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Genomic Profiling in Pancreatic Ductal Adenocarcinoma and a Pathway towards Therapy Individualization: A Scoping Review

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Abstract

Context: Pancreatic cancer (PDAC) is one of the most challenging cancers to treat with modest recent improvements in survival from new systemic therapies. There is growing interest in individualized therapy underpinned by somatic and germline genomic alterations.

Objective: A systematic review of data on therapies targeting somatic and germline alterations, and their downstream pathways in PDAC.

Method: A systematic literature search was conducted using PRISMA guidelines to include relevant results published after January 1, 2008.

Results: A total of 71 relevant studies were included. We identified 36 studies targeting the *KRAS*-pathway, the most common being with MEK-inhibitor therapy. Twenty-two studies were identified that evaluated platinum-based chemotherapy and PARP inhibitors in patients with deleterious mutations in DNA damage repair genes and have shown encouraging results.

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Immunotherapy has demonstrated activity in patients with mismatch repair deficiency/ microsatellite instability.

Conclusion: Evidence from translational and clinical research presents an exciting platform for genomic targeted therapy in PDAC. Validity for targeting BRCA with platinum and PARP inhibitors and microsatellite instability with immune therapy has been established, nonetheless, evidence for targeting the common driver oncogenes is lacking and much work is needed. Of importance is identifying the subgroup of KRAS -wild type PDAC (approximately 5%) where there is enrichment for targetable opportunities.

Keywords

Pancreatic ductal adenocarcinoma (PDAC); genomic alteration (GA); DNA damage repair; somatic mutation; germline mutation; mismatch repair (MMR); microsatellite instability

Background

Pancreatic ductal adenocarcinoma (PDAC) has gained increasing attention over the last decade as its incidence continues to rise in contrast to other solid organ malignancies, and this trend is unlikely to change with the increasing life expectancy. Despite being an uncommon solid tumor (estimated 3.2 percent of all new cancer cases in 2018) PDAC is a large contributor to the toll of cancer deaths (estimated 7.3 percent for 2018)[1, 2]. It has surpassed breast cancer as the third leading cause of cancer deaths, and with the current trend PDAC is predicted to overtake colorectal cancer to become the second leading cause of cancer-related mortality by the end of this decade[3].

The prognosis associated with PDAC has been enigmatic for years. The medical community is challenged with difficulties in early diagnosis due to delayed clinical presentation, along with lack of early diagnostic method or a consistent premalignant lesion, and the tendency to early metastasis. Collectively these are substantive constraints to better outcome. PDAC microenvironment features are characterized by marked heterogeneity with low epithelial tumor component, a dominant stroma and a lack of effector immune cells, also in part contributing to poor prognosis.

There have been subtle but definite improvements in survival, measurable in weeks to a few months with currently available multi-agent cytotoxic regimens for advanced PDAC[4–7]. However, unlike many other cancers its natural history has largely remained unchanged[3, 8]. While this trend is disappointing, it has triggered tremendous focus into the putative causes, most notably the molecular and genetic drivers of carcinogenesis. There are several genomic alterations (GA) with a primary or secondary role in tumorigenesis, including familial cancer syndromes underpinned by known single germline mutations and most individuals have mutations in key oncogenes/tumor suppressor genes. Nonetheless, translation to actionability and therapeutics from potentiality to reality for most individuals diagnosed with this disease remains to be realized.

There is growing data on the role of platinum-based chemotherapy and poly ADP ribose polymerase inhibitors (PARPi) in patients with germline mutations in the genes associated

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with DNA damage repair (DDR) mechanisms or homologous recombination repair (HRR) [9–12]. Somatic mutation testing on the other hand has consistently detected mutations in one or more of the tumor suppressor genes or proto-oncogenes namely, Kirsten RAS (*KRAS*), tumor protein P53 (*P53*), Mothers against decapentaplegic homolog 4 (*SMAD4*), cyclin-dependent kinase inhibitor 2A (*CDKN2A*)[13–16]. Recently, there has been tremendous research towards identification of potential targets to alter pathogenic GA, both somatic and germline or their downstream pathways. Nonetheless, there are only a few such agents approved in PDAC[17, 18].

Aims and Objectives

While there is substantive data in both translational and clinical settings addressing the potential application of genomic targeted therapies for individuals with PDAC, there is a dearth of clear evidence for specific applications in patients with GA's to guide clinical use. Therefore, we choose to systematically review the available literature on genetically targeted therapies, specifically those targeting somatic and germline drivers of PDAC and their downstream pathways.

Methods

Preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement was followed for reporting this review[19].

Search Methods

An extensive literature search was conducted on September 5, 2018 in Medline (PubMed), Embase.com, and Cochrane Library (Wiley) by a medical librarian (JG) at Memorial Sloan Kettering (MSK), New York. Controlled vocabulary (MeSH, Emtree) and keywords were used. The searches had no language or publication type restriction. Additional keyword searches were completed using ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform. Results were limited to items published on or after January 1, 2008.

Three main categories were included in the search, combined using the Boolean operator AND: 1) pancreatic adenocarcinoma; 2) genetic alterations, including general genetic terms (e.g., genotype, genetic variation) and specific genes (e.g., *KRAS, P53*); and 3) therapeutics, including chemotherapy, immunotherapy, radiotherapy, and drugs and treatment more generally. All search results were saved to a citation management tool (EndNote), and the Bramer Method was used to remove duplicates[20].

For a complete list of MeSH headers and keywords, refer to the PubMed search strategy accompanying this paper.

Selection of manuscripts

The below outlined criteria were used to include and exclude studies for the systematic review. Two authors (RRS and EOR) independently screened all the abstracts for eligibility

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and then reviewed the full text of relevant manuscripts. The conflicts were resolved by common consensus.

