BReast CAncer (*BRCA*) gene mutations as an emerging biomarker for the treatment of gastrointestinal malignancies

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Abstract: BReast CAncer (*BRCA*) genes 1 and 2 were discovered in the 1990's by Hall *et al.* and Wooster *et al.* respectively. *BRCA* genes have been shown to be associated with an increased risk of various gastrointestinal (GI) cancers beyond known risk of breast, ovary and prostate cancers. Studies have demonstrated the role of *BRCA* genes in the DNA repair pathway and modalities to exploit this pathway are being currently explored. Using the concept of synthetic lethality, poly-ADP ribose polymerase inhibitors (PARPi) have significant activity in *BRCA* deficient cells. Targeted therapy is gaining popularity worldwide and *BRCA* genes have received much attention since the development and approval of PARPis. Multiple studies have also identified the predictive value of *BRCA* genes related to platinum and other DNA-damaging cytotoxic agents. *BRCA* deficient cells are about 5-fold more sensitive to platinum-based agents and almost 1,000-fold more with PARPis. Genomic instability has been established as the hallmark of *BRCA* deficient tumors and the specific roles of *BRCA* genes in DNA damage repair is increasingly clear. Herein, we discuss the risks and incidence of individual GI cancers seen with *BRCA* mutations, highlight tumor biology and provide a comprehensive review of the available preclinical and clinical data and upcoming trials related to this topic. The "POLO" trial in metastatic pancreas cancer establishes a "proof of principle" regarding treatment of BRCA-related cancer and PARPi. In pancreatic cancer routine germline genetic testing is now recommended in most major guidelines. Newer studies are emerging, which will expand the concept of *BRCA*ness and ways to effectively detect this phenotype in GI cancers and impact clinical practice.

Keywords: BReast CAncer (*BRCA*); poly-ADP ribose polymerase inhibitors (PARP inhibitors); gastrointestinal cancer; pancreatic cancer; synthetic lethality; Pancreas cancer OLaparib Ongoing (POLO)

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BReast CAncer 1/2 (*BRCA1/2*) and DNA repair pathways

BRCA1 and *BRCA2* are tumor suppressor genes. Discovered in the early 1990's as BReast CAncer susceptibility genes (1,2), they have been increasingly under the spotlight since 2013 after a renowned Hollywood actor announced her story (Angelina Jolie, "My medical choice", *New York Times*; 2013). Among the scientific community there has been a growing interest in *BRCA* mutations following the discovery and development of poly-ADP ribose polymerase (PARP) inhibitors (PARPis) (3-5). It has been known for several decades that mutations in the *BRCA* genes increase the risk of breast cancer, ovarian cancer and other malignancies. A recent study showed that the cumulative risk of breast cancer by age 80 in *BRCA1* and *BRCA2* mutation carriers was as high as 72% and 69% respectively (6). Both have an increased risk of esophageal, gastric, cholangiocarcinoma (CCA) and pancreatic cancer (PDAC), only *BRCA1*

mutation carriers have an increased risk for colorectal cancer (CRC) (7-10). In a Korean population stomach cancer was the most common cancer site among *BRCA* carriers after breast and ovarian cancer (11).

BRCA mutations can be inherited as a germline mutation in an autosomal dominant fashion or can be acquired as somatic mutations in the tumor. Multiple variants of *BRCA* mutations have been identified in the population. A majority of the pathogenic variants are protein truncating variants (frame shift or stop gain variants) which induces a loss of function (12). *BRCA* genes follow Knudson's two hit hypothesis where the second hit in the wild type allele of a germline mutation carrier is accrued by loss of allele or infrequently as a somatic mutation or promoter hypermethylation (*BRCA1* only) (13). Germline inherited mutations have been associated with a younger age at first cancer diagnosis along with a higher proportion of independent cancer diagnoses compared to patients with wild type in the germline (13).

The increased risk of cancer in *BRCA*-mutated genes has been conferred primarily related to their role in DNA damage repair (DDR). The collective mechanisms by which a cell deals with DNA damage acquired during replication or exogenously is termed the DDR pathway. DNA damage can lead to three main consequences: (I) initiate pathways required to repair the damaged DNA; (II) activate factors to cause cell cycle arrest to allow time for cells to repair themselves; (III) direct cells with irreparable damage towards apoptosis pathways (14).

There are five main types of DDR pathways identified, namely base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR) and non-homologous end joining (NHEJ) (15). DNA damage can be due mismatch during replication, single-strand breaks (SSB) or double-strand breaks (DSB). Replication errors and mismatch errors are often repaired through MMR. SSB, which are among the most common form of damage, are repaired through pathways initiated by PARPis (16). DSB's are more lethal to the cells and need immediate repair primarily by two main pathways. The slower error free homologous recombination repair (HRR) pathway which uses an existing chromatid as a template and a NHEJ pathway (17).

It is essential to understand the HR pathway to understand certain unique characteristics of *BRCA* deficient tumors for effective targeting. DSB in DNA are generally identified by the Mre11-Rad50-Nbs1 (MRN) complex. A series of events are initiated beginning with activation of kinases like ATM (ataxia telangiectasia mutated), ATR and DNA-dependent protein kinase (DNA-PK). These kinases cause phosphorylation of numerous proteins including *BRCA1* which promotes DNA end resection by nucleases like EXO-1 to form a 3' tail. *BRCA1* then activates *BRCA2* genes which helps recombinase RAD51 locate and bind to the single strand DNA to form a presynaptic filament (18). These filaments, with the help of *BRCA1*, invade into the sister chromatid to form a displacement loop or D-Loop (heteroduplex formation). D loops serve as a template for replication followed by holiday junction resolution of the heteroduplex complex (19,20). Beyond HRR, *BRCA* genes also play an important role in replication fork stability. In the absence of *BRCA* genes meiotic recombination 11-like (MRE11) nuclease leads to degradation of the replication fork causing increased genomic instability (21). Thus, *BRCA* deficient tumors must rely on error prone NHEJ pathway leading to high levels of genomic instability in tumors ultimately leading to cell death. Thus, in the absence of HRR pathway, tumors with *BRCA* mutations have increased sensitivity to agents that cause DSB like platinum-based chemotherapy, ionizing radiation and PARPis (22-24).

PARP are enzymes that are involved in DNA repair pathways. These enzymes are activated when endogenous or exogenous factors cause SSB or DSB. PARP binds to SSB and leads to further binding of branched poly-ADP ribose (PAR) chains in a process called PARylation (17,20). PARPis work on the principle of synthetic lethality which is a concept defined as early as 1945 (25). Synthetic lethality essentially refers to a set of two genes or molecular pathway where damage to either gene or pathway is not lethal but when there is damage to both, cell death occurs (26). PARP enzymes and *BRCA* genes are such a pair which are essential for SSB and DSB repair respectively. In the absence of both components there is accumulation of SSB which are converted to DSB during S phase and later leading to replication fork collapse (27) followed by activation of apoptosis pathway. When PARP enzymes are attached to SSB, followed by exposure to PARPis, the phenomenon of "PARP trapping" occurs which is more toxic to cells than being deficient in PARP (28). PARP enzymes are also involved in activating DNA-PK which leads to activation of NHEJ, the alternate pathway involved in DSB repair in cells where HRR is interrupted (29). Collectively, these mechanisms underpin the rationale for the exquisite sensitivity observed in tumors with *BRCA* gene mutation exposed to PARPis (30).

