0.002; *PALB2*: 6.7% vs 1.3 %, p=0.18), PD-L1 expression of >1.0% (*BRCA*: 21.8% vs wt 11.2%, p<0.001, *PALB2*: 0.0% vs 12.4 %, p=0.38) and high TMB (*BRCA*: mean 8.7 vs 6.5 mut/MB, p<0.001; *PALB2*: 10.6 mut/Mb vs 6.6 mut/Mb, p=0.0007). Also, PD-L1 expression and TMB differed between *BRCA* and *PALB2* mutation and wt samples in MSS tumours (p<0.05). *BRCA*-mutated and *PALB2*-mutated PDACs were characterised by a different mutational profile than was observed in wt tumours.

Conclusions *BRCA* and *PALB2* mutations were found in a significant subgroup of PDACs. These mutations were associated with a distinct molecular profile potentially predictive for response to immune-checkpoint inhibitor therapy. Therefore, these data provide a rationale to evaluate PARP inhibitors in combination with immune-checkpoint inhibitors in patients with *BRCA/PALB2*-mutated PDAC.

Key questions

What is already known about this subject?

► Patients with pancreatic ductal adenocarcinoma (PDAC) have an overall poor prognosis and new therapeutic strategies are needed. *BRCA* and *PALB2* mutations have been described in a subset of pancreatic cancer patients but their molecular landscape is unknown. Especially the correlation of *BRCA* and *PALB2* mutations with immune-related biomarkers are missing.

What does this study add?

► We present a large study investigating the molecular landscape of patients with *BRCA*-mutated and *PALB2*-mutated pancreatic cancer. These subgroups appear to be characterised by a distinct molecular profile. Of note, cancers that carry theses mutations are associated with the expression of biomarkers that are potentially associated with response to immunotherapy such as TMB, PD-L1 expression and MSI status.

How might this impact on clinical practice?

► This study addresses a current topic, since the recent approval of maintenance olaparib has completely modified the therapeutic strategy of *BRCA*-mutated PDACs during the last 2 years. Additionally, our findings suggest an intriguing speculation regarding the promising efficacy of testing Poly-(ADP)-ribose polymerase (*PARP*)-inhibitors with immune-checkpoint inhibitors in this poor-prognosis tumour. Thus, clinical trials testing both *PARP*-inhibitors with immune-checkpoint inhibitors are clearly warranted in the near future.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the fourth-leading cause of cancer-related death worldwide.[1] In early-stage disease, the 5-year overall survival for patients with stage IA PDAC is about 14%. In the metastatic stage only <1% of patients are alive at 5 years after diagnosis.[2] The identification of molecular

mechanisms leading to the development of PDAC is of utmost importance for understanding the nature of pancreatic cancer in order to elucidate new therapeutic options. For PDACs, four subtypes have been defined and characterised as stable, locally rearranged, scattered, unstable. The unstable subtype describes PDACs with genomic instability due to defects in DNA repair.[3] The family of DNA damage response (DDR) proteins includes, besides others, *BRCA* and *PALB2*. A family history of PDAC can be found in 5%–10% of PDAC patients,[4] and is associated with hereditary ovarian and breast cancer syndromes.[5 6] *BRCA1* and *BRCA2* are the most common of the known germline mutations involved in familial pancreatic cancer.[7] Somatic *BRCA*1 and *BRCA2* mutations, on the other hand, are found in 1%–4% of PDACs.[3 8] Similarly, germline mutations in *PALB2* have been associated with an increased risk of PDAC development.[9] *PALB2* encodes a protein essential for double strand break repair and homologous recombination by serving as a bridging molecule, which connects the *BRCA* complex and stimulates the strand invasion of *RAD51*.[10]

Targeting *BRCA1/2* and *PALB2* is considered an attractive therapeutic concept in various cancers, since resistance to genotoxic therapies has been associated with increased DDR signalling and many cancers harbour defects in components of this system.[11] Preclinical and early phase clinical trials have demonstrated promising effects.[12 13] Consequently, this provides justification for the development of clinical trials to test DDR targeting agents either as single agents or in combination. Several preclinical studies provided a rationale for the use of Poly-(ADP)-ribose polymerase (PARP) inhibitors in patients with mutations in DNA-repair proteins such as *BRCA1/2* and *PALB2*. In *BRCA*-mutated breast or ovarian cancer patients, the introduction of such targeted agents has resulted in improved outcomes in the first-line setting and beyond.[14 15] Only recently, a phase III trial investigating the PARP inhibitor olaparib in PDAC with *BRCA* mutations has been published.[16] According to this study, maintenance treatment with olaparib after chemotherapy lead to a significantly longer progression-free survival compared with placebo (7.4 months vs 3.8 months, p=0.004, HR=0.53). Moreover, a study investigating rucaparib, another PARP inhibitor, showed promising efficacy in patients with *BRCA* as well as *PALB2* mutations.[17]