Inclusion criteria:

Studies with

1. PDAC
2. Prospective or retrospective design with GA directed therapy or current therapies with GA implications,
3. Age 18 years and above,
4. Human subjects.
5. Clinical outcomes.

Exclusion criteria:

Studies with

1. Animal subjects,
2. In-vitro (preclinical) design or outcome,
3. Review articles, and
4. Transcriptomic, proteomic or other molecular alterations.

Results

Six thousand and forty abstracts were available for review. After initial screening of the abstracts 220 were found relevant. Full-text review of these studies was performed, and 149 studies were excluded for reasons outlined in Figure 1. Thus, 71 studies were selected for final review.

Somatic mutations

KRAS-targeted therapies:

Thirty-six studies were included that directly or indirectly target the *KRAS* pathway.

Mitogen-activated protein kinase (MEK) inhibitors

Phase 2 studies:

Three phase 2 trials evaluated MEK inhibitors in combination with gemcitabine in locally advanced and/or metastatic PDAC[21–23]. Single-agent MEK inhibitor, selumetinib was compared to capecitabine in metastatic PDAC and failed to show any survival benefit[24]. Subsequently, two phase 2 studies assessed the role of dual inhibition of *KRAS* downstream pathways, selumetinib in combination with erlotinib[25] and selumetinib with MK 2206 (*AKT* inhibitor)[26]. These clinical trials have been summarized in table 1.

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Molecularly targeted therapy based on tumor molecular profiling versus conventional therapy for advanced cancer (SHIVA), a multicenter, open label, phase 2 randomized controlled trial (RCT) for refractory cancers assigned 195 patients with various solid tumors, including 5 with PDAC. There was no significant difference in progression free survival (PFS) or objective responses between the two arms in the overall study[27]. A retrospective analysis of 52 advanced PDAC patients for whom next generation sequencing (NGS) data was available identified 6 patients who received trametinib after experiencing three or more lines of therapy and found a PFS of 1.9 months and median overall survival (mOS) of 5.1 months. However, the main objective of the study, to find a difference in mOS based on presence or absence of *KRAS* or *P53* was not different[28].

Phase 1 studies:

We identified four phase 1 clinical trials that evaluated the safety and efficacy of MEK inhibitors alone[29] or in combination with other modulators of *KRAS* pathway (phosphoinositide 3-kinase or PI3K inhibitor, Extracellular Receptor Kinase or ERK inhibitor, and multi-target kinase inhibitor, sorafenib)[30–32]. The combination of a MEK inhibitor with PI3K inhibitor or ERK inhibitor was not well tolerated with high cumulative toxicity.

Studies targeting other *KRAS* pathways have been summarized in Table 2.

Immune Targeting of KRAS

Four studies were identified that evaluated *KRAS* vaccines in PDAC patients. This included three observational studies that looked at *RAS* peptide vaccines and one studied GI-4000, a tarmogen (targeted molecular immunogen) designed to target cells with mutant *KRAS*[33–36].

In addition, an open label, phase 2 trial assessed the safety and efficacy of adding personalized peptide vaccine to 41 patients with advanced PDAC whose disease had progressed following at least one line of chemotherapy. Median OS was 7.9 months and 26.8% (11/41) were alive at one year. Patients who received concurrent chemotherapy (N=33) fared better than who did not (N=8) with improved mOS (9.6 versus 3.1 months; p=0.0013)[37].

Farnesyl Transferase Inhibition

Tipifarnib, a farnesyl transferase inhibitor and S-trans, trans-farnesyl thiosalicylic acid (FTS, salirasib) that inhibits *Ras*-dependent growth of cells were tested in a large phase 3 trial and a phase 1 dose escalation trial in combination with gemcitabine in advanced PDAC. There was no measurable survival benefit or objective response[38, 39].

Ribonucleic Acid Interference (RNAi)

In a first in-human phase 1/2a study, Golan et al. studied the safety and efficacy of RNAi approach utilizing *siG12D-LODER*^{TM} (Silenseed Ltd.) in patients with locally advanced PDAC. *siG12D-LODER*^{TM} was inserted into the tumor to slowly release anti-*KRASG12D*

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siRNA. Fifteen patients were enrolled, who received standard chemotherapy in conjunction with anti-*KRASG12D* siRNA. Median OS was 15.4 months after a single dose of the investigational drug/device[40]. An ongoing randomized phase 2 study is evaluating gemcitabine and nab-paclitaxel with or without *siG12D-LODER*^{TM}. (NCT01676259)

Polo-like kinase 1 (*PLK1*) and *PI3K* Pathway

Rigosertib, a multi-kinase inhibitor of PLK1 and PI3K, was studied in a multicenter, randomized phase 2 trial in treatment naïve metastatic PDAC in combination with gemcitabine. Majority of the tumors for which adequate sample for mutational analysis was available had mutation in *KRAS* while one had mutation in *PI3KCA*. The results are summarized in table 2[41].

Epidermal growth factor receptor (EGFR) Targeting

Seven studies, four RCT's, two nonrandomized trials and a meta-analysis of RCT's were found that evaluated the role of EGFR inhibition in combination with gemcitabine or other cytotoxic agents in advanced PDAC[42–48]. Although considered to a marker of tyrosine kinase inhibitor (TKI) resistance, *KRAS* status did not affect the outcomes[44]. The development of grade 2 or more rash was associated with improved outcome, as previously observed with TKI therapy[49].