*BRCA*ness, homologous recombination defect (HRD)ness and PARPness

The term "*BRCA*ness" was first coined by Turner *et al*. in 2004 to explain the features exhibited by cancers that were *BRCA* mutated and to include cancers that exhibited similar characteristics without a specific *BRCA* mutation (31). Their original paper "Hallmarks of *BRCA*ness" reported subtle phenotypic characteristics seen in some of the *BRCA* mutated breast cancers like basal cell type, high histological grade, higher chance of being triple negative [estrogen receptor (ER), progesterone receptor (PR), HER-2 negative], presence of "pushing margins" showing an increased tendency towards lymphocytic infiltration and genotypic features with more *TP53* mutations, amplification of c-MYC and lack of ERBB2 and clinically by sensitivity to DNA damage inducing agents like cisplatin and mitomycin C. The presence of similar defining features were identified in cancer cells without *BRCA* mutations but with epigenetic changes like *de novo* methylation (silencing) of *BRCA1* promoter region, EMSY amplification and in cells with other defects in the same DNA repair pathways modulated by *BRCA* genes, defining a group of cancers with *BRCA*ness with serious clinical implications like sensitivity to specific chemotherapy and prognosis (31).

Following the approval of the first PARPi (olaparib in ovary cancer) in 2014 initially by the European Medicines Agency (EMA) (32) followed by the Food and Drug Administration (FDA) (33), there has been a growing interest in the scientific community to further explore the function of *BRCA1* and *BRCA2* genes and their role in DDR via the homologous repair pathway and others. Advances in whole genome sequencing (WGS) have led to the development of HRDetect by Davies *et al*. using six specific mutational signatures which allows detection of *BRCA* deficient tumors with a 98.7% sensitivity to broaden the spectrum of *BRCA*ness tumors (34). Pilié *et al*. has proposed the broader term HRDness (35) to include the group of cancers that are sensitive to PARPis in the absence of *BRCA* mutations or *BRCA* like phenotypes but also loss of function of other genes which are not canonical DDR genes, or presence of oncometabolites (36) and lead to a HRD. Studies have shown that DDR is affected more in cells exposed to PARPis than cells completely lacking PARP due to a phenomenon called "PARP trapping" (27,28). Cerrato *et al*. (37) described multiple factors that act as a surrogate for PARPi sensitivity like TMPRSS2: ERG (38), EWS fusions (39), CDK12 attenuation (40), low expression of ERCC1 (41) and BAP1 deficiency (42) to name a few. Pilié's group also proposes another term "PARPness" to describe markers predicting PARP sensitivity which are not involved in the HRR pathway like expression of Schlafen 11 (SLFN11) (35) or E-cadherin, or NAD^+ depletion (43).

BRCA in gastrointestinal (GI) cancers

Despite major advances in cancer detection and treatment, GI cancers continue to have one of the lowest 5-year survival rates according to the Centers for Disease Control and Prevention (CDC) data. PDAC followed by primary liver cancer [hepatocellular cancer (HCC)], CCA and esophageal cancer lead the order regarding lethality. There is a growing trend towards personalization of cancer therapy along with integration of targeted therapy and supportive care to maximize the quality of life of life and survival. Precision medicine in oncology refers to utilizing the molecular profiles and biologic characteristic of individual tumor to guide therapeutic choices. Modalities to detect specific driving mutation and target them are being refined and developed. Amongst GI cancers, PDAC continues to have least favorable outcome, nevertheless, understanding of DNA repair mechanisms is most advanced in this disease. This has translated into more studies in periclinal and clinical settings with recent translation into improved outcomes for subsets of patients.

PDAC

Risk of PDAC and BRCA

A year after the discovery of *BRCA2* gene, Goggins *et al*. in 1996 analyzed *BRCA* germline mutations in PDAC patients and identified a prevalence of 7.3% of cases with *BRCA2* (44). The Breast Cancer Linkage Consortium also reported a relative risk (RR) of 3.51 in patients harboring *BRCA2* mutations (8). Later the cumulative age adjusted lifetime risk PDAC with *BRCA1* mutations was reported to be 3.6% in 2002 (9). In an unselected population about 6–9% of the PDAC are associated with *BRCA1/2* mutations (45). Waddell and colleagues performed WGS and copy number variation analysis on 100 samples and classified PDAC into 4 subtypes based on structural rearrangements (45). Stable, locally rearranged, scattered and unstable subtypes. In the unstable group constituting 14% of cases, the majority, about 70%, had a *BRCA* signature. Another study which looked at mutational signatures to classify PDAC, identified

that about 10% of cases had HRD and were termed as the DSB group (46). The mean age of diagnosis of 62 in individuals with *BRCA* mutations was about 10 years lower than the age reported in SEER data for PDAC (47). A deep sequencing study in PDAC individuals identified ~4% patients with germline *BRCA2* mutation and another 3.9% with somatic *BRCA* mutations (48). A more promising study from Kondo's group had noted 47% of patients in a small cohort of 28 consecutive patients with PDAC to have HRR related using a next generation sequencing assay (23).

Therapy and BRCA in PDAC

In a retrospective analysis of a large cohort of patients with PDAC and a germline *BRCA* mutation, Golan *et al*. reported an overall survival (OS) benefit in patients treated with platinum-based regimen compared to others supporting the hypothesis of the predictive significance of *BRCA* (49). The superiority of platinum-based regimen in tumors with *BRCA*ness has since been replicated in multiple studies (50). Although, in surgically resected *BRCA* associated PDAC no difference has been noted in OS compared to wild type. However, was a trend towards increased disease-free survival in patients who received platinum-based chemotherapy in the *BRCA* mutated group (51). Hence the prognostic significance of *BRCA* is not well defined.

