Pancreatic ductal adenocarcinoma in *BRCA2* mutation carriers

Louis de Mestier[1], Jean-Baptiste Danset[2], Cindy Neuzillet[3], Vinciane Rebours[1], Jérôme Cros[4], Nadem Soufir[5] and Pascal Hammel[3]

[1]Department of Gastroenterology and Pancreatology, Beaujon Hospital, Paris 7 University, APHP, Clichy, France
[2]Department of Hepato-Gastroenterology, European Georges-Pompidou Hospital, APHP, Paris, France
[3]Department of Digestive Oncology, Beaujon Hospital, Paris 7 University, APHP, Clichy, France
[4]Department of Pathology, Beaujon Hospital, Paris 7 University, APHP, Clichy, France
[5]Department of Genetics, Bichat Hospital, Paris 7 University, APHP, Clichy, France

Correspondence should be addressed to P Hammel
Email
pascal.hammel@aphp.fr

Abstract

Germline *BRCA2* mutations are the first known cause of inherited (familial) pancreatic ductal adenocarcinoma (PDAC). This tumor is the third most frequent cancer in carriers of germline *BRCA2* mutations, as it occurs in around 10% of *BRCA2* families. PDAC is known as one of the most highly lethal cancers, mainly because of its chemoresistance and frequently late diagnosis. Based on recent developments in molecular biology, a subgroup of *BRCA2*-associated PDAC has been created, allowing screening, early surgical treatment and personalized systemic treatment. *BRCA2* germline mutation carriers who have ≥1 first-degree relative, or ≥2 blood relatives with PDAC, should undergo screening and regular follow-up based on magnetic resonance imaging and endoscopic ultrasound. The goal of screening is to detect early invasive PDAC and advanced precancerous lesions suitable for a stepwise surgical complete (R0) resection. Increasing evidence on the molecular role of the BRCA2 protein in the homologous recombination of DNA damages suggest that *BRCA2*-related PDAC are sensitive to agents causing DNA cross-linking damage, such as platinum salts, and treatments targeting rescue DNA repair pathways, such as poly(ADP-ribose) polymerase inhibitors that are currently under investigation.

Key Words
- BRCA2
- pancreatic cancer
- screening
- treatment
- PARP inhibitors

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the eleventh most frequent cancer in the USA with 53,070 new cases per year, and it will become the second cause of cancer-related death by 2030 (Rahib *et al.* 2014, Ryan *et al.* 2014, Neuzillet *et al.* 2015, Siegel *et al.* 2016). The low 5-year survival rate (about 7%) is due to its highly invasive progression, with tumors that are frequently non-resectable at initial diagnosis, a fibrotic, immunosuppressive and hypoxic microenvironment promoting tumor resistance to chemotherapy, and rapid clinical deterioration due to pain, systemic inflammation and cachexia. The main known risk factors for PDAC are cigarette smoking, diabetes mellitus, obesity, chronic pancreatitis and a family history of PDAC (Raimondi *et al.* 2009, Ryan *et al.* 2014, Neuzillet *et al.* 2015).

Familial PDAC is defined by the occurrence of PDAC in a pair of first-degree relatives and accounts for 10% of all cases of PDAC (Vincent *et al.* 2011, Ryan *et al.* 2014, Neuzillet *et al.* 2015). The risk of developing PDAC increases along with the number of first-degree relatives with familial PDAC, with a standardized incidence ratio of between 17 and 32 for subjects with ≥3 first-degree relatives with PDAC (Klein *et al.* 2004, Brune *et al.* 2010). Moreover, relatives with familial PDAC harbor more

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precancerous pancreatic lesions and have a higher risk of extra-pancreatic tumors compared with patients with sporadic PDAC (Shi *et al.* 2009, Wang *et al.* 2009).

The identification of PDAC predisposition genes in patients with familial PDAC is highly important because it allows family members to undergo genetic testing, PDAC screening, earlier prophylactic resection of precancerous lesions and personalized therapy. Germline mutations have been described in *BRCA2*, *BRCA1*, *p16/CDKN2A*, *PALB2*, *PRSS1*, *STK11*, *TP53*, *ATM* and Lynch syndrome-associated genes (Klein 2012, Salo-Mullen *et al.* 2015, Zhen *et al.* 2015, Hu *et al.* 2016, Roberts *et al.* 2016). However, no germline mutations have been identified in up to 80–85% of cases of familial PDAC. *BRCA2*-related PDAC is a prototypical example of familial PDAC for cancer biology, screening strategy and personalized therapeutic opportunities. The aim of this paper is to comprehensively review the current knowledge about PDAC in *BRCA2* mutation carriers.