Oncolytic Viruses

Pelareorep, a formulation of human Reovirus serotype 3 strain, which has cytotoxic effects on cancer cells with *RAS* oncogene mutation, was tested in combination with chemotherapy in two phase 2 RCT's. The results are summarized in Table 2[50, 51].

ERK Inhibition

GDC0994, an oral ERK 1/2 inhibitor, was evaluated in two phase 1 trials involving 45 and 23 locally advanced or metastatic solid tumors. There was also demonstration of MAPK pathway inhibition (19 to 51%) in the paired pre- and post-treatment biopsies. GDC0994 showed some promise in advanced PDAC and BRAF-mutated colorectal cancer, although the efficacy data is limited for PDAC due to a small sample size[52, 53]. Combination of GDC0994 and cobimetinib demonstrated cumulative toxicity that were not manageable, discouraging future undertaking of trials on above combination therapy[53].

ErbB family: Epidermal Growth Factor Receptors (EGFR)

NRG1 rearrangement was identified in three of 4 *KRAS* wild-type PDAC in a molecular analysis of 17 PDAC patients. All had metastatic disease and received one or more prior lines of therapy. Two of the three received ERBB targeted therapy, afatinib (pan-ERBB inhibitor) and pertuzumab (monoclonal antibody that prevents interaction between ERBB receptors) while the third received trastuzumab in combination with erlotinib, nab-paclitaxel and 5-fluorouracil. All three patients showed an objective partial response (PR) at 7,8 and 12 weeks, respectively[54].

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ALK Rearrangements

ALK gene translocations have been identified in 0.14 to 0.16% of PDAC[55, 56]. Although rare, they constitute a larger proportion (1.3%) of younger PDAC patients (less than 50 years). Singhi, et al performed comprehensive genomic profiling on 3,170 samples of PDAC patients and discovered *ALK* gene translocation in five (0.16%). Of significant and important note, all these patients were younger (<50 years) and lacked a KRAS gene alteration. Four of the 5 patients were treated with an *ALK*-inhibitor and three demonstrated stable disease (SD), or radiographic or biomarker response[55, 56].

NTRK fusion

Entrectinib, a TRK- and ROS-inhibitor was evaluated in three patients with PDAC (all part of a phase 2, non-randomized trial, NCT02568267), including two with *TPR-NTRK* fusion. All three patients showed clinical improvement with confirmed partial response in both the patients with *TPR-NTRK* fusion[57]. Larotrectinib, a highly selective *TRK*-inhibitor was evaluated in 55 selected *TRK*-fusion positive cancer patients (including one with PDAC). Overall response rate was 75% (13% or 7 patients complete and 62% or 34 patients partial) as determined by an independent review committee. The only patient with PDAC had 30% reduction in tumor size[58].

SMAD4

Seven studies were identified that investigated direct and indirect implications of *SMAD4* expression on treatment of PDAC, however most of these address prediction of disease progression and recurrence patterns in relation to *SMAD4* status. A phase 2 trial evaluated the efficacy and safety of cetuximab first in combination with gemcitabine and oxaliplatin and later with capecitabine and radiation therapy in treatment-naïve locally advanced PDAC. Median OS was 19.1 months and 1-year OS rate was 66% (Primary end-point >45% 1-year OS). *SMAD4* expression was associated with local disease spread compared to metastatic spread in those with *SMAD4* loss (p=0.016)[59].

A retrospective analysis of 471 resected PDAC's demonstrated benefit from adjuvant gemcitabine-based chemotherapy in patients with*SMAD4* loss (HR=0.59; 95% CI 0.42–0.82; p=0.002) compared to those with intact *SMAD4*[60]. In another study, intact *SMAD4* correlated with improved recurrence-free survival in patients receiving erlotinib in combination with adjuvant chemo- or chemoradiotherapy compared with *SMAD4* loss (17.5 versus 11.5 months; p=0.003)[61].

In a retrospective cohort of 641 advanced PDAC patients, *SMAD4/DPC4* expression was associated with higher risk of locoregional recurrence and benefit from intensive local disease control in addition to systemic chemotherapy compared to those with *SMAD4/DPC4* loss (HR=0.25; p=0.002)[62]. However, the above studies did not find survival difference based on SMAD4 status.

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TP53

Three studies were identified that evaluated role of *P53* mutation in treatment outcome. A subgroup analysis of CONKO-001 (multicenter, phase 3 randomized trial to evaluate gemcitabine in patients with PDAC following complete tumor resection)[63] cohort that received gemcitabine and overexpressed *p53* in the tumor cells was compared to those with wild-type *p53* expression, and found to have shorter median disease-free survival and mOS (8.5/18.2 months compared to 12.8/28.8 months; p=0.03)[64]. The above relation between *P53* overexpression and diminished response to gemcitabine was not replicated in a study of 137 patients with advanced PDAC.[53] *MDM2*, a negative regulator of *p53* expression was associated with diminished response to gemcitabine-based regimen (mOS=3.7 versus 5.8 months; p=0.048)[65].

In another analysis of patients from the CONKO-001 trial, NGS was performed on 187 patient-samples of which 97 were analyzable and 57 had a *TP53* mutation which was found to be a positive predictor of benefit from adjuvant gemcitabine with improved disease-free survival (HR=0.22) compared to observation[66].

CDK pathway

There is limited clinical data on manipulation of *CDK* pathway in PDAC. As described below, palbociclib (CDK4/6 inhibitor) was studied in 2 patients with CDK4/6 amplification in the COMPASS trial (a prospective study to establish the feasibility of whole genome sequencing (WGS) to identify predictive genomic and transcriptomic features to guide personalized therapy), however there was no benefit in outcome[67].