The first reports demonstrating the effectiveness of PARPi in PDAC surfaced in 2011 (52). Kaufman *et al*. conducted a pivotal trial which led to the FDA approval of PARPi in ovary cancer. In this trial a cohort of PDAC patients with a germline *BRCA* mutation were treated with single-agent olaparib and a response rate of 22% was observed in a group of individuals that had already received an average of two lines of prior therapy (33). This led to series of clinical trials evaluating the efficacy of PARPis (53,54). Notably, Yarchoan *et al*. evaluated olaparib in combination with irinotecan, cisplatin and mitomycin C and reported an overall response rate (ORR) of 23% among evaluable patients (55). However, myelosuppression was significant and dose-limiting, and the combination was halted from further development. A concerning fact was that two out of the three patients who had received more than 12 cycles of therapy and had an objective response had developed myelodysplastic syndrome of which one progressed to acute myeloid leukemia and died about 5 years after the start of treatment for PDAC. Another notable study was a phase II trial by Lowery and colleagues in 16 patients with known germline *BRCA*1/2 or PALB2 with prior treatment who received single agent veliparib, but failed to show any overall improvement in survival; however, all but one of these patients were platinum exposed/resistant likely accounting for the low objective response rate (56). The authors had proposed multiple reasons for these findings including the likelihood of olaparib being a stronger PARPi and a higher proportion of people with platinum resistance included in this study. The RUCAPANC trial, a phase 2 study in germline or somatic *BRCA* mutated PDAC patients who had received prior lines of treatment showed a response rate of 16% and a disease control rate of 32% with single agent rucaparib (57). Major grade ≥3 adverse events noted where anemia in 32% and fatigue in 16% of the patients. Interestingly in an untreated population with advanced PDAC a phase I trial by O'Reilly *et al*. with veliparib, cisplatin and gemcitabine showed an objective response rate of 78% in the *BRCA* mutated cohort (58). The phase 2 of this randomized trial NCT01585805 evaluating cisplatin, gemcitabine with/without veliparib in front-line *BRCA*1/2 or PALB2 mutated pancreas cancer has since completed accrual and demonstrated a very high response rate in both treatment arms 74.1% and 65% (P=0.55) for the triplet *vs.* the doublet, median PFS of 10.1 *vs.* 9.7 months (P=0.73) and OS of 15.5 *vs.* 16.4 months (P=0.6) (59). The triplet of cisplatin, gemcitabine and veliparib incurred significantly more grade 3–4 hematologic toxicity. Of further note, the 2-year survival rate for the combined study cohort was 30.6% and 3-year OS of 17.8%. Collectively these data endorse the value of platinum-based therapy in *BRCA/PALB2* mutated PDAC and endorse cisplatin/gemcitabine as a standard treatment option, and an alternative to mFOLFIRINOX, in this patient population.

It is key to note that in most of these studies responses where seen in patients who were platinum-sensitive rather than resistant or refractory leading to the question of the best timing for introduction of PARPis. The POLO (Pancreas cancer OLaparib Ongoing) provides some insight into this question. This randomized, double blind, placebo-controlled phase III trial in metastatic PDAC looked at olaparib in a maintenance setting for patients with a known germline *BRCA* mutation and without disease progression after 16 weeks or greater therapy with platinum-based agent as first line treatment and has shown promising results (60). One hundred and fifty-four patients across 12 countries were randomized as 3:2 in favor of olaparib *vs.* placebo. The primary endpoint of progression-free survival (PFS) was

7.4 months in the olaparib *vs.* 3.8 months in the placebo arm with a hazard ratio for disease progression or death of 0.53 with a 95% confidence interval (CI): 0.35–0.82 and P=0.004. The median duration of response of 24.9 months in the olaparib arm compared to 3.7 months with placebo is very notable in this disease. On an intent to treat analysis thus far no difference in OS has been identified for the olaparib-treated patients over placebo in an interim analysis at 46% data maturity. Albeit, some experts have commented regarding PFS as being an inadequate end point in maintenance therapy trials compared to OS (61). Another paper from the same study which analyzed the health-related quality of life using global health scale found that there was no statistical difference between the two groups during the first 6 months of treatment [between-group difference –2.47; 95% CI: –7.27 to 2.33; P=0.31] meaning that in the maintenance setting olaparib was able to achieve significant PFS while maintaining overall quality of life (62). One other important point of discussion related to the POLO trial pertains to the use of a control arm of placebo rather than continuation of cytotoxic therapy, which in many parts of the world is a standard approach for these patients. Of specific note in late 2019, the FDA approved olaparib as a maintenance therapy following 4 months of platinum-based treatment in germline *BRCA*-mutated pancreas cancer based on the results of the polo trial.

Current National Comprehensive Cancer Network (NCCN) guidelines endorse routine germline testing for all individuals diagnosed with PDAC based on recently published data (63-65). In 2019 implemented this recommendation for universal germline testing, a recommendation which is independent of age, ethnicity, heritage, or personal or family history of malignancy. In addition, somatic profiling is recommended for patients who are candidates for further treatment. Until recently germline testing was only recommended in patients of high-risk groups like Ashkenazi Jewish descent and individuals with personal history or a strong family history of breast, ovarian or PDAC in one or more family members. These recommendations came in the light of new evidence from studies that have demonstrated that a significant number of patients with genetic mutations and potentially targetable heritable mutations in PDAC were identified even in individuals without a strong family or personal history of cancer. In a study published in *JAMA*, Hu *et al.* identified 21 cancer predisposition genes by genomic sequencing from peripheral blood in 3,030 adults diagnosed with PDAC included in the mayo clinic registry spanning over 16 years (65). They identified 6 genes with significantly higher association with PDAC, including *BRCA1* and *BRCA2* in 5.5%. However, interestingly while these genes existed in about 7.9% of patients with a family history of PDAC about 5.2% of patients without such a history also had these genes uncovering a large group of individuals who would have been missed.

Pishvaian and colleagues analyzed data from Know Your Tumor program which collected tumor samples from 640 patients from 287 different centers (66). These tumor samples where send for next-generation sequencing (NGS) and immunohistochemistry (IHC) analysis revealing 27% of these samples with highly actionable targets. Of these 8.4% of the actionable targets where in DNA repair genes *BRCA1/2* and *ATM*. In patients who received matched therapy significantly longer PFS was observed compared to those who received unmatched therapy; PFS 4.1 *vs.* 1.9 months (hazard ratio, 0.47; 95% CI: 0.24–0.94; $P_{adj.}$ =0.03), making a strong argument in favor of precision oncology. As part of the same initiative their group analyzed 820 patients with PDAC in whom comprehensive genetic testing data was available to clearly define the prognostic and predictive role of HRD in PDAC. They reported that no significant difference was seen in median OS in platinum naïve patients with HRD and without HRD both in resected disease and advanced disease (67). This meant that HRD did not carry a prognostic significance in the absence of platinum exposure. Even though no significant difference in OS was noted between the two groups that received platinum-based therapy in surgically resected patients, there existed a very significant difference in advanced disease between HRD and without. Among the 311 patients with advanced disease who received platinum-based therapy the median OS was 2.37 years for patients with HRD *vs.* 1.45 years for patients without defects in HRD or DDR pathway [P=0.000072; hazard ratio, 0.44 (95% CI: 0.29–0.66)]. This study has now very clearly established the predictive value of HRD in pancreas cancer and the fact that the survival benefit is lost in platinum naïve patients calling for genetic testing in all patients.