Epidemiological links between *BRCA2* mutations and PDAC

Germline *BRCA2* mutations are inherited in an autosomal dominant fashion with incomplete penetrance and are associated with increased risks of breast and ovarian cancers and, to a lesser extent, prostate, colorectal and pancreatic cancers. About 10% of all *BRCA2* families have at least one relative with PDAC (Kim *et al.* 2009). Mutation carriers have a three- to six-fold increased risk of developing PDAC compared with non-carriers (Luo *et al.* 2015). In two series of 173 and 139 *BRCA2* families, the relative risk of PDAC was estimated to be 3.5 (95% CI, 1.9–6.6) (Breast Cancer Linkage Consortium 1999) and 5.9 (95% CI: 3.2–10) (van Asperen 2005), respectively. The relative risk of PDAC was 2.13 (95% CI: 0.36–7.03) in a cohort of over 5,149 women with *BRCA2* mutations (Iqbal *et al.* 2012). In these studies, the risk of PDAC in *BRCA2* mutation carriers was higher in patients over 65 years old.

However, the prevalence of *BRCA2* germline mutations in patients with apparently sporadic PDAC is 4–7% (Goggins *et al.* 1996, Ferrone *et al.* 2008, Holter *et al.* 2015, Zhen *et al.* 2015, Hu *et al.* 2016) compared with 0.2% in the Caucasian population (Anglian Breast Cancer Study Group 2000). However, these data are based on heterogeneous studies (Luo *et al.* 2015). It should be noted that the *BRCA2* mutation rate was lower in series of unselected PDAC patients than in PDAC cell lines (Goggins *et al.* 1996, Ferrone *et al.* 2008).

Germline *BRCA2* mutations are identified in 4–17% of families with familial PDAC and are the most common germline genetic alteration identified in this condition (Murphy *et al.* 2002, Hahn *et al.* 2003, Couch *et al.* 2007, Salo-Mullen *et al.* 2015, Zhen *et al.* 2015, Hu *et al.* 2016, Roberts *et al.* 2016). However, this rate varies depending on the definition of familial PDAC, i.e., the number of relatives affected to define a population at risk. Couch *et al.* (2007) reported a 4% prevalence of PDAC in families with two first- or second-degree relatives with PDAC and 10% in families with ≥3 involved relatives. However, all *BRCA2*-related PDAC families are not affected with a family history of breast, ovarian and/or prostate cancers, and PDAC can result as the single family cancer in some families with *BRCA2* germline mutations, suggesting variable penetrance and phenotypic expression (Goggins *et al.* 1996, Couch *et al.* 2007, Klein 2012, Holter *et al.* 2015, Zhen *et al.* 2015). Germline *BRCA2* mutations, particularly the founder 6174delT mutation, are associated with 10–20% of unselected and apparently sporadic PDAC in the Jewish Ashkenazi population (Ozçelik *et al.* 1997, Ferrone *et al.* 2008, Lucas *et al.* 2013).

Patients with *BRCA2*-associated PDAC are younger than their counterparts with sporadic PDAC, with a median age difference of 7 years (63 vs 70 years, respectively) in two large studies, but a similar sex ratio (Kim *et al.* 2009, Lucas *et al.* 2013). Other clinicopathological features were similar in both populations except for a personal and family history of cancer (Ferrone *et al.* 2008, Golan *et al.* 2014). The survival rate in patients with familial history of PDAC may be increased compared with that in those with sporadic PDAC, possibly due to increased chemosensitivity to platinum salts (see below) (Golan *et al.* 2014, Fogelman *et al.* 2015).

Somatic mutations in genes involved in DNA repair, including *BRCA2*, but also *BRCA1*, *PALB2* or *ATM*, have been described in 10–15% of all sporadic PDAC (Waddell *et al.* 2015, Bailey *et al.* 2016). Indeed, a recent study on PDAC whole genome sequencing classified PDAC into 'stable', 'locally rearranged', 'scattered' and 'unstable' subtypes based on the variations in chromosomal structures (Waddell *et al.* 2015). The 'unstable' subtype represented 14% of all PDAC and was characterized by a large number of structural variation events, suggesting defects in DNA repair pathways related to a 'BRCA mutational signature' (Waddell *et al.* 2015, Bailey *et al.* 2016).