In this study, we aimed to analyse the molecular portrait of *BRCA1/2*-mutated and *PALB2*-mutated PDACs to support rational decision making for the emerging treatment options in this entity.

MATERIAL AND METHODS

Samples

Formalin-fixed paraffin-embedded specimens derived from patients from around the world with PDAC were sent for analysis. Between April 2015 and January 2018, 2818 tumour tissue specimens were analysed in a commercial CLIA-certified laboratory (Caris Life Sciences, Phoenix, Arizona, USA). Patients agreed to submission of their tumour specimen alone, but no clinical data on survival or treatment were submitted to Caris Life Science. The only information that was available was basic demographic data such as age, sex, origin and date of the tumour sample. The analysis of this study was performed following the guidelines of the Declaration of Helsinki, Belmont report and US Common rule. Deidentified, retrospective data were used in keeping with 45 CFR 46.101(b)(4). As such, no patient consent was necessary as this study is considered IRB exempt.

Next-generation sequencing and immunohistochemistry

Immunohistochemistry and next-generation sequencing was performed on 2818 tumour samples. The methods used for testing were already extensively described in our recent publication.[18]

Statistical analysis

All statistical analyses were performed with JMP V.10.0 (SAS Institute), or R V.3.5.1 (R Development Core Team). The comparisons of continuous data were performed using Student's t-test, and those of categorical data were done using Fisher's exact test.

RESULTS

Patient characteristics

In total, 2818 patients with histologically confirmed PDAC were molecularly profiled. *BRCA1*, *BRCA2* and *PALB2* mutations were detected in 1.3% (n=37), 3.1% (n=89) and 0.6% (n=15), respectively (see table 1). No patient with a *BRCA*1/2 mutation showed a concomitant *PALB2* mutation and vice versa. *BRCA2*-mutated (mut) PDAC patients were significantly older than wild-type (wt) cases (64 vs 61 years, p=0.002). Whereas age was similar in *BRCA1*-mut or *PALB2*-mut PDAC compared with wt patients. In *PALB2*-mut PDAC a female predominance was observed whereas there was no significant association with gender for *BRCA1*-mut and *BRCA2*-mut PDAC.

BRCA1/2-mutated and PALB2-mutated PDACs have a distinct molecular profile

To investigate genetic co-alterations in *BRCA1/2* as well as *PALB2* mutations we investigated the molecular portrait and compared them with wt cases. Since the molecular profile of *BRCA1*-mut and *BRCA2*-mut PDACs was similar, we combined these cohorts for further analysis. Figure 1 depicts the most significantly altered genetic alterations in *BRCA*-mut versus *BRCA*-wt PDACs (see also online supplemental table 1).

The mutational landscape of *BRCA*-mut tumours differed significantly from *BRCA*-wt cases: *TP53* (59.3% vs 72.8%, p=0.001), *CDKN2A* (12.9% vs 24.9%, p=0.005), *APC* (6.5% vs 2.2%, p=0.008), *SETD2* (3.7% vs 0.4%, p=0.001), *FLCN* (2.8% vs 0.2%, p=0.003), *ERBB3* (1.9% vs 0.2%, p=0.025), *SUFU* (1.9% vs 0.0%, p=0.006), *WT1* (1.0% vs 0.0%, p=0.043) as well as *KMT2A* (1.9% vs 0.2%, p=0.037).

Table 1 Patients characteristics

	BRCA1			*BRCA2*			*PALB2*		
	Mutation	Wild-type	P value	Mutation	Wild-type	P value	Mutation	Wild-type	P value
Total cases No (%)	37 (1.3)	2818 (98.7)		89 (3.1)	2754 (96.9)		15 (0.6)	2405 (99.4)	
Median Age (years)	64	60	0.055	64	61	0.002	67	65	0.5426
Gender (%)									
Female	15 (40.5)	1318 (46.8)	ns	41 (46.1)	1289 (46.8)	ns	11 (73.3)	1114 (46.3)	0.0265
Male	22 (59.5)	1500 (53.2)		48 (53.9)	1465 (53.2)		4 (26.7)	1291 (53.7)	

ns, not significant.