Studies Evaluating Other Alterations

In a large, multicenter, non-randomized sample of 640 patients as part of the Know Your Tumor (KYT) initiative, 591 patients with PDAC histology were identified. The most common actionable GA (15%; N=92) were found in DDR genes, *ATM* (N=28), breast related cancer antigen (*BRCA*)*2* (N=18), partner and localizer of BRCA2 (*PALB2*), Fanconi anemia complementation group (*FANCA/C/G*), *RAD50*, and checkpoint kinase 1/2 (*CHEK1/2*). Other actionable alterations were in *ERBB2* (N=17) and isocitrate dehydrogenase (*IDH1*) (N= 3), PI3K/mechanistic target of rapamycin (mTOR)/AKT pathway was present in 19% of patients. Eighteen of 81 patients with wild-type *KRAS* had alterations in other elements of the MAPK pathway including 14 *BRAF* mutations. One hundred and twenty-six patients started treatment based on the KYT report, including off-label molecular targeted therapy (N=20) and clinical trial (N=26) enrollment. Patients who received matched therapy for actionable GA achieved an improved PFS (*HR*=0.47; p=0.03) and mOS (1.5 years versus 0.9 years) compared to those who did not[68].

Early results of the COMPASS trial indicate feasibility of prospective genomic sequencing in PDAC. Sixty-two (98%) of 63 included patients had successful WGS with a median reporting time of 35 days. Eighteen (33%) of the advanced PDAC patients had actionable GA's. All patients received standard chemotherapy as first line therapy and 50 progressed. Five of the 50 (10%) received second line therapy based on the trial results, one with a

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KRAS mutation achieved disease stability with dual blockade of *RAS* pathway while four others, two with *CDK4/6* amplification treated with palbociclib, one with high neoantigen load treated with programmed death ligand 1 (PD-L1) inhibitor and one with polyploid genome treated with PLK4 inhibitor did not experience any benefit[67].

Egeli, et al. attempted to find an association of *KRAS* and *EGFR* mutational status and the micro-RNA (miRNA) related to these GA's with potential effect on resistance to radiotherapy. Of the six miRNAs evaluated, miR-216b and miR-217 were downregulated in tumor tissues compared to normal tissues. Fifteen patients without *KRAS* and *EGFR* mutation or induced expression did not benefit from gemcitabine or radiotherapy, including 12 patients with downregulated miR-216b expression who had reduced median survival[69].

Lowery, et al. assessed feasibility of comprehensive genetic analysis within a clinically relevant timeframe and its clinical applicability in 338 tumor samples (N=336 patients) using Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT)[70]. Median turn-around time after tissue acquisition was 20 days. Actionability scale of 1–4 was used to classify GA, where 1–2a implied standard therapeutic and 2b-4 investigational therapies including clinical trials. Using this classification 222 (68% patients) had alterations that could be or potentially be targeted (2b-4). Two of the three patients who received molecular targeted therapy had ERBB2 mutations and received trastuzumab (no response in one and details unknown in second) and one with KRAS mutation received combination of PI3K and MEK inhibitor (no response)[71].

An ongoing phase 1 trial is evaluating the role of dinaciclib in combination with an AKT inhibitor MK2206 in inoperable PDAC. (NCT01783171) Molecular Analysis for Therapy Choice (MATCH), a phase 2 trial is evaluating the benefit of genetically targeted therapy in solid tumors (including PDAC) and lymphomas that have progressed on at least one standard treatment. (NCT02465060) The study aims to evaluate different genomic targets and designed to have 30 sub-protocols to include various targets, *EGFR, HER2, RAS, BRCA, mTOR, AKT, ALK, ROS, PIK3CA, MLH/MSH, BRAF, PTEN, CDK*, and more.

Germline Mutation and Targeted Therapies

DNA Damage Repair (DDR) Genes

Twenty-two studies were identified that looked at the association between various DDR gene (*BRCA2/1, ATM, PALB2, CHEK 1/2, ATR*) mutations and therapy, particularly platinum agents and PARPi. While most of the studies are observational or retrospective, six prospective clinical trials with *BRCA* or *PALB2* mutations were identified including two phase 1 and four phase 2, as depicted in Table 3.

A multicenter, randomized, phase 2 trial is evaluating the role of adding PARPi, veliparib to the combination of cisplatin and gemcitabine in *BRCA1/2*- or *PALB2*-mutated PDAC. As part of the above trial, a nonrandomized single arm evaluated the role of single-agent veliparib in 16 previously treated, stage III/IV PDAC patients (who had received median of 2 lines of therapy) with *BRCA1* (N=5) or *BRCA2* (N=11) mutation. One patient had unconfirmed PR, four (25%) had SD while the rest 11 (69%) had progression. Notably, 14

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patients (88%) were previously exposed to platinum agents and likely explained the poor response to the PARPi[10].

Two studies identified eight and four patients with *ATM*-mutated PDAC and suggested significantly improved survival with oxaliplatin-based therapy[2, 72]. A study from Japan assessed the outcome of *BRCA*ness (*BRCA2* N= 6, *ATM* N=4, *ATR* N=2, *BRCA1* N=2, *PALB2* N=1) in 17 PDAC patients who received oxaliplatin-based therapy. *BRCA*ness was defined as defects in individual genes involved in HRR. Median time to treatment failure was 294 days and 52 days in *BRCA*ness group and non-*BRCA*ness group, respectively (p=0.027). The result is limited by small sample size[72]. The same group subsequently showed improved survival with oxaliplatin-based therapy in HRR gene mutated patients (median PFS 20.8 months versus 1.7 months; p=0.49) compared to those without HRR gene mutations. The HRR related gene mutations comprised of *BRCA2* (N=10), *ATM* (N=8), *BRCA1* (N=2), *CHEK2* (N=2), *ATR* (N=1), and *PALB2* (N=1)[2].