Finally, the histogeneses of 'conventional' PDAC and intraductal papillary mucinous neoplasms (IPMN) are

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different, with specific genomic signatures (Bailey *et al.* 2016). This might explain why the prevalence of *BRCA2* germline mutations in patients with 'conventional' PDAC or PDAC derived from IPMN are different, for example, 19 vs 29%, respectively, in the study of high-risk Ashkenazi individuals by Lucas *et al.* (2013).

PDAC risk assessment and screening strategies in *BRCA2* mutation carriers

Pancreatic screening in high-risk patients such as *BRCA2* mutation carriers has been proposed to reduce PDAC-related mortality. In 2012, the International Cancer of the Pancreas Screening (CAPS) Consortium published guidelines on the management of patients with increased risk for familial PDAC (Canto *et al.* 2013). The aim of screening is to detect and remove precancerous lesions such as multifocal high-grade pancreatic intraepithelial neoplasia (PanIN) lesions and IPMN with high-grade dysplasia (Shi *et al.* 2009, Matthaei *et al.* 2011, Lucas *et al.* 2013) in patients eligible for pancreatic surgery (Klapman & Malafa 2008, Bartsch *et al.* 2016).

BRCA2 mutation carriers should be considered for PDAC screening if they have ≥1 first-degree relative, or ≥2 any degree relatives with PDAC (Canto *et al.* 2013). Iqbal *et al.* (2012) have reported a relative risk of 46.5 (95% CI: 9.4–230) in developing PDAC in *BRCA2* mutation carriers with a first-degree relative affected by PDAC compared with those without. Subjects with Jewish Ashkenazi ancestry and a family history of PDAC should also be considered for genetic counseling and testing for the founder *BRCA2* gene mutation (6174delT), which is present in 1% of Ashkenazi Jewish individuals (Ferrone *et al.* 2008, Canto *et al.* 2013, Lucas *et al.* 2014).

The age to initiate screening in high-risk *BRCA2* mutation carriers is a subject of debate. Certain authors recommend to begin screening at the age of 40 years, or 10 years earlier than the youngest relative with PDAC (Ludwig *et al.* 2011, Canto *et al.* 2012). The CAPS consortium guidelines recommend to start screening at the age of 50 years (Canto *et al.* 2013) because the incidence of PDAC appears to be low in younger subjects. This was confirmed in the study by Bartsch *et al.* (2016), in which high-risk individuals developing PDAC were not younger at the time of PDAC diagnosis than index cases, and with no significant lesions before the age of 50 years. Thus, although medico-economic studies are needed, screening before the age of 50 years may not be cost-effective in this setting (Ludwig *et al.* 2011, Canto *et al.* 2013, Bartsch *et al.* 2016). Finally, although tobacco consumption increases the risk of PDAC in subjects with familial PDAC history, there is no recommendation for earlier screening in smokers.

The most widely accepted tools for PDAC screening are endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI) cholangiopancreaticography (Klapman & Malafa 2008, Canto *et al.* 2013, Lu 2015, Bartsch *et al.* 2016). The prevalence of small, mostly cystic, pancreatic lesions was 42.6 and 33.3% by EUS and MRI, respectively, in the CAPS3 study (Canto *et al.* 2012). These rates are higher than those obtained with computed tomography (11%). However, benign cystic lesions are frequent in the general population and can be misdiagnosed as malignant during EUS and/or MRI screening, leading to a risk of surgical overtreatment with potential morbidity and even mortality (Tanaka *et al.* 2012, Neuzillet *et al.* 2015). According to the 2012 Fukuoka consensus guidelines for sporadic pancreatic cystic lesions (Tanaka *et al.* 2012), the high-risk signs of malignancy include obstructive jaundice associated with cystic lesions of the head of the pancreas, enhancing solid component in cysts and a main pancreatic duct >10 mm. In patients without these signs, suggestive features must be searched for, i.e., cysts >3 cm, thickened/enhancing cyst walls, main duct size of 5–9 mm, non-enhancing mural nodule, rapid change in size of the pancreatic duct with distal pancreatic atrophy and regional lymphadenopathy.

The follow-up of *BRCA2* mutation carriers at a high risk of developing PDAC is based on a combination of EUS and MRI (Canto *et al.* 2013, Lu 2015). Repeated carcinoembryonic antigen and carbohydrate antigen 19.9 dosages have not been shown to be effective in detecting precancerous lesions, as they usually do not express these markers in serum (Langer *et al.* 2009). A 12-month follow-up interval is proposed in patients with no baseline pancreatic abnormalities. In case of non-suspicious cysts, the interval can be reduced to 6 months and to 3 months in case of newly detected undetermined solid lesions if upfront surgery is not indicated or in case of undetermined main pancreatic duct strictures. In addition, branch–duct IPMN without signs of malignancy should be followed up according to the Fukuoka consensus guidelines (Tanaka *et al.* 2012).