Significant differences in copy number alterations between *BRCA*-mut and *BRCA*-wt were observed for *ALDH2* (1.0% vs 0.0%, p=0.044) and *SH2B3* (1.0% vs 0.0%, p=0.044).

Concerning *PALB2* mutations, significant differences in concomitant gene alterations as compared with *PALB2*-wt were observed in *TP53* (46.7% vs 74.3% p=0.03), *PTEN* (14.3% vs 0.8 %, p=0.007), *DICER1* (7.1% vs 0.2 %, p=0.035), *FANCA* (6.7% vs 0.2%, p=0.03) and *TSC2* (6.7% vs 0.0%, p=0.01). Other frequently altered genes were *KRAS* (66.7% vs 83.5 %, p=0.08), *ARID1A* (50.0% vs 19.9%, p=0.18) and *CDKN2A* (30.8% vs 24.4 %, p=0.53) (figure 2, online supplemental table 2). With regard to copy number alterations, no significant difference were observed.

BRCA/PALB2 mutations are associated with biomarkers predicting response to immune-checkpoint inhibitors

Mutations in *BRCA*1/2 as well as in *PALB2* were associated with a higher programmed-death ligand 1 (PD-L1) expression compared with wt samples (figure 3). PD-L1 expression of more than 1% was detected in 21.8% of *BRCA*-mut samples as compared with 11.2% in *BRCA*-wt PDAC (p<0.0001). No difference in PD-L1 staining >1% between *PALB2*-mut and *PALB2*-wt were observed. Mean tumour mutational burden (TMB) was 8.91 mut/Mb and 6.51 mut/Mb (median=7 mut/MB vs 6 mut/MB) for *BRCA*-mut and *BRCA*-wt PDAC, respectively (p<0.0001; figure 4A). Similarly, in *PALB2*-mut PDAC a significant higher TMB was found than in *PALB2*-wt (median 9.5 vs 6 mut/MB, mean 10.57 vs 6.6 mt/MB; p=0.0007) (figure 4C).

BRCA/PALB2-mutated pancreatic cancer is related to MSI-H/dMMR status

In 1.3% of tested PDAC samples a microsatellite instability-high (MSI-H)/damaged mismatch repair (dMMR) was observed. 4.8% of *BRCA*-mut tumours showed an MSI-H/dMMR, whereas 1.2% of *BRCA*-wt samples yielded a MSI-H/dMMR status (p=0.01; figure 5). MSI-H/dMMR in *PALB2*-mut PDAC specimens was detected in 6.7% compared with 1.3% in *PALB2*-wt samples (p=0.18).

Within the MSI-H/dMMR subgroup, *BRCA*-mut PDACs yielded a higher TMB (median 7 mt/Mb; mean 7.52 mt/Mb) as compared with *BRCA*-wt (median 6 mt/Mb; mean 6.34 mt/Mb; p≤0.001). TMB was also higher in the MSS group (median 7 vs 6 mt/MB; mean 7.4 vs 6.3 mt/Mb; p<0.0001, figure 4B).

A numerically higher frequency of MSI-H/dMMR (6.7% vs 1.3%, p=0.18) and higher TMB (median 9.5 vs 6 mt/