Several groups have retrospectively analyzed available genomic data in PDAC patients with *BRCA1/2* and other DDR gene (*ATM, PALB2, CHEK, ATR*) mutations and demonstrated encouraging results with platinum-based therapy. Despite the retrospective design and small sample size in majority of the studies, collectively they represent data from more than 200 patients and demonstrate the role of platinum agents in the treatment of PDAC with mutation in DNA damage repair (DDR) genes[2, 72–80].

Somatic Mutations in DDR Genes

While most of the studies on DDR genes have assessed vulnerability of the tumor based on germline mutational status, a few have looked at somatic alterations as well. Shroff, et al in a single-arm, open label, phase 2 trial examined the effect of somatic or germline mutation in *BRCA* gene on response to rucaparib in advanced PDAC who had previously received one or two lines of therapy. Disease control rate (PR or SD at 12 weeks) was 32% (6/19) including 50% (3/6) in those who received only one prior therapy[81].

Sehdev, et al[75] assessed the effect of somatic or germline DDR gene mutations in *BRCA1* (N=7), *BRCA2* (N=5), *PALB2* (N=3), *MSH2* (N=1) and *FANCF* (N=1) on response to FOLFIRINOX therapy in metastatic PDAC. There is no data available to interpret results on somatic gene mutations separately. OS was improved in those with mutations in DDR genes (N=12) compared to those without mutations (N=24) (14 versus 5 months), which did not reach statistical significance (HR 0.58; p=0.08). However, multivariate logistic and Cox regression analysis determined significantly improved mOS in those with DDR gene mutations (OR=1.47; p=0.04 and HR=0.37; p=0.04).

Lowery et al. analyzed 336 PDAC patients who underwent somatic profiling at MSK for matched systemic therapy. Although a very small number of patients received matched therapy, a sizable number (N=50) had a somatic mutation in one or more DDR genes[71] Another prospective analysis of genetic data identified 15 *BRCA*-mutated patients. Median OS was 27.6 months in all the patients. All the 3 patients who received a PARPi and 5 of the

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6 who received platinum-based chemotherapy as first line therapy for metastatic disease had at least PR by RECIST (Response Evaluation Criteria in Solid Tumors)[82].

In a prospective observational study of deep WGS in 100 PDAC's Waddell, et al found deleterious *BRCA* signature gene mutations in 11 patients (*BRCA1* N=2, *BRCA2* N=7, and *PALB2* N=2), 5 having a somatic *BRCA* mutation (*BRCA1* N=2, *BRCA2* N=3). Eight patients received platinum-based therapy including 5 with a deleterious *BRCA* mutation. Three of the 5 had a somatic *BRCA2* mutation, two experienced exceptional response and two PR while one with somatic *BRCA1* mutation had no response[73]. Loss of heterozygosity (LOH) or loss of the second allele may explain the differential response to platinum agents and PARPi in this population of PDAC with DDR gene mutations[83].

Deficient Mismatch Repair (MMR-d) and Microsatellite Instability (MSI)

Three studies with immunotherapy directed at MMR-d PDAC were found. In an analysis of 833 PDAC patients with available NGS at MSK, 7 with MMR-d were identified and all had Lynch syndrome with an underlying germline mutation. Five of the 7 patients received immunotherapy with a programmed death (PD)-1 inhibitor (N=3) or a PD-L1 inhibitor (N=2) and either had SD (N=1) or durable response (N=3)[84]. In a phase 2 study to evaluate the clinical activity of pembrolizumab in MMR-d tumors, Dung et al. demonstrated the benefit of single-agent PD-1 inhibitor in 2 MSI-high PDAC patients[85]. A retrospective review of gastrointestinal cancer patients (N=9) who received pembrolizumab (PD-1 inhibitor) for MMR-d included 2 patients with PDAC. Response data was available for one of the two patients and showed 56.7% response from baseline per RECIST criteria with time to progression >5 months[86].

Discussion

Lessons learned from failure of anti-cancer drugs across multiple malignancies at different stages of development suggest that a biomarker-driven strategy in drug selection can improve outcomes. A systematic review to evaluate reasons for experimental drug failure showed that 57% (21/37) of successful drug-programs adopted a biomarker-driven rationale compared to 16% (7/43) of failed drug-programs[87]. Similar results have been shown in phase 2 and phase 3 trials. The extrapolation of biomarker-based drug selection remains unproven in PDAC, nevertheless it is a potential strategy[88, 89].

Our qualitative analysis of the literature identifies several genomic targets that have been explored in the treatment of PDAC. While DDR gene mutations and MMR-d have demonstrated greatest potential for actionability several other targets, notably common somatic mutations await further attestation in large prospective studies to provide unambiguous answers to personalizing therapy in PDAC. The most interesting data regarding GA driven therapy relate to platinum-based therapy and PARPi in patients with germline mutations in DDR- or HHR-genes, and immune checkpoint inhibitors in patients with MMR-d genes.