Nevertheless, studies on PDAC screening have reported a low prevalence of diagnosed lesions and there is no clear consensus on the precise definition of a 'significant' lesion (Langer *et al.* 2009, Ludwig *et al.* 2011, Canto *et al.* 2012, Lu 2015). Although pancreatic lesions were frequently detected (42%) in the CAPS3 study, 5/225 patients underwent pancreatic surgical

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resection and only three of them had high-grade lesions (Canto *et al.* 2012). Similarly, in the study by Bartsch *et al.* (2016), pancreatic lesions were identified in 134/253 patients, including 21 (8.3%) who underwent surgical resection and only six (2.4%) with malignant or high-grade lesions on the resected specimen. Similarly, in the German study, after an average 7-year screening period, 6/76 (7.9%) patients underwent pancreatic surgical resection for suspicious lesions, including only one patient (1.3%) with a high-grade lesion (Langer *et al.* 2009). A systematic review of nine studies on familial PDAC screening found that although the pancreatic tumor detection rate was 7.9–50%, the PDAC detection rate was only 0–6.8%, with no PDAC detected in 4/9 studies. Finally, although a recent large European study highlighted the relevance of close follow-up in asymptomatic *CDKN2A* mutation carriers, it was less effective in other individuals with a family history of PDAC. In the latter group, the screening program resulted in pancreatic resection in 3/214 patients for suspected PDAC (1.4%, including only one with a final diagnosis of PDAC) and in 13/214 patients because of suspected cystic precursor lesions (6.1%, including only four with high-grade lesions) (Vasen *et al.* 2016).

To summarize, a non-negligible number of mutation carriers undergo unnecessary surgery, i.e., have non-cancerous lesions. In addition, pancreatic surgery carries significant morbidity and even mortality, and screening programs generate anxiety (Breitkopf *et al.* 2012). Thus, additional studies are needed to better define the high-risk groups that will benefit from screening programs. The diagnostic value of the current screening methods should be increased to improve the relevance of screening for familial PDAC. The goal of future research should be to establish reliable blood or urine biomarkers to develop a non-invasive, accurate and cost-effective method to detect PDAC precursor lesions in *BRCA2* mutation carriers.

Specific aspects of surgical management in *BRCA2* mutation carriers with PDAC

Pancreatic resection should be performed at high-volume specialized centers, as center volume correlates with surgical results and morbidity (Gooiker *et al.* 2014). Solid lesions detected on EUS or MRI (generally by both), particularly when they appear during systematic yearly screening, should be considered potentially malignant. A biopsy can be proposed in case of doubt and surgical resection should be considered whatever their size (Canto *et al.* 2013). In contrast, prophylactic surgery is not recommended in high-risk *BRCA2* mutation carriers without identifiable lesion because of potential morbidity and ill-defined benefit:risk ratio.

Most lesions discovered during screening are branch–duct IPMN, whose treatment depends on the risk of malignancy according to the Fukuoka consensus guidelines (Tanaka *et al.* 2012). In particular, surgical resection should be considered in the presence of cyst-related symptoms (obstructive jaundice and pancreatitis) or any other high-risk signs of malignancy. Conversely, in the absence of these signs but in the presence of suspicious features, surgical resection is not systematically recommended but should be considered in case of definite mural nodules, main duct features suggesting involvement and/or when cytology suggests malignancy (Tanaka *et al.* 2012). The usual cyst size threshold used to indicate surgery could probably be lowered in *BRCA2* mutation carriers. Indeed, pathological analysis of surgically resected pancreatic specimens from *BRCA2* mutation carriers with IPMN <10 mm were found to have concomitant high-grade PanIN lesions, high-grade dysplasia and/or main duct involvement with IPMN (Canto *et al.* 2012, 2013).

Resection margins should be examined during the surgical intervention for IPMN of either the main or branch ducts. If high-grade PanIN are detected on resection margins, larger pancreatic resection should be considered to achieve R0 surgery, although this was not set out in the CAPS expert consensus (Canto *et al.* 2013). However, additional pancreatic resection should not be performed in the presence of low-grade PanIN on resection margins (Tanaka *et al.* 2012, Canto *et al.* 2013). Postoperatively, the presence of high-grade PanIN at a distance from the main lesion and determined by histopathological examination of the resected specimen is important, but this management is a subject of debate. In this situation, a total pancreatectomy may be considered, as there is a risk of second (and different) PDAC in these patients. In all cases, close and early imaging follow-up (<6 months) should be performed in these patients (Canto *et al.* 2013). It is important to obtain an individual multidisciplinary assessment of the benefit:risk ratio of extensive pancreatic resection for each patient. Obviously, this strategy does not apply to patients with macroscopic invasive PDAC, in whom standard curative intent resection is recommended without additional pancreatic resection (Matthaei *et al.* 2011).