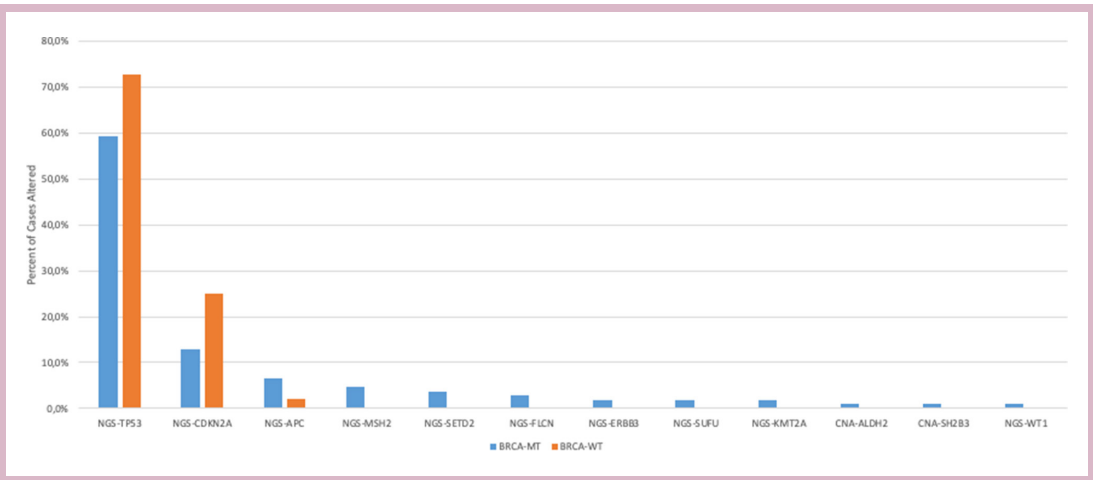


Figure 1 The genetic landscape of BRCA-mutated PDAC (p<0.05). NGS, next-generation sequencing; PDAC, Pancreatic ductal adenocarcinoma.

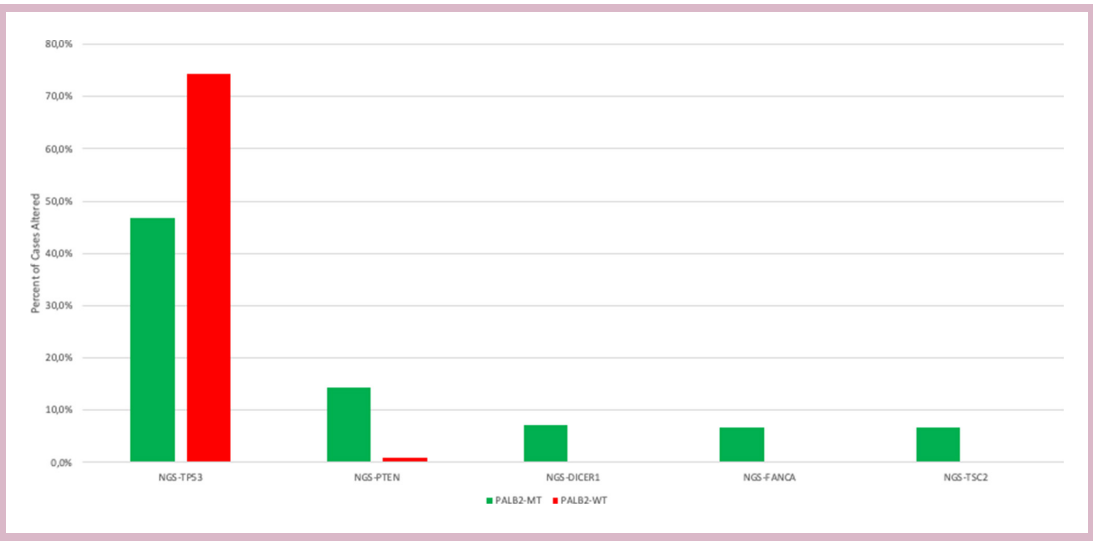


Figure 2 The molecular landscape of PALB2-mutated PDAC (p<0.05). NGS, next-generation sequencing; PDAC, Pancreatic ductal adenocarcinoma.

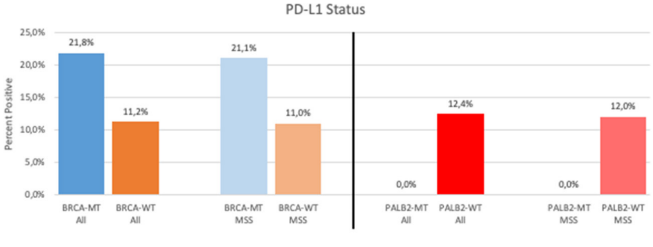
MB, mean 10.57 vs 6.6 mt/Mb, p=0.0007) was observed in *PALB2*-mut compared with *PALB2*-wt cancers. In the MSS subgroup, *PALB2*-mut tumours had a TMB of median 9 vs 6 mt/MB (mean of 9.57 mt/Mb) in contrast to 6.38 mt/Mb in *PALB2*-wt cases (figure 4D).