Pathogenic germline mutations in *BRCA1/2* and related genes are found in 4.6 to 8% of PDAC in different series[90–92]. While germline alterations in DNA double-stranded break-

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repair and HRR predispose to tumorigenesis, they also provide vulnerable targets for agents like platinum which induce double-strand breaks and PARPi which block single-strand break repair subsequently leading to double-strand breaks. This concept has been tested in retrospective analyses and prospective trials, further replication of the results is awaited from ongoing clinical trials[13]. Single-agent olaparib is being evaluated in a phase 3 RCT (POLO) for maintenance therapy in germline *BRCA* mutated metastatic PDAC whose disease has not progressed on first line platinum-based therapy. (NCT02184195) Meanwhile, a phase 2 clinical trial is evaluating veliparib combined with platinum-based therapy in patients with *BRCA1/2* or *PALB2* mutation. (NCT01585805)

There is a paucity of data on somatic alterations in *BRCA1/2* and related genes in PDAC. This has been investigated more recently with identification of somatic mutations at varying rates in pancreatic cancer specimen across different studies, ranging from as low as about 4% in an earlier study by Chantrill, et al[93] to over 35% in a sample of 109 micro-dissected pancreatic cancer cases which identified multiple Fanconi anemia genes, *ATM, CHEK2, BCLAF1, BRCA1, BRCA2*[94]. The benefit of treatment with platinum agents in these tumors has been comparable to those with germline DDR gene mutations in small retrospective and prospective series[73, 75].

It has been appreciated that tumors with MMR-d have enhanced expression of mutation-associated neoantigens and strong expression of immune check-point ligands. Correspondingly, they have 10–100 times higher number of somatic mutations compared to those with proficient MMR genes[85]. This concept has been successfully manipulated in tumors like melanoma, renal cell cancers and lung cancers[85, 95, 96]. Although MMR-d is detected in a very small number (approximately 1%) of PDAC the benefit from PD-1 and PD-L1 has been shown to prolong survival in this population (OS=30–214 months)[84–86].

Mutations affecting the *KRAS* gene although the most common somatic gene alteration has yet to be effectively targeted. Recent discovery of *KRAS-G12C* inhibitors have potential, however *G12D* and *G12V* account for about 80% of PDAC *KRAS* mutations and G12C mutations are rare.[97, 98] Attempts to target the downstream *KRAS* pathways through MEK inhibitors have largely been disappointing. This is attributed to the adaptive reactivation of MAPK signaling and multiple pathway redundancy[99]. *SHP2* or *PTPN11* are mediators of the adaptive MAPK response to MEK inhibitor treatment, and consequent discovery of *SHP2* inhibitors reopens interest in this target[100]. Dual targeting of this pathway with a MEK inhibitor and EGFR inhibitor or dual inhibition of the EGFR pathway has shown some positive results[44, 45]. Furthermore, solely targeting other *KRAS* pathway molecules like PI3K or mTOR have been unsuccessful. A translational study investigated the bypass mechanisms in *KRAS*-mutant colorectal cancer and revealed enhancement of other pathways like EGFR, ERBB2 and ERBB3 accounting for resistance to the targeted therapy. This observation suggests potential role of combining multiple pathways to overcome the resistance barrier[101]. On the other hand, tumors with a wild-type *KRAS* gene are found to have enrichment of kinases, like Neuregulin 1 (*NRG1*) rearrangement, anaplastic lymphoma kinase (*ALK*) rearrangement, *ROS* and *NTRK* fusions. These are attractive targets in this subset of patients with wild-type *KRAS* gene.

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Cell cycle checkpoints and the corresponding CDK's are vulnerable sites for oncogenesis. Preclinical xenograft and in-vitro studies have shown growth inhibition by targeting multi-CDK inhibitors. Two ongoing phase 1 trials (NCT02501902, NCT02897375) are evaluating palbociclib in combination with chemotherapy (nab-paclitaxel or cisplatin/carboplatin). Ribociclib, another CDK inhibitor, is being evaluated in phase 1/2 trials (NCT02985125, NCT02703571) in previously treated PDAC in combination with other targets, everolimus and trametinib, respectively.

Although there have been glimpses of success with some of the paths employed to target the *KRAS* pathway, there is little correlation between the somatic gene (*KRAS, SMAD4, P53, CDKN2A*) mutational status and efficacy of these tested therapies. These outcomes speak to the complex inter-relationship between drivers of oncogenesis, pathway redundancy, factors known and unknown, and activation of bypass tracks.

Severe clinical trials are on way to provide more consolidated evidence to guide individualized approach to treating PDAC. These studies have been summarized in Table 4.

Ongoing endeavors to personalize therapy in PDAC has elucidated several potentially actionable somatic GA (e.g. *KRAS*-wild type, *ALK* rearrangement, MMR-d, DDR)[54, 56, 71] most of which individually account for a small fraction of PDAC population, although for individual patients there are significant implications. Detection of these sporadic GA is only feasible through widespread application of somatic and germline genetic testing in PDAC patients. Until recently, genetic testing was limited to patients with family history of hereditary breast or ovarian cancer-related cancers, or Ashkenazi Jewish ancestry. Over the last few years germline and somatic testing has been integrated at many large dedicated cancer centers and the current National Comprehensive Cancer Network (NCCN) guideline has boosted those efforts. The updated NCCN guidelines recommend consideration of routine testing for somatic and germline mutations in all individuals with a diagnosis of PDAC[102].

Conclusion

Evidence from translational and clinical research presents an exciting platform for genomic targeted therapy in PDAC. Current literature supports the use of platinum-based therapy in patients with germline mutations in *BRCA*-mutated PDAC and to consider PARPi therapy. Evidence is mounting that all patients with advanced PDAC should undergo both germline and somatic profiling and that there is a significant minority of patients who will benefit from a targeted therapeutic strategy. For many GA identified in PDAC beyond BRCA and MSI, it remains to be seen what the impact from targeted therapy will be. Other approaches that will yield therapeutic refinements include pathologic and transcriptomic profiling where increasing data suggests that there are several subtypes of PDAC, a classical and basal type. The latter demonstrating increased treatment resistance compared to the former. Ongoing work will help utilize this information in real-time to optimize treatment decision making. [14, 67]

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Supplementary Material

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Highlights

- Genomic alterations in PDAC, both germline and somatic, represent potential targeting opportunities to individualize and tailor therapy.
- Attempts to target key somatic driver mutations in PDAC (*KRAS, p53, SMAD4, CDKN2A*) have yielded no impact on outcome.
- DNA-damage repair gene mutations confer vulnerability to platinum agents and PARP-inhibitors and early promise has been identified in PDAC.
- Microsatellite unstable PDAC, approximately 1% of all PDAC's, can benefit from checkpoint point inhibitor therapy.
- Identification of the *KRAS* wild-type subset of PDAC (about 5%) is important in view of the enrichment for actionable targets, including, *ALK, ROS, NTRK, NRG*-1 fusions and others.
- Universal genetic profiling is recommended for patients with advanced PDAC.