The 2019 American Society of Clinical Oncology (ASCO) meeting at Chicago witnessed a sudden boom in that 3 different works were presented on pancreas cancer in the realm of HRD. Using MSK-IMPACT data Park and colleagues prospectively followed 461 patients and analyzed their outcomes with regards to germline and somatic HRD status (68). Although the OS was not different among patients that received platinum *vs.* non platinum-

based regimen in the first-line setting, the OS was found to be better among patients harboring a germline HRD *vs.* patients without the defect irrespective of first-line platinum-based therapy. In the updated analysis additional predictors of response to platinum therapy included biallelic status and the presence of a core gene mutation in *BRCA1/2* or *PALB2* (69). Like Pishvaian's group the investigators identified that OS was also significantly higher in the germline or somatic HRD patients. Chiorean and colleagues presented data from their phase II trial in metastatic PDAC who received a combination of modified FOLFIRI with veliparib *vs.* FOLFIRI in the second-line setting (70). One hundred and eight of 123 patients analyzed as per protocol at 35% of PFS events did not reveal a superiority with the combination compared to the control arm. 9% of the analyzed patients had HRD and about 30% of all patients had a defect in DDR genes. Pishvaian's group also had promising results from their phase I/II trial combining veliparib with 5-FU and oxaliplatin (mFOLFOX6) in metastatic PDAC in 64 patients (71). The study achieved its primary end point of ORR ≥25% and was well tolerated. Notably the ORR in platinum naïve patients with a family history of breast or ovarian cancers and or DDR gene defects was about 58%. The results on these completed trials have been summarized in *Table 1*.

Summing up in PDAC, there are many ongoing trials further exploring DDR and treatment targeting possibilities. We anticipate that moving forward there will be an integration of both germline and somatic profiling information at the time of diagnosis to optimally define a treatment strategy for an individual patient.

CCA

Risk of CCA and BRCA and outcomes

The Breast Cancer Linkage Consortium had reported an increased incidence of CCA in *BRCA2* mutated individuals with a RR of 4.97 (8), later confirmed by other studies (72). Mutations in the *BRCA1* associated protein, BAP1, have been reported in intrahepatic cholangiocarcinoma (ICC) with a prevalence as high as 14.3% in several studies (73-76). In patients with ICC, low BAP1 expression has been associated with an aggressive biology, early recurrence post-surgery and poorer prognosis (77,78). In 2019, Lin and colleagues identified mutations in DDR genes in 26% of analyzed patients with primary liver cancers including HCC (80% of cases), ICC and hepatocellular CCA. In the ICC group *BRCA1/2* mutations were detected in 9% of the individuals (79). About 6.7% of the 357 patients with primary liver cancer had at least one actionable target (79). This group of individuals with targetable mutations was notably higher at 47% in an analysis reported by Lowery and colleagues in CCA using the MSK-IMPACT platform (80). Parasramka *et al.* in 2017 were able to go a step further and show that ICC cell lines with low BAP1 expression was associated with increased sensitivity to gemcitabine and olaparib and uncovered the presence of a synergistic effect with the combination of the two (81). Multiple ongoing trials are underway which have been summarized in *Table 2*.

Therapy, BRCA and biliary cancers

Overall, there are relatively limited data regarding DDR-targeted approaches in biliary cancers. A multicenter retrospective cohort study in patients with germline or somatic mutations in *BRCA* genes showed superior outcomes in patients who received platinum-based regimens and/or PARPis with a median OS in stage I/II of 40.27 months and stages III/IV as 25 months (82). PARPis have also been shown to sensitize CCA to radiation therapy even in the absence of *BRCA* mutations (83). Targeting strategies in biliary cancers are early in development, however, this disease is recognized as one where platinum agents and PARPis may have a key role moving forward.

Esophageal cancer

Risk of esophageal cancer and BRCA

In 2007 germline DNA analysis of 197 Turkmen with esophageal squamous cell carcinoma (ESCC) identified *BRCA2* mutations in 7.6% of cases (84). Later in 2011 Moran *et al.* published the first study which demonstrated an increased RR of esophageal cancer in *BRCA1* mutation carriers. They reported a RR of 2.9 in *BRCA1* carriers and a RR of 4.1 in *BRCA2* carriers (85). Familial ESCC has also been found to have an increased frequency of *BRCA2* mutations in a study from china (72). WGS analysis in esophageal adenocarcinoma showed three dominant categories based on mutational signatures, of which the DDR impaired cells lines comprised of 18% of the analyzed samples and showed promising results when treated with the PARPi olaparib combined with a DNA damaging agent, topotecan (86). Deng *et al.* in 2019 studied the germline mutational profile of 77 individuals with ESCC

Table 1 Completed Trials with PARP inhibitors

NCT number	Primary cancer	Study design	Phase	Gene selection	Drugs	Drug class	Results
NCT00515866	Locally advanced/ metastatic pancreatic cancer	Randomized	1	Unselected	Olaparib, gemcitabine	PARP inhibitor, antimetabolite	Combination of olaparib 100 mg BID (intermittent dosing on days 1, 8, 15 every 4 weeks) with gemcitabine 600 mg/m^2 was found to acceptable tolerability profile ORR for the combination was 27.0% [95% CI: 10.9–52.0% (n=4/15)] compared with 14.0% [95% CI: 2.6–51.3% (n=1/7)] with gemcitabine alone; the difference was not significant 81% patients treated with olaparib capsule and gemcitabine reported grade ≥3 TEAEs. The most common were hematological toxicities, which occurred in 26/47 (55%) patients
NCT02042378	Locally advanced/ metastatic pancreatic cancer	Non-randomized	2	Germline or somatic BRCA mutation	Rucaparib	PARP inhibitor	Among 19 patients enrolled ORR was 16% and observed DCR was 32% Grade ≥3 TEAEs included nausea in 63% and anemia in 47% Showed a role for PARP inhibitor for advanced PDAC with BRCA mutation as durable and clinically significant responses seen in this population
NCT01585805	Locally advanced or metastatic pancreas adenocarcinoma	Single group	2	BRCA 1 or 2 or PALB2 mutation	Veliparib	PARP inhibitor	Of the 16 patients enrolled no confirmed PR was seen, however stable disease ≥8 weeks was observed in 25% of the patients. About 54% of patients experienced grade ≥3 toxicities
NCT01585805	Untreated locally advanced or metastatic pancreas adenocarcinoma	Randomized	1	BRCA 1 or 2 or PALB2 mutation	Gemcitabine, cisplatin +/– veliparib	Antimetabolite, DNA damaging agent, PARP inhibitor	RP2D was established for veliparib with the combination. Among the 17 patients enrolled 9 had BRCA mutation and 7/9 (78%) had ORR paving way for the phase II trial. There was a stunning 66.7% reduction in tumor volume among BRCA mutated patients
NCT02184195	Metastatic pancreatic cancer	Randomized, double blind, placebo controlled	3	Germline BRCA	Olaparib	PARP inhibitor	POLO trial evaluated olaparib in maintenance setting in patients without progression on platinum therapy for ≥16 weeks and found a significant PFS of 7.4 *vs.* 3.8 months No overall survival benefit has identified at data maturity of 46%

Table 1 (*continued*)