DISCUSSION

In this study, we aimed to delineate the genetic profile of *BRCA1/2*-mut and *PALB2*-mut PDACs. To the best of our knowledge, this is the largest study investigating the mutational profile of *BRCA*1/2-mut as well as *PALB2*-mut PDACs. *BRCA1, BRCA2* and *PALB2* mutations were found in 1.3%, 3.1%, and 0.6% of the patients, which is in line with previous series.[3 8]

The therapeutic implications of identifying mutations in these genes, either germline or somatic, have increased dramatically over the past few years. The inhibiting of PARP to generate a synthetic lethal effect in cancer cells with DDR-gene mutations has led to promising outcomes in many cancer entities.[19] PARP inhibitors cause multiple double strand breaks, and in tumours with *BRCA* and *PALB2* mutations, these double strand breaks cannot be efficiently repaired, leading to the death of cancer cells. In contrast, normal cells do not replicate their DNA as often as cancer cells, and they frequently have other DDR genes, which allow them to survive the inhibition of PARP.[20]

Only recently the PARP inhibitor olaparib has been tested within the phase III POLO trial as a maintenance treatment in *BRCA*-mut PDAC after platinum-based therapy. A prolonged progression-free survival (7.4 vs 3.8 months) and higher response rates (RR; 23% vs 12 %) were observed within the cohort treated in the olaparib arm compared with placebo.[16] A randomised multicentre phase II trial investigated the combination of gemcitabine and cisplatin with or without veliparib in 52 patients with metastatic *BRCA/PALB2*-mut PDAC. The addition of veliparib, however, failed to improve patient outcomes in this study, although, the RR in both treatment arms were encouraging (65.2% and 74.2%), indicating that



	ALL CASES									MSS CASES								
	Pos	Neg	Total	BRCA-MT	Pos	Neg	Total	BRCA-WT	P-value	Pos	Neg	Total	BRCA-MT	Pos	Neg	Total	BRCA-WT	P-value
PD-L1 Status	26	93	119	21.8%	286	2258	2544	11.2%	0.000438	24	90	114	21.1%	276	2243	2519	11.0%	0.000906
	Pos	Neg	Total	PALB2-MT	Pos	Neg	Total	PALB2-WT	P-value	Pos	Neg	Total	PALB2-MT	Pos	Neg	Total	PALB2-WT	P-value
PD-L1 Status	0	12	12	0.0%	280	1980	2260	12.4%	0.381622	0	12	12	0.0%	268	1962	2230	12.0%	0.200607

Figure 3 PD-L1 staining in PALB2/BRCA wild-type and mutated cases.

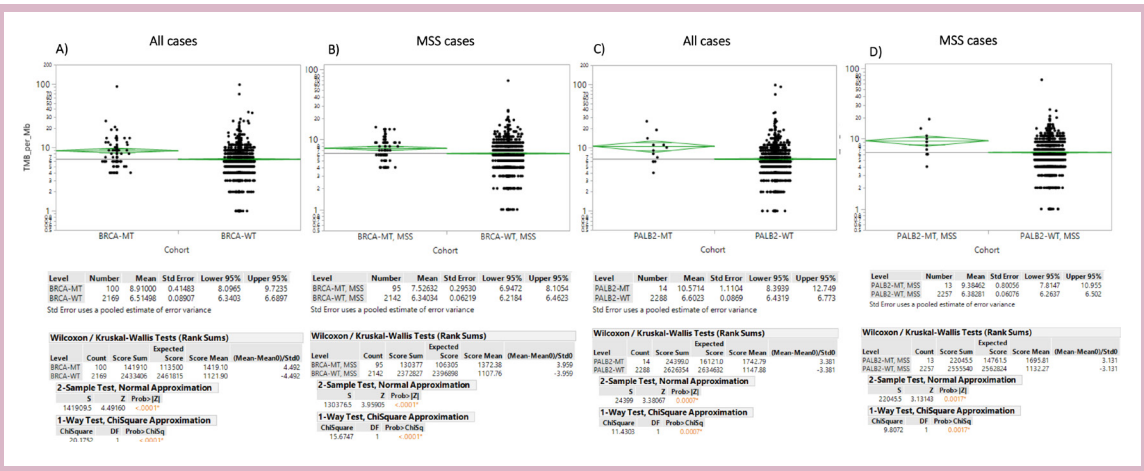
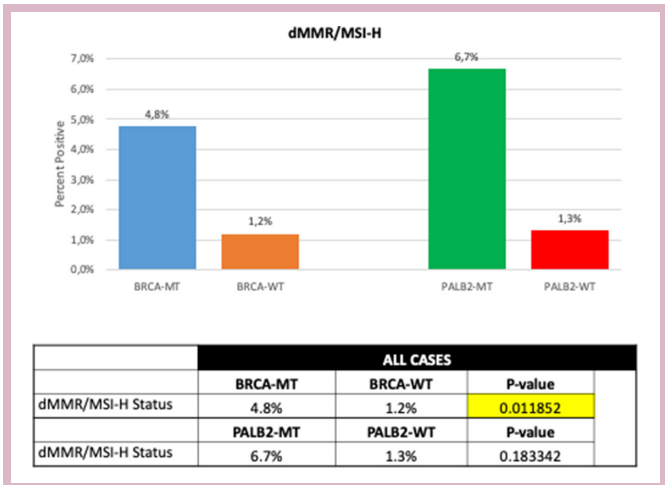