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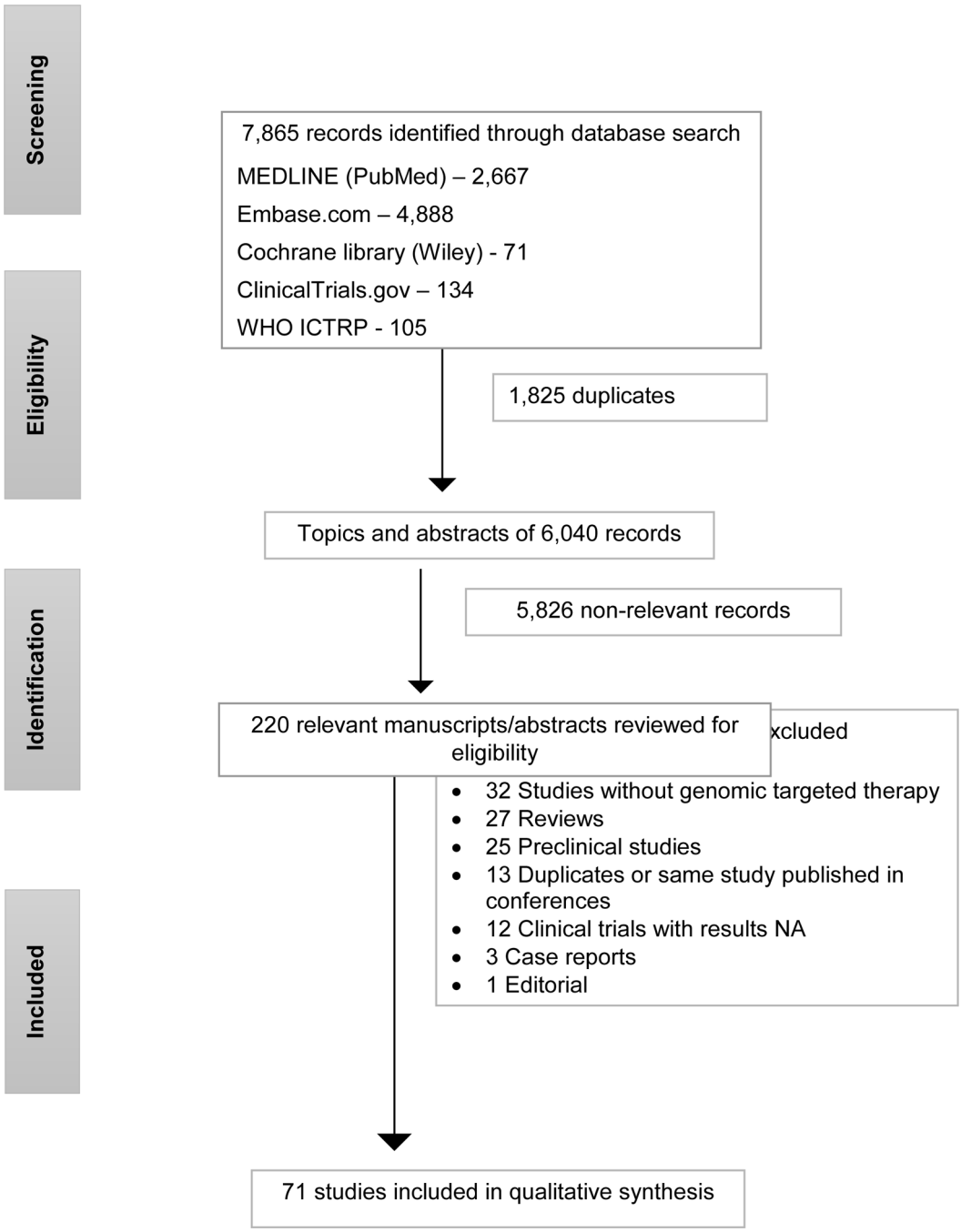

Figure 1.
Flow diagram of literature search and selection of relevant studies

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Table 1.