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NCT number	Primary cancer	Study design	Phase	Gene selection	Drugs	Drug class	Results
NCT01489865	Metastatic Pancreatic cancer with *BRCA* mutation	Single group	1/2	BRCA-associated mutation Personal or family history of a deleterious (or indeterminate) mutation in the *BRCA1*, *BRCA2*, *PALBB2*, or one of the FANC genes	Veliparib and mFOLFOX-6	PARP inhibitor	Study achieved the primary end point of ORR of ≥25%. Significant ORR of 58% noted among platinum naïve patients with family history and or DDR defects. Minimal grade ≥3 TEAE noted as myelosuppression in 16%
NCT02890355	Metastatic pancreatic cancer	Randomized	2	Unselected	Veliparib and mFOLFIRI *vs.* FOLFIRI	PARP Inhibitor	Interim futility analysis at 35% of PFS events has failed to show any significant difference in OS in the veliparib arm compared to control 5.1 *vs.* 5.9 months (HR 1.3, 95% CI: 0.9–2.0, P=0.21) nor was there a difference in PFS 2.1 *vs.* 2.9 months (HR 1.5, 95% CI: 1.0–2.2, P=0.05). Grade ≥3 toxicities noted were neutropenia 33% and fatigue 19%
NCT01063517	Recurrent or metastatic gastric cancer	Randomized	2	ATM negative	Olaparib, paclitaxel	PARP inhibitor, microtubule inhibitor	GOLD trial was undertaken after study39 the phase 2 showed promising results with OS improvement in the ATM deficient group, but similar results were not replicated in this phase 3 trial
NCT01051596	Colorectal cancer	Single group assignment	2	Unselected	Veliparib, temozolomide	PARP inhibitor, alkylating agent	Study reached its primary end point of DCR of 24% in a heavily pretreated population and the median OS was 6.6 months and PFS was 1.8 months. In a small group who received high dose the DCR was close to 35%
NCT00912743	Metastatic colorectal cancer	Single group	2	Unselected	Olaparib	PARP inhibitor	Olaparib did not demonstrate any significant activity in this unenriched patient population. No patients had complete or partial response and median PFS for all patients was 1.84 months
NCT02305758	Untreated metastatic colorectal cancer	Randomized	2	Unselected	Veliparib FOLFIRI ± bevacizumab	PARP inhibitor, VEGF inhibitor, topoisomerase inhibitor, antimetabolite	Median PFS was 12 *vs.* 11 months (veliparib *vs.* placebo) [HR 0.94 (95% CI: 0.60–1.48)]. Median OS was 25 *vs.* 27 months (veliparib *vs.* placebo) [HR 1.26 (95% CI: 0.74–2.16)]. Most common adverse event that led to dose interruption was neutropenia. No new safety concerns were identified

DCR, disease control rate; TEAE, treatment emergent adverse events; ORR, objective response rate; DCR, disease control rate; PDAC, pancreatic cancer; PFS, progression free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval

Table 2 Active clinical trials with PARP inhibitors in gastrointestinal cancers

NCT number	Primary cancer	Study design and status	Phase	Gene selection	Drugs tested	Drug class	Study endpoints
NCT03601923	Locally advanced or metastatic pancreatic cancer with HRD	Single group, recruiting	2	Germline and somatic *BRCA*1/2, PALB2, CHEK2 or ATM mutations	Niraparib	PARP inhibitor	PFS
NCT02890355	Metastatic pancreatic cancer	Randomized, not recruiting	2	Unselected	Veliparib and FOLFIRI	PARP inhibitor	OS
NCT04005690	Non-metastatic, resectable pancreatic cancer	Non-randomized, recruiting	2	Unselected	Cobimetinib and olaparib	PARP inhibitor, MEK inhibitor	Proportion of subjects that complete window treatment with cobimetinib or olaparib, and undergo collection of both pre-treatment and post-treatment tumor tissue samples
NCT01489865	Metastatic pancreatic cancer with *BRCA* mutation	Single group, not recruiting	1/2	*BRCA*-associated mutation Personal or family history of a deleterious (or indeterminate) mutation in the *BRCA*1, *BRCA*2, PALBB2, or one of the FANC genes	Veliparib and mFOLFOX-6	PARP inhibitor	DLT
NCT03140670	Locally advanced or metastatic pancreatic cancer with deleterious *BRCA*1/2 or *PALB*2 mutation without progression on FOLFIRINOX for >16 weeks	Single group, recruiting	2	Deleterious *BRCA*1/2 or PALB2 mutation (germline or somatic)	Rucaparib	PARP inhibitor	Number of AE
NCT01585805	Locally advanced or metastatic pancreas adenocarcinoma with a *BRCA*1/2 or *PALB*2 mutation	Randomized, not recruiting	2	*BRCA* 1 or 2 or *PALB*2 mutation	Gemcitabine, cisplatin +/– veliparib; single-agent veliparib	PARP inhibitor	Optimal dose of combination Response rate of combination Response rate of single-agent veliparib
NCT03553004	Pancreas adenocarcinoma with mutation in DNA repair genes	Single group, recruiting	2	Germline or somatic mutation in genes involved in DNA repair	Niraparib	PARP inhibitor	ORR

Table 2 (*continued*)

Table 2 (*continued*)

NCT number	Primary cancer	Study design and status	Phase	Gene selection	Drugs tested	Drug class	Study endpoints
NCT02677038	Metastatic pancreas adenocarcinoma with *BRCA*ness phenotype but absent germline *BRCA*1/2	Single group, recruiting	2	Germline *BRCA* 1 or 2 negative Patients with previously identified genetic aberrations that are associated with HRD will be eligible even in the absence of family history (e.g., somatic *BRCA* mutation, Fanconi anemia gene, ATM or RAD51 mutations)	Olaparib	PARP inhibitor	ORR
NCT03404960	Locally advanced or metastatic pancreatic cancer without progression on platinum-based regimen for >16 weeks	Randomized, recruiting	1/2	Unselected	Niraparib + nivolumab; niraparib + ipilimumab	PARP inhibitor; CTLA4 monoclonal antibody; anti-PD-1 monoclonal antibody	PFS
NCT03851614	Locally advanced or metastatic pancreatic adenocarcinoma or mismatch repair proficient CRC	Randomized, recruiting	2	Mismatch repair proficient colorectal cancer	Durvalumab + olaparib	PARP inhibitor; anti-PD-1 monoclonal antibody	Changes in genomic and immune biomarkers that will be measured in the baseline biopsy and the first on-treatment biopsy
NCT03682289	Locally advanced or metastatic pancreatic adenocarcinoma with progression on or after treatment	Non-randomized, recruiting	2	Unselected	AZD6738 + olaparib	PARP inhibitor; ATR kinase inhibitor	ORR
NCT02498613	Locally advanced or metastatic pancreatic adenocarcinoma post at least 1 line of treatment	Single group, recruiting	2	Unselected	Cediranib + olaparib	PARP inhibitor; VEGF receptor tyrosine kinase inhibitor	ORR
NCT03637491	Locally advanced or metastatic pancreatic adenocarcinoma with progression on or after treatment	Randomized, recruiting	2	Positive KRAS or NRAS mutation	Avelumab + binimetinib + talazoparib	PARP inhibitor; anti-PD-1 monoclonal antibody; MEK inhibitor	DLT ORR

Table 2 (*continued*)

Table 2 (*continued*)