Figure 4 Mean TMB in BRCA and PALB2 mutated versus wild-type PDAC: (A) BRCA mutations in all cases, (B) BRCA mutations in MSS, (C) PALB2 mutations in all cases, (D) PALB2 mutations in MSS. TMB, Tumour mutational burden; MSS, microsatellite status stable.

patients with PDAC with alterations in DDR genes may benefit from platinum-based treatment regimens.[21] This finding is in line with data from another study by Golan *et al* investigating the effect of neo-adjuvant FOLFIRINOX in *BRCA2*-mut PDACs, which lead to complete pathological responses in 44.4% of *BRCA2*-mut patients vs 10% in *BRCA2*-wt patients.[22] A meta-analysis including six trials confirmed the strategy of intitial treatment with platinum-based chemotherapy in patients with a germline *BRCA* mutation. At the same time, the authors called for more and higher-quality trials in this setting.[23]

Further studies are desirable to evaluate PARP inhibitors in different treatment settings in DDR-altered PDACs.

Taking into consideration the broadly accepted model of PDAC development, which postulates stepwise mutations in *KRAS*, *CDKN2A*, *TP53* and SMAD4,[24] it revealed that *BRCA*-mut as well as *PALB2*-mut PDACs are associated with a distinct molecular profile as compared with wt cases. In our cohort, *BRCA*-mut samples had significantly fewer mutations in *TP53* and *CDKN2A* than *BRCA*-wt specimens. However, no differences were found in the prevalence of *KRAS* and *SMAD4* alterations. In *PALB2*-mut samples, a lower mutational rate of *TP53* was observed. *BRCA1/2* mutations lead to DDR deficiency driving their susceptibility to cancer development.[3 25] Therefore, our data support the hypothesis that carcinogenesis in *BRCA1/2* and *PALB2* patients differs from patients with PDAC-wt tumours.



	ALL CASES		
	BRCA-MT	BRCA-WT	P-value
dMMR/MSI-H Status	4.8%	1.2%	0.011852
	PALB2-MT	PALB2-WT	P-value
dMMR/MSI-H Status	6.7%	1.3%	0.183342

Figure 5 dMMR/MSI-H in PALB2/BRCA wild-typeversus mutated patients. MSI-H/dMMR, Microsatellite instability-high / damaged mismatch repair.

The DNA damage caused by PARP inhibition leads to increased neoantigen and tumour-associated antigen expression.[26] This reshapes the tumour microenvironment and has the potential to restore the antitumour immune response, which can be further enhanced by treatment with immune-checkpoint inhibitors. Additionally, preclinical data suggest PARP inhibition may have immunomodulatory potential.[27] Two prostate carcinoma cell lines, one with a known *BRCA2* mutation and the other without mutations in *BRCA1/2* were exposed to olaparib. Natural killer cell-mediated lysis increased in both cell lines regardless of *BRCA* phenotype.[28] Of note, we detected a higher prevalence of MSI-H/dMMR status in *BRCA*-mut than *BRCA*-wt samples (4.8% vs 1.2%) and a numerically higher MSI-H/dMMR status in *PALB2*-mut than in *PALB2*-wt specimens (6.7% vs 1.3%). Compared with another series conducted by Hu and colleagues the prevalence of MSI-H/dMMR appears higher, since in that study a prevalence of only 0.8% in PDAC was observed.[29] Of note, only germline variants were reported in that study, whereas in our cohort we included both germline variants and somatic mutations. Due to the study design that included only tumour DNA of the available specimens we were unable to make a distinction between germline and somatic mutations.