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Pathophysiological pathways leading to the development of PDAC in *BRCA2* mutation carriers: moving toward personalized treatment

The causes of DNA replication errors include free oxygen radicals generated by the cellular metabolism, ultraviolet light, radiation and chemicals. Homologous recombination (HR) is a high-fidelity repair system of double-strand DNA breaks and DNA cross-linking damages induced by DNA-damaging agents. The BRCA1 and BRCA2 proteins are key regulators of the HR system and are localized in the nucleus in response to the formation of RAD51 foci, following DNA damage. BRCA1 plays a central role in identifying double-strand DNA breaks and in initiating the process of DNA repair by recruiting the HR machinery (Moynahan *et al.* 2001, Lee *et al.* 2014, Fradet-Turcotte *et al.* 2016). BRCA2 regulates the formation of RAD51 nucleoprotein filaments and the strand invasion by the single-strand DNA used for HR repair (Thorslund & West 2007, Holloman 2011, Lee 2014, Fradet-Turcotte *et al.* 2016). Thus, BRCA2 loss-of-function prevents the HR-mediated double-strand break repair, accounting for high levels of spontaneous chromosomal aberrations and genetic instability.

Following the two-hit Knudson model in *BRCA2* germline mutation carriers, PDAC contains a loss of heterozygosity in the *BRCA2* gene due to second allele damage. The loss of functional *BRCA2* gene in tumor tissue impairs HR function. For example, Lucas *et al.* (2013) reported a loss of heterozygosity in 50% of *BRCA1*-associated and 75% of *BRCA2*-associated PDAC in a series of 39 *BRCA1/2* mutation carriers with Jewish Ashkenazi ancestry. In addition, micro-dissection of PDAC samples from IPMN in one patient revealed partial and complete loss of heterozygosity in IPMN and PDAC lesions, respectively. As IPMN may progress to PDAC, biallelic loss of *BRCA* is a plausible contributor to PDAC formation (Fam 2014).

Multiple somatic events occur in PDAC carcinogenesis, such as p53 and SMAD4 inactivation (Lucas *et al.* 2013, Neuzillet *et al.* 2014). Indeed, chromosome breaks due to incomplete or inadequate DNA repair normally activate p53-dependent checkpoint controls and/or apoptosis to prevent tumor formation. PDAC murine models suggest that *TP53* mutations may occur before *BRCA1/2* loss of heterozygosity in PDAC oncogenesis and that monoallelic *BRCA1/2* loss-of-function could promote *TP53* and *KRAS*-driven tumorigenesis (Skoulidis *et al.* 2010, Rowley *et al.* 2011, Fam 2014).

Use of cross-linking cytotoxic agents in *BRCA2* mutation carriers with PDAC

Therapies exploiting the inability of *BRCA2*-associated tumor cells to repair double-strand DNA breaks could improve the outcome in these patients compared with those with *BRCA2* wild-type tumors. DNA-targeting cytotoxic agents generating DNA strand breaks include platinum salts, topoisomerase inhibitors, alkylating agents and mitomycin C. Intra- and inter-strand platinum–DNA cross-links induce double-strand DNA break damage. DNA reparation requires functioning BRCA2 (Thompson 2005). *BRCA2*-mutated cancers lack HR repair, thus platinum-induced double-strand breaks are not fixed, and further genomic damage goes on, leading to cell death (Dhillon *et al.* 2016).

Cancerous tumors of *BRCA2* mutation carriers have a peculiar sensitivity to platinum salts (and other DNA-damaging agents), and prolonged survival can be expected (Waddell *et al.* 2015). This was first suggested in studies reporting overall survival that was nearly double than that expected in patients with *BRCA*-associated epithelial ovarian cancers who received platinum-based combination chemotherapies or pegylated liposomal doxorubicin (Gallagher *et al.* 2011, Kaye *et al.* 2012). Similarly, a significant response rate (9/10) was obtained with neoadjuvant cisplatin in *BRCA1* mutation carriers with breast cancer, a rate that is clearly higher than that, 15–34%, reported in previous studies using taxanes and anthracycline combinations (Byrski *et al.* 2009).