NCT number	Primary cancer	Study design and status	Phase	Gene selection	Drugs tested	Drug class	Study endpoints
NCT03337087	Metastatic gastrointestinal malignancies; metastatic pancreatic cancer with HRD	Single group, recruiting	1/2	Phase Ib only: unselected and selected for *BRCA*1 or *BRCA*2 or PALB2 mutation Phase II only: genomic markers (signature) of homologous recombination deficiency (HRD) or *BRCA*1 or *BRCA*2 or PALB2 mutation, or HRD (non-*BRCA*, non-PALB)	Liposomal irinotecan + fluorouracil + leucovorin + rucaparib	PARP inhibitor; topoisomerase 1 inhibitor	MTD of the combination ORR Best response rate
NCT03008278	Gastroesophageal junction adenocarcinoma and metastatic gastric cancer	Single group, recruiting	1/2	Unselected	Olaparib and ramucirumab	PARP inhibitor; VEGFR2 inhibiting monoclonal antibody	DLT and MTD of olaparib ORR
NCT03212274	Cholangiocarcinoma with IDH mutation	Single group, recruiting	2	IDH1 or IDH2 mutation	Olaparib	PARP inhibitor	Overall response rate
NCT03207347	Cholangiocarcinoma and DDR deficient tumors (except prostrate)	Non-randomized, recruiting	2	Known DNA damage repair mutation including variants of unknown significance	Niraparib	PARP inhibitor	ORR
NCT03991832	Cholangiocarcinoma and other solid tumors with IDH mutation	Non-randomized, not yet recruiting	2	IDH mutation	Olaparib and durvalumab	PARP inhibitor; PD-L1 inhibitor	Overall response rate Overall disease control rate
NCT03878095	Cholangiocarcinoma and other solid tumors with IDH mutation	Single group, not yet recruiting	2	IDH1 or IDH2 mutation	Olaparib and ceralasertib	PARP inhibitor; ATR inhibitor	ORR
NCT04042831	Advanced biliary tract cancer	Single group, not yet recruiting	2	Homologous recombinant repair pathway defect	Olaparib	PARP inhibitor	Best objective response rate
NCT02734004	Metastatic or relapsed gastric cancer	Single group, recruiting	1/2	Unselected	Olaparib, MEDI4736 and bevacizumab	PARP inhibitor; anti-PD-L1 monoclonal antibody; VEGF inhibitor	DCR Safety and tolerability of MEDI4736 in combination with olaparib (± bevacizumab) ORR

Table 2 (*continued*)

Table 2 (*continued*)

NCT number	Primary cancer	Study design and status	Phase	Gene selection	Drugs tested	Drug class	Study endpoints
NCT03026881	Recurrent or metastatic gastric cancer	Single group, unknown	1	Unselected	Fluzoparib, apatinib and paclitaxel	PARP inhibitor VEGF receptor tyrosine kinase inhibitor; microtubule inhibitor	DLT and safety
NCT03427814	Advanced or Inoperable gastric cancer	Randomized, double blind, placebo controlled, recruiting	3	Unselected	Pamiparib	PARP inhibitor	PFS
NCT03875313	Locally advanced or metastatic CRC	Non-randomized, recruiting	1	Unselected	CB-839 + talazoparib	PARP inhibitor; glutaminase inhibitor	Safety and tolerability of CB-839 in combination with talazoparib MTD and/or RP2D
NCT00576654	Locally advanced or metastatic pancreatic adenocarcinoma and CRC	Non-randomized, not recruiting	1	Unselected	Irinotecan + veliparib	PARP inhibitor	OBD Maximum administered dose of study drugs MTD RP2D
NCT02921256	Locally advanced stage II or III rectal adenocarcinoma	Randomized, suspended	2	Unselected	mFOLFOX6 + RT + capecitabine + veliparib	PARP inhibitor	Change in neoadjuvant rectal cancer score

PFS, progression-free survival; OS, overall survival, DLT, dose limiting toxicity; AE, adverse events; ORR, overall response rate; MTD, maximum tolerated dose; DCR, disease control rate; RP2D, recommended phase 2 dose; OBD, optimal biologic dose.

and found that 11.7% of patients had a HRD which was associated with a well differentiated tumor and a greater degree of lymph node metastasis (87). These studies have demonstrated a potentially actionable group for further exploration with PARPi. Miyamoto *et al*. in 2019 were able to demonstrate a synergistic effect of olaparib in ESCC cell lines when combined with chemo therapeutic agents (88).

Currently there is a relative dearth of trials in esophageal cancer although a clear actionable sub-group is evident in this disease type. We anticipate that further clinical data will ensue soon as interest in DDR genomic based treatment strategies expands in GI cancers.

Gastric cancer

Risk of gastric cancer and BRCA

The breast cancer linkage consortium study in 1999 reported an increased risk of gastric cancer in *BRCA2* carriers with a RR of 2.59 while similar results were not observed with *BRCA1* (8). Other studies have described *BRCA1* as conferring an increased risk of gastric cancer (89,90). *BRCA1* carriers were reported to have a cumulative age adjusted lifetime risk of 5.5%, four times the observed risk in the general population (9). *BRCA1* nuclear expression was evaluated by Kim *et al*. in 2013 who found that decreased nuclear expression was associated with more advanced disease and perineural invasion and served as a marker for poor prognosis (91). They also observed that adjuvant chemotherapy was able to overcome this adverse prognosis and that decreased *BRCA1* nuclear expression could serve as a predictive marker for response to adjuvant chemotherapy. Chen *et al*. identified that gastric cancer cells had *BRCA1* protein detected in the cytoplasm as compared to nucleus and that decreased expression was associated with response to platinum-based therapy (92). Similarly, decreased expression of *BRCA1* associated protein (BAP) was also found to correlate with advanced disease and poor prognosis and a potential prognostic marker (93). Recent evidence suggests that gastric cancer cells with lack of *BRCA2* expression is associated with younger age and signet ring cell variant (94).

Alexandrov's group analyzed gastric cancers for mutational signature 3, a base substitution signature that has been observed to be associated with *BRCA* mutations and serving as a surrogate for platinum sensitivity including in individuals without *BRCA* mutations (45). They noted that as many as 7–12% of gastric cancers had signature 3 which demonstrated the hallmarks of cancers with HRR in the absence of *BRCA* mutations and could potentially be targeted (95). Mihailidou's group in 2017 suggested that gastric cancers with *BRCA* deficiency are susceptible to c-MET inhibition in the presence of DNA damaging agents (96). *BRCA1* expression loss was associated with a poorer prognosis and had a 2-year survival rates close to 50% of that seen among *BRCA1* wild type tumors (97). Using IHC Wang *et al*. showed that high *BRCA1* and *BRCA2* expression in cytoplasm predicted a favorable prognosis in gastric cancers while increased *BRCA1* expression in the nucleus was shown to have a poor prognosis (98). *In vitro* analysis performed by Kim *et al*. showed an inverse correlation with *BRCA1* expression level sensitivity to platinum agents (99).