The association of *BRCA* mutations and an MSI-H/dMMR status may have implications on the use of immune-checkpoint inhibitors in *BRCA*-mut and *PALB2*-mut PDAC, as pembrolizumab has been approved as a site

agnostic drug for use in any tumour manifesting MSI-H/dMMR tumours by the FDA.[30] Furthermore, immune-related biomarkers such as TMB and PD-L1 expression levels were highly expressed in *BRCA*-mut tumours. This is in line with data coming from other tumours, showing that PDL-1 status correlates with "*BRCAness*", TMB as well as MSI-H/dMMR status.[31 32] However, the best predictive marker for response to immunotherapy is still to be defined. Of note, recently Shim *et al*[33] presented a human leucocyte antigen corrected TMB, that included loss of heterozygosity and enabled a better prediction of response to immune-checkpoint inhibitors. Moreover, the value of PD-L1 expression as a predictive biomarker for the treatment with PD-1/PD-L1 inhibitors in PDAC remains inconclusive.[34 35]

For *PALB2*-mut *PDAC* we observed a numerical difference in PD-L1 staining in contrast to the findings in tumours that were PALB2-wt. However, this finding did not reach statistical significance. Taking into consideration the high rate of MSI-H/dMMR and the low rate of PD-L1 positivity in *PALB2*-mut PDACs, further studies are required to elucidate how *PALB2* mutations influence the immune microenvironment in PDAC and other entities. This can help to understand how *PALB2* mutations may affect the efficiency of treatment for these patients with an immune-checkpoint inhibitor.

Further limitations in our study need to be mentioned as well. Due to the retrospective nature of our study, a selection bias may be present. Moreover, no clinical and personal data, such as survival, treatment protocols and patient's outcome are available. Therefore, we are not able to analyse the prognostic and predictive value of *BRCA* and *PALB2* mutations in PDAC.

Since our results show that a subset of *BRCA*-mut PDACs express immuno-related biomarkers, it might be reasonable to test PARP-inhibitor with immune-checkpoint inhibitors.[26] Such combinations are currently being tested in several other tumour types. Promising combinations include those tested in the TOPACIO trial (NCT 02657889)[36] that combines pembrolizumab with niraparib in triple-negative breast and ovarian cancer, and in the MEDIOLA trial (NCT 02734004) which combines durvalumab with olaparib in advanced solid tumours. Single-agent checkpoint inhibition showed only low activity in PDAC, so far.[37] However, when looking on MSI-H/dMMR status, response rates increased from 0% to approximately 18%.[30]

CONCLUSION

To the best of our knowledge, this is the largest study describing the molecular portrait of *BRCA*1/2- and *PALB2*-mutated PDACs. We showed that these mutations are associated with a distinct genetic profile and are associated with predictive immunotherapy-related biomarkers suggesting a potential rationale to combine PARP-inhibitors with immune-checkpoint inhibitors. The hypothesis generated in this study should be evaluated further and must be proven in investigational trials.

Author affiliations
[1]Hematology and Oncology, Comprehensive Cancer Center Innsbruck, Medical University Innsbruck, Innsbruck, Austria
[2]Oncologia Medica 1, Ospedale Policlinico San Martino – IRCCS, Genoa, Italy
[3]Caris Life Sciences, Phoenix, Arizona, USA
[4]West Virginia University Cancer Institute, Morgantown, West Virginia, USA
[5]West Cancer Center, Germantown, Tennessee, USA
[6]Department of Oncology, Karmanos Cancer Institute Wayne State University, Detroit, Michigan, USA
[7]University of Southern California - Norris Comprehensive Cancer Center and Hospital, Los Angeles, California, USA
[8]Brown University, Providence, Rhode Island, USA
[9]Ruesch Center for The Cure of Gastrointestinal Cancers, Lombardi Comprehensive Cancer Center, Washington, DC, USA
[10]Fox Chase Cancer Institute, Philadelphia, Pennsylvania, USA
[11]Department of Internal Medicine, Oncologic Day Hospital, Hospital of Bressanone-Brixen, Bressanone-Brixen, Italy

Twitter Axel Grothey @agrothey

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ORCID iDs
Andreas Seeber http://orcid.org/0000-0001-8529-7824
Alberto Puccini http://orcid.org/0000-0002-2492-4043
Gilbert Spizzo http://orcid.org/0000-0003-4121-0146

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