In the above-mentioned PDAC genomic study by Waddell *et al.* (2015), the 'unstable' PDAC subtype associated with defects in DNA repair pathways was characterized by platinum salt sensitivity. Preclinical models using PDAC cell lines as well as patient-derived murine xenografts have shown that tumor *BRCA2* deficiency was significantly associated with sensitivity to DNA cross-linking agents (such as platinum salts), as well as radiation therapy compared with *BRCA2* proficiency (Porcelli *et al.* 2013, Andrei *et al.* 2015, Lohse *et al.* 2015). In addition to case reports (Sonnenblick *et al.* 2011), several retrospective case series have described marked efficacy of platinum salts in *BRCA2* mutation carriers with advanced PDAC (Lowery *et al.* 2011, Golan *et al.* 2014, Luo *et al.* 2015, Vyas *et al.* 2015). In one study, median overall survival was 22 months vs 9 months in *BRCA1/2* mutation carriers with stage III–IV PDAC who received platinum ($n=22$) vs another chemotherapy ($n=21$), respectively ($P<0.039$) (Golan *et al.* 2014). Interestingly, Fogelman and colleagues (2015)

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reported that a familial history of PDAC was a marker of sensitivity to platinum in patients with PDAC. More precisely, overall survival was improved in those receiving first-line platinum therapy along with the number of relatives with pancreatic, ovarian and/or breast cancers, which was not the case with other first-line chemotherapies. Nevertheless, most *BRCA2*-associated tumors in general, and PDAC in particular, become resistant to platinum salts over time. Secondary acquired intragenic *BRCA* mutations that restore the protein function were reported in cases of primary or secondary resistance to cisplatin (Sakai *et al.* 2008).

Development of PARP inhibitors for patients with *BRCA2*-associated PDAC

In compensation for HR deficiency to *BRCA2* loss-of-function, DNA repair mainly relies on base excision repair, which is a backup single-strand DNA break repair system. The limiting base excision repair enzyme is the poly(ADP-ribose) polymerase (PARP)1, which adds branched chains of poly(ADP-ribose) polymerase to damaged DNA and thus induces separation of histones from DNA to enable DNA repair. PARP1 identifies the site of DNA injury and recruits repair complexes involved in non-homologous end-joining activity, which is a low-fidelity alternative reparation mechanism (Lee *et al.* 2014). Hence, PARP1 activity is essential in HR-deficient *BRCA2*-mutated tumor cells.

Synthetic lethality is a phenomenon in which two non-lethal genetic mutations are innocuous when they occur individually, but result in cell death when combined. Based on this principle, PARP1/2 inhibitors (PARPi) have been developed to target tumor cells in *BRCA1/2* mutation carriers, in which loss-of-function of both HR and base excision repair leaves DNA double-strand breaks unrepaired, leading to accumulation of DNA damage, genomic instability and ultimately cell death (Bryant *et al.* 2005, Farmer *et al.* 2005, Sandhu *et al.* 2010, Yap *et al.* 2011, Dhillon *et al.* 2016). Moreover, PARPi exert direct DNA toxicity by trapping PARP1 (and PARP2) at damaged DNA where the PARP–DNA complexes are more cytotoxic than unrepaired single-strand DNA breaks themselves (Murai *et al.* 2012). These preclinical results have been confirmed *in vivo*, where *BRCA2*-deficient tumors showed hypersensitivity to PARPi therapy with significant tumor regression (Hay *et al.* 2009).

Clinically, patients with *BRCA2* (and *BRCA1*) mutation-associated cancers have a marked sensitivity to PARPi, as demonstrated for the first time by Fong *et al.* (2009) in a phase I tolerance study. In that study, 63% of mutation carriers with breast, ovarian or prostate cancers who received olaparib were likely to have a clinical benefit based on a radiological and/or an objective biological response. This suggests that *BRCA1/2* mutations are predictive genetic biomarkers of response to PARPi. This was confirmed in a multicenter phase II study in 298 patients with *BRCA1/2* germline mutations, who received olaparib 400 mg twice a day, resulting in tumor control in 64% (tumor response rate: 26%, stability: 42%) (Kaufman *et al.* 2015). Several PARPi are under clinical development, alone or in combination therapy (Lee *et al.* 2014). The loss of the base excision repair capacity produced by PARPi has encouraged their combination with DNA-damaging agents, such as platinum salts, alkylating agents or radiation therapy.