Therapy, BRCA and gastric cancer

Borrowing ideas from their mantle cell lymphoma study Kubota *et al*. in 2014 demonstrated that gastric cancer cells lacking expression of *ATM* gene had increased sensitivity to olaparib (100). Bang *et al*. applied this *in vivo* and a phase II trial showed an increased OS with olaparib/paclitaxel combination in study population and not just the *ATM* low expression subgroup (101) paving way to a phase III trial, olaparib in combination with paclitaxel in patients with advanced gastric cancer who had progressed following first-line therapy (GOLD) trial. The GOLD trial was a double-blind, randomized, placebo-controlled phase III study which failed to demonstrate an improved OS with olaparib/paclitaxel *vs*. placebo/paclitaxel in the overall population [median OS 8.8 months in the olaparib group *vs*. 6.9 months in the placebo group; hazard ratio, 0.79 (97.5% CI: 0.63–1.00); P=0.026] and in the *ATM* deficient population [median OS 12.0 months in the olaparib group *vs*. 10.0 months in the placebo group; hazard ratio, 0.73 (97.5% CI: 0.40–1.34), P=0.25] (102). *In vitro* studies with combination of phosphoinositide 3-kinase (PI3K) and olaparib in cells with AT-rich interactive domain containing protein 1A (ARID1A) deficiency have shown promising results and would need further studies (103).

Like other GI cancers we anticipate an expansion of trials targeting DDR pathways in gastric cancer in the proximate future.

CRC

Risk of CRC and BRCA

The association between *BRCA* genes and CRC is

controversial. Studies by Yurgelun *et al*. (104) had demonstrated an increased risk of CRC in *BRCA1/2* mutation carriers while other studies like Brose *et al*. (9) demonstrated an increased risk only in *BRCA1* mutation carriers. Phelan *et al*. (105) noted that the incidence of CRC was 4 times higher in women less than 50 years with mutated *BRCA1*, however no meaningful association was found in other groups (106,107). A comprehensive systematic review and metanalysis by Oh and colleagues showed no increased risk of CRC in *BRCA2* mutation carriers and a 1.49-fold increased risk in *BRCA1* mutation carriers (108). A more recent study demonstrated that 15% of the CRC analyzed had DDR gene alterations (109).

Preclinical and clinical data in CRC

Davidson *et al*. in 2013 noted that PARPis acted synergistically with platinum agents *in vitro* conditions (110) followed by Shelton *et al*. who showed *in vivo* response as well as an increased sensitivity to radiation therapy in the presence of PARPis (111). A preclinical study showed increased sensitivity of CRC cell lines with *ATM* deficiency to PARPi (112). However, a phase 2 trial in an unselected population failed to show any substantial activity with a single agent PARPi regardless of the microsatellite status (113). In a heavily pretreated population Wang and colleagues in their phase 2 trial achieved a disease control rate of 24% using a combination of veliparib with temozolomide (114). In a randomized, blinded, placebo-controlled phase 2 trial by Gorbunova's group the addition of veliparib to first-line standard of care FOLFIRI ± bevacizumab in metastatic CRC did not reveal an improvement in PFS; 12 *vs*. 11 months (veliparib *vs*. placebo) [hazard ratio, 0.94 (95% CI: 0.60–1.48)] (115). The authors concluded that the increased incidence of hematological toxicities due to addition of the PARPi with chemotherapy had resulted in a shorter treatment duration.

Moving forward the value of DDR targeted approaches in CRC remains unclear. Arguably a population of interest is the subgroup with microsatellite instability from either a germline or somatic etiology and may represent a subgroup where such targeted approaches are relevant along with the small subset of patients harboring a germline *BRCA* mutation where CRC arises.

Looking forward

During the last few years of research, it has become more evident that not all individuals with *BRCA* mutations have the same response to PARPis or DNA damaging agents. Lord *et al*. proposed that there is a growing need for functional biomarkers for *BRCA*ness given the differential sensitivity seen with PARPis in patients with hypermethylation of promoter region of *BRCA* in comparison to patients with germline mutations (116). This is in part because *BRCA* mutation status is not synonymous with HRD. Curtin and colleagues explain this in their paper on why *BRCA* mutation is not a tumor agnostic biomarker (117). This would explain why many recent trials did not produce the expected results or failed to show an efficacy or OS benefit (56,102,115). An ideal biomarker would be one which detects the presence of errors in DDR pathway and correlates well with PARPi sensitivity (118). Another concern is the development of second reactivating or reversion mutations during treatment (119), hence there needs to more studies on strategies to overcome resistance or better prevent or retard the development of resistance. IHC detection of RAD51 foci was a method proposed and evaluated in multiple studies. A major drawback is that RAD51 is not necessarily expressed in the nuclear foci of normal cells until there is DNA damage. Mutational signature 3 has been well correlated with HRD and might hold the key for population selection than merely the presence of germline or somatic *BRCA* mutation. Johnson *et al*. in an important recent paper, has postulated that not all pathogenic *BRCA* germline mutations are drivers of cancers and may be mere passengers based on their observation that as many as 8% of the cancer cells had lost the pathogenic germline *BRCA* mutation due to somatic loss of allele mutations (13). They also noted that only four types of cancers were enriched in germline *BRCA* mutation carriers after ancestry-adjusted association was applied namely breast, ovarian, prostrate and PDAC which they named *BRCA* associated cancers. They used HRD scores generated from mutational signatures or large-scale transitions in copy number alterations to evaluate different tumors. This led to an important hypothesis from the analysis that there was a near complete absence of HRD in non *BRCA* associated cancers (cancers beyond the four types afore mentioned) with heterozygous *BRCA* mutation that were not the cause of tumorigenesis but often produced somatically during tumor evolution. Research is underway to identify new molecules that act as surrogate marker for PARPi sensitivity and the presence of recombination deficiency.

Another area of growing interest has been the use of combination strategies with PARPis including with VEGF

inhibitors and immunotherapy. The proof of concept studies for combination of PARP with VEGF inhibitors comes partly from the preclinical studies which demonstrated that hypoxia causes cells to develop HRD (120,121). In ovarian cancers, Liu and colleagues were able to demonstrate this clinically in a phase 2 study that showed significantly longer PFS (17.7 *vs.* 9.0 months, hazard ratio, 0.42; P=0.005) (122). Multiple clinical trials are ongoing to explore this concept (NCT02498613, NCT03008278, NCT03026881). Combining DNA repair inhibitors with Immunotherapy is an emerging field (123-126). In DDR deficient breast cancer, Parkes *et al*. identified a novel mechanism by which cytosolic DNA leads to activation of STING innate immune response upregulating the PD-L1 expression and making an argument for immune check point inhibitors in this subset in combination with S phase DNA damaging agents (123). In the field of urothelial cancer, Teo and colleagues identified a strong association between DDR alterations and response to anti-PD-L1 with a higher ORR in DDR deficient subtype compared to those without any DDR alterations (67.9% *vs.* 18.8%; P=0.001) (124). Mutations in the RAS signaling pathway was another suggested mechanism of PARPi resistance leading to combination with MEK inhibitors (NCT04005690, NCT03637491). Inspired from preclinical data, newer trials are combining PARPi with durvalumab, nivolumab and ipilimumab to test this hypothesis (NCT03851614, NCT03991832, NCT03404960).