Trials on MEK 1/2 Inhibitors

Author, Year	Drug tested	Study design	Population	N	Outcome
Phase 1 trials					
Adjei, et al 2011 [26]	Refametinib + sorafenib	Dose escalation	HCC/non-HCC	62 (4 PDAC)	MTD; DCR[†]=65.8 %
Infante, et al 2012[25]	Trametinib	Dose escalation	Advanced cancer	206 (26 PDAC)	MTD, RP2D; DCR=50%
Bedard, et al 2015[27]	Trametinib + buparlisib	Dose escalation	*RAS-/BRAF*-mutant advanced cancer	113 (24 PDAC)	MTD, RP2D; PFS=2 mo; mOS=5 mo
Weekes, et al 2017[28]	Cobimetinib + GDC-0994	Dose escalation	Advanced cancer with limited options	23 (7 PDAC)	MTD; BOR (SD+PR) = 55%
Phase 2 trials					
Infante, et al 2014[17]	Trametinib + Gem	Placebo controlled multicenter RCT	Untreated metastatic PDAC	160	mOS=8.4 Vs 6.7 mo; p= 0.453
Bodoky, et al 2011[20]	Selumetinib Vs Capecitabine	Multicenter RCT	Metastatic PDAC	70	mOS=5.4 Vs 5.0 mo; p= 0.92
Van Cutsem, et al 2018[18]	Pimasertib + Gem	Double blind multicenter RCT	Metastatic PDAC	88	PFS 3.7 Vs 2.8 mo; p= 0.68
Van Laethem, et al 2016[19]	Refametinib + Gem	Single arm non-randomized trial	Advanced PDAC	60	ORR 23%
Ko, et al 2016[21]	Selumetinib + Erlotinib	Single arm non-randomized study	Inoperable PDAC	46	24-week OS[¶]=58%
Chung, et al 2017[22]	Selumetinib + MK-2206	Open-label RCT	Metastatic PDAC (Failed Gem)	137	OS: 3.9 Vs 6.7 mo; HR 1.37, p=0.15

[†]Secondary outcome;

[¶]24-week OS rate of at least 43.5% was a pre-specified indicator of “Positive response”.

HCC hepatocellular carcinoma; RCT randomized controlled trial; MTD maximum tolerated dose; DCR disease control rate; RP2D recommended phase 2 dose; PFS progression free survival; mo month; mOS median overall survival; Vs versus; BOR Best overall response; SD stable disease; PR partial response; Gem gemcitabine; ORR objective response rate; HR hazard ratio.

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Table 2.

Studies Targeting other *KRAS* Pathways

Author, Year	Drug tested	Control	Study design	Population	N	Outcome
			Studies targeting EGFR			
Wang, et al 2015[44]	Erlotinib + Gem	Gem	Single center, RCT	Metastatic CT naïve PDAC	88	DCR=64 Vs 25%; p<0.001;mOS7.2 Vs 4.4mo; p<0.001[§]
Philip, et al 2010[43]	Cetuximab + Gem	Gem	Phase 3 RCT	LA/metastatic PDAC	745	mOS 6.3 Vs 5.9 mo; p=0.23[§]
Kim, et al 2011[41]	Panitumumab + erlotinib + Gem	Erlotinib + Gem	Phase 2 RCT	Metastatic CT naive PDAC	92	mOS 8.4 Vs 4.4 mo; p=0.077
Chiramel, et al 2017[39]	Multiple EGFR inhibitors + CT	Standard CT	Metanalysis of RCT's (28 studies)	LA/metastatic PDAC	3718	mOS (p=0.18); PFS (p=0.15)
Assenat, et al 2015[38]	Trastuzumab + erlotinib + Gem	NA	Phase 2, open label nonrandomized	Metastatic PDAC	62	DCR 74.6%
Fontzilas, et al 2009[40]	Gefitinib + Gem	Gem	Single arm, phase 2, nonrandomized	Advanced PDAC	53	mOS 4.1 mo; PFS 7.3 mo; 1-year survival 27%
			Studies on immunologically targeting *KRAS*			
Weden, et al 2010[32]	KRAS peptide vaccine	NA	Phase 2 nonrandomized	Resected PDAC	23	5-year survival 29 Vs 22%; 10-year survival 20 Vs 0%[//]
Dueland, et al 2017[29]	TG01/GM-CSF	NA	Nonrandomized	Resected *RAS*-mutant PDAC	19	mOS 33.1 mo; DFS 13.9 mo.
Erickson, et al 2017[30]	TG01/GM-CSF	NA	Observational	Treatment naive unresectable PDAC	25	mOS5.1 (DLT)Vs 3.6 mo (no DLT); DLT 14/25
Richards, et al 2012[31]	GI-4000	Gem	Randomized, placebo-controlled	Resected RAS-mutant PDAC	176	RFS 41 Vs 36 wk; mOS 75 Vs 63 wk
			Farnesyl transferase inhibition			
Laheru, et al 2012[34]	Salirasib (FTS) + Gem	NA	Phase 1, dose escalation	CT naive LA/metastatic PDAC	19	mOS 6.2 mo; PFS 3.9 mo; No objective response
Van Custom, et al 2004[35]	Tipifarnib + Gem	Gem + placebo	Phase 3	CT naïve advanced PDAC	688	mOS 193 (Tipifarnib) Vs 182 (placebo); p=0.75
			RNA interference (RNAi)			

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Author, Year	Drug tested	Control	Study design	Population	N	Outcome
Golan, et al 2015[36]	RNAi	NA	Phase 1/2a	LA PDAC	15	mOS 15.4 mo; 18-mo survival 38.5%
			Polo-like kinase 1 *(PLK1)* and phosphoinositide 3-kinase *(PI3K)* inhibitor			
O'Neil, et al 2015[37]	Rigosertib + Gem	Gem	Multicenter, phase 2/3 RCT	Metastatic CT naïve PDAC	160	mOS6.1 Vs6.4 mo; CI 0.85–1.81
			ERBB inhibitor			
Heining, et al 2018[50]	Afatinib, pertuzumab, trastuzumab	NA	Retrospective analysis	*KRAS* § PDAC	17 (4/17 *KRAS*-WT)	Objective partial response (3/3) with POD
			ALK inhibitors			
Singhi, et al 2017[51]	Crizotinib, ceritinib	NA	Nonrandomize d (case-series)	PDAC	5	SD=3/4
			Oncolytic virus			
Noonan, et al 2016[47]	Pelareorep + paclitaxel/carbo platin	Paclitaxel + carboplatin