PARPi have been shown to have relevant antitumor efficacy in *BRCA1/2*-associated advanced PDAC (Sandhu *et al.* 2010, Yap *et al.* 2011, Luo *et al.* 2015). Preclinical models have shown that tumor *BRCA2* deficiency was significantly associated with sensitivity to PARPi (Andrei *et al.* 2015). A phase II study included 23 patients with advanced *BRCA2*-mutated PDAC who had previously received an average of two lines of chemotherapy (including platinum-based chemotherapy in 65%) (Kaufman *et al.* 2015). Five patients (22%) and eight patients (35%) had an objective response and stable disease (disease control rate: 57%) using olaparib, respectively, with a median response of 4.4 months. These results in a heavily pretreated advanced PDAC population are promising and support further evaluation of PARPi in *BRCA1/2*-associated PDAC.

Besides their potential use as a single agent, PARPi are promising in combination with cytotoxic chemotherapies classically used in PDAC. Following preclinical models suggesting the greater efficacy of gemcitabine combined with PARPi than alone (Jacob *et al.* 2007), there have been reports of a marked response to gemcitabine plus iniparib (Fogelman *et al.* 2011, Lowery *et al.* 2011). A phase I trial showed that this association was safe (except with doses >600 mg/m^2 of gemcitabine) in patients with PDAC, although only a few had *BRCA1/2* germline mutations (Bendell *et al.* 2015). In that trial, a dose expansion phase including 15 patients who received olaparib (100 mg) plus gemcitabine (600 mg/m^2) showed that the overall response rate doubled without additional toxicity compared with seven patients who received gemcitabine alone.

Although these results are promising, most published studies are non-randomized, non-comparative,

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retrospective, monocentric and limited in size. Moreover, most previous studies have been performed in the Ashkenazi Jewish population, which may limit extrapolation of the results to PDAC patients with different *BRCA2* mutations (Luo *et al.* 2015). Phase II and phase III studies in larger size populations are currently ongoing to assess the efficacy and tolerance of PARPi such as olaparib, rucaparib, talazoparib and veliparib, alone or in combination with cytotoxic agents in patients with advanced PDAC (Table 1).

Safety data are now robust because thousands of patients have been treated with PARPi. The largest clinical experience to date was performed with olaparib monotherapy, which has been assessed in various malignancies. It is generally well tolerated at doses of 300–400 mg twice daily, and some patients were even able to continue for several years. Studies have reported manageable side effects including bone marrow toxicity, fatigue, headache, nausea and abdominal pain (Lee *et al.* 2014, Kaufman *et al.* 2015). Because of the potential increased toxicity in combination with DNA-targeting agents, the combination of olaparib with platinum salts may require reducing the dose of both drugs.

As with platinum salts, most *BRCA*-associated PDAC develop resistance to PARPi, often through the secondary development of intragenic *BRCA2* mutations as well as *PARP1/2* mutations that restore the protein function (Sakai *et al.* 2008). However, primary or acquired resistance to platinum is insufficient to predict PARPi resistance, as some *BRCA* wild-type PDAC remain sensitive to PARPi but resistant to platinum salts (Luo *et al.* 2015).

Other gene mutations favoring PDAC development

Germline mutations in genes coding for other members of the HR pathway have been associated with familial PDAC (Canto *et al.* 2013, Waddell *et al.* 2015, Zhen *et al.* 2015, Hu *et al.* 2016, Roberts *et al.* 2016). Germline *BRCA1* mutations only account for a small proportion of familial PDAC, although the risk of developing PDAC in *BRCA1* mutation carriers appears to be similar to that of *BRCA2* mutation carriers (Ford *et al.* 1994, Thompson *et al.* 2002, Al-Sukhni *et al.* 2008, Vincent *et al.* 2011, Ryan *et al.* 2014, Neuzillet *et al.* 2015). The PALB2 (partner and localizer of BRCA2) protein binds to the BRCA1/2 proteins and ensures nuclear addressing (Zhang *et al.* 2009). Germline mutations in the *PALB2* gene account for 2–3% of familial PDAC (Jones *et al.* 2009, Tischkowitz *et al.* 2009, Slater *et al.* 2010, Peterlongo *et al.* 2011). Germline mutations in genes coding for *ATM* as well as genes encoding for other partners of the Fanconi DNA repair pathway (FANC-C and FANC-G) have also been associated with familial PDAC but are much rarer (van der Heijden *et al.* 2003, Couch *et al.* 2005, Roberts *et al.* 2016).

Interestingly, the marked sensitivity of PDAC to PARPi and DNA-damaging agents such as platinum salts is not specific to *BRCA2* mutations but also applies to the

Table 1 Ongoing trials exploring the efficacy and toxicity of PARPi specifically in locally advanced and/or metastatic PDAC.