Other ways of targeting *BRCA*ness beyond PARPis are under investigation. RAD52 inhibitors have been found to be synthetically lethal in cells with *BRCA1*, *BRCA2* and *PALB2* mutations (127-130). WEE1 is a tyrosine kinase inhibitor of CDK1/2 which leads to arrest of mitosis in cells that sustain DNA damage. WEE1 inhibitors as monotherapy and in combination with ATR inhibitors have rendered cells sensitive to PARP inhibition and platinum agents (131). In PDAC a combination of a WEE1 and PARPi acts as a radiosensitizer (132). *BRCA* deficient cells switch to the alternative error prone pathway, NHEJ, and inhibition of polymerase theta has been shown to inhibit NHEJ and serve as a potential target (133). Inhibitors against DDR proteins like MTH1 and DNA damage signaling inhibitors like ATR, ATM, CHK1, USP7 (134) are all being studied (135). *Table 3* provides a summary of relevant ongoing trials.

There have been major developments in the last couple of years regarding the recognition of *BRCA* mutations, their association with GI cancers and the targeted therapy implications. Importantly, a proof of principle has been secured with the recent FDA approval for olaparib in the setting of *BRCA*-related pancreas cancer, and even prior to that routine guideline endorsement for universal germline (and somatic) profiling in that disease. More routine evaluation of HR gene mutations across the spectrum of GI malignancies is warranted, including more widespread evaluation of germline and somatic profiling. Another GI malignancy with rich targeting opportunities is CCA, specifically ICC and increasing literature is emerging in this disease utilizing DDR strategies. Summing up, while these patient subsets are relatively uncommon, a broader group of patients with GI malignancies and underlying HR gene mutations beyond *BRCA*1/2 exist, and these patients need to be identified for potential syndrome identification, cascade family testing and treatment implications. It is now evidently clear that DNA-repair treatment approaches are established with the use of platinum therapies and PARPis, and we need to build on these early signals with novel combinations and expand the applicable patient population. A recent paper based on the National Cancer Database pointed out that even though clear superiority in terms of OS has been observed in patients enrolled in clinical trials, only 0.1% of patients are able to participate in clinical trials (136). Thus, a related key mission is expansion of the number of high priority clinical trials

To quote Robert Frost "*And miles to go before I sleep, and miles to go before I sleep*."

Table 3 Selected ongoing trials with other agents in gastrointestinal cancers

NCT number	Study name	Primary cancer	Study design and status	Phase	Drug tested	Drug class	Primary outcome
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	Solid tumors with *BRCA*1 or *BRCA*2 mutation	Non-randomized, recruiting	2	Adavosertib	WEE1 inhibitor	ORR
NCT02264678	A Modular Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumor Activity of AZD6738 in Combination with Cytotoxic Chemotherapy and/or DNA Damage Repair/Novel Anti-cancer Agents in Patients with Advanced Solid Malignancies	Gastric adenocarcinoma and GEJ adenocarcinoma	Non-randomized, recruiting	1	AZD6738	ATR kinase inhibitor	Safety and tolerability in terms of AE and SAE
NCT03641313	A Phase 2 Single-Arm Study of M6620 in Combination with Irinotecan in Patients with Progressive TP53 Mutant Gastric and Gastro-Esophageal Junction Cancer	Metastatic or unresectable gastric or GEJ adenocarcinoma	Single group, not yet recruiting	2	M6620	ATR kinase inhibitor	ORR
NCT02950064	Escalation Study of BTP-114 in Patients with Advanced Solid Tumors and BRCA or DNA Repair Mutation	BRCA mutation-positive pancreatic cancer	Single group, not recruiting	1	BTP-114	Novel platinum product	MTD
		Advanced DNA repair mutation-positive solid tumor					RP2D
							Number of patients with TEAE
							ORR
							DCR
							DOR
							PFS
NCT02194829	A Phase I and Randomized Phase II Study of Nab-Paclitaxel/ Gemcitabine with or Without AZD1775 for Treatment of Metastatic Adenocarcinoma of the Pancreas	Locally advanced or metastatic pancreatic cancer	Randomized, not recruiting	1/2	Adavosertib	WEE1 inhibitor	MTD
							PFS
NCT02797964	A Phase 1/2 Trial of SRA737 (a Chk1 Inhibitor) Administered Orally in Subjects with Advanced Cancer	Metastatic colorectal cancer	Sequential assignment, no recruiting	1/2	SRA737	Chk1 inhibitor	AE
							MTD
							RP2D
							ORR

Table 3 (*continued*)

Table 3 (*continued*)

NCT number	Study name	Primary cancer	Study design and status	Phase	Drug tested	Drug class	Primary outcome
NCT02906059	A Phase Ib Study Combining Irinotecan with AZD1775, a Selective Wee 1 Inhibitor, in RAS (KRAS or NRAS) or BRAF Mutated Metastatic Colorectal Cancer Patients Who Have Progressed on First-Line Therapy	Metastatic colorectal cancer after 1st line therapy	Single group, recruiting	1	Adavosertib + irinotecan	WEE1 inhibitor	DLT with TEAE
NCT03284385	A Phase 2 Study of AZD1775 in SETD2-Deficient Advanced Solid Tumor Malignancies	Locally advanced or metastatic solid tumor malignancy	Single group, recruiting	2	Adavosertib	WEE1 inhibitor	ORR
NCT03253679	A Phase 2 Study of AZD1775, a Wee1 Inhibitor, in Patients with CCNE1 Amplification	Advanced solid tumors harboring CCNE1 amplification	Single group, recruiting	2	Adavosertib	WEE1 inhibitor	ORR
NCT01827384	Molecular Profiling-Based Assignment of Cancer Therapy for Patients with Advanced Solid Tumors	Advanced malignant solid neoplasm	Non-randomized, recruiting	2	Adavosertib	WEE1 inhibitor	ORR
NCT02595931	Phase I Clinical Trial of VX-970 in Combination with the Topoisomerase I Inhibitor Irinotecan in Patients with Advanced Solid Tumors	Metastatic or unresectable malignancy	Single group, recruiting	1	M6620	ATR kinase inhibitor	MTD RP2D
NCT04095273	A Multicenter, Non-randomized, Open-label Phase Ib Study to Determine the Maximum Tolerated and Recommended Phase 2 Dose of the ATR Inhibitor BAY1895344 in Combination with Pembrolizumab and to Characterize Its Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumor Activity in Patients with Advanced Solid Tumors	Histologically confirmed solid tumors with putative biomarkers of DDR deficiency	Non-randomized, not yet recruiting	1	BAY1895344	ATR inhibitor	Incidence of TEAE Severity of TEAE Frequency of DLT

ORR, objective response rate; AE, adverse events; SAE, serious adverse events; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; DCR, disease control rate; DOR, duration of response; PFS, progression-free survival; TEAE, treatment emergent adverse events; DLT, dose limiting toxicity.

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