Identifier	Drug	Phase	Arms	Inclusion criteria	Measured criteria
NCT01296763	Olaparib	Phase I	Olaparib–irinotecan–cisplatin–mitomycin C	Stages III–IV, germline *BRCA1/2* negative, first to second line	Dose-limiting toxicity, OS
NCT02677038	Olaparib	Non-randomized phase II	Olaparib	Stage IV, second line, germline *BRCA1/2* negative	ORR and AEs
NCT02511223	Olaparib	Non-randomized phase II	Olaparib–irinotecan–cisplatin–mitomycin C	Stage IV, germline *BRCA1/2* negative, first to second line	ORR, OS, PFS and AEs
NCT02184195	Olaparib	Phase III	Olaparib and placebo	BRCA mutation, stage IV, no progression after 16 weeks of platinum	PFS, OS, ORR, AEs and QoL
NCT02042378	Rucaparib	Non-randomized phase II	Rucaparib	Second line, BRCA mutation	ORR, PFS, OS and AEs
NCT01908478	Veliparib	Phase I	Veliparib-gem-IMRT	Locally advanced or borderline	Dose-limiting toxicity, OS
NCT01489865	Veliparib	Non-randomized phase I–II	Veliparib-FOLFOX6	Stage IV, BRCA-associated mutation	Veliparib dosing, AEs and ORR
NCT01585805	Veliparib	Randomized phase II	Veliparib-gem-cis, gem-cis and veliparib	*BRCA1/2* or *PALB2* mutation, stage III–IV, second to third line	Veliparib dosing, ORR, AEs, OS, PFS and genetic reversion of BRCA mutations

AEs, adverse events; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life.

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germline mutations of the other above-mentioned genes of the Fanconi pathway (Bryant *et al.* 2005, Farmer *et al.* 2005, van der Heijden *et al.* 2005, Villarroel *et al.* 2011).

Other genetic alterations in familial PDAC include germline *CDKN2A/p16* mutations, which are generally associated with atypical familial multiple-mole melanoma (FAMMM) syndrome, germline *STK11* mutations observed in Peutz–Jeghers syndrome and germline *PRSS1* mutations that are responsible for hereditary pancreatitis (Hruban *et al.* 2010, Vincent *et al.* 2011, Ryan *et al.* 2014, Neuzillet *et al.* 2015). In addition, patients with Lynch syndrome have a four- to eight-fold increased risk of developing PDAC compared with the general population.

Concluding remarks

BRCA2 mutation carriers who develop PDAC are a small and unique subset of patients with biological specificities. PDAC occurs in around 10% of *BRCA2*-mutated families. Four to seven percent of sporadic PDAC and 10–17% of familial PDAC occur in relation to *BRCA2* mutations, especially in the Jewish Ashkenazi population. Although this population is quite rare, there is unique opportunity for early diagnosis through screening and appropriate follow-up. However, the efficacy of EUS/MRI yearly screening has not yet been confirmed and the anxiety and cost of these investigations must be kept in mind. Future developments will probably include blood and urine markers.

Based on the understanding of the role of BRCA2 in HR, DNA-targeted chemotherapy (such as platinum salts) and radiation therapy, as well as inhibition of DNA repair (such as PARPi), offer promising therapeutic results with acceptable toxicity, although further evidence is needed on *BRCA2*-tailored treatment. Several PARPi are under investigation as monotherapy or in combination with cytotoxic agents.

Predicting the efficacy of these drugs is currently based on identification of germline *BRCA2* mutations (as well as *BRCA1*, *PALB2* or other HR-related genes), and research should continue to identify simpler and reproducible markers of HR deficiency and response to PARPi, such as immunohistochemistry, quick molecular testing on pathological samples or screening of circulating tumor cells or DNA. Next-generation sequencing will also help providing rapid assessment of *BRCA* gene status.

Germline mutations in the above-mentioned genes account for less than 20% of all 'unstable phenotype' PDAC as determined by whole genome sequencing (Waddell *et al.* 2015, Bailey *et al.* 2016). Thus, other PDAC germline mutations involving other DNA repair pathways may identify '*BRCA*-like PDAC', which may also respond to platinum salts and PARPi. However, it is not known whether these treatments will benefit patients without germline but with somatic gene mutations. Better knowledge of the molecular alterations involved in this subset of PDAC tumors is essential to allow larger but more accurate patient selection for PARP inhibition.

Declaration of interest
L M, J B, C N, V R and N S declared no competing interests. P H is a member of the advisory board with AstraZeneca in the POLO study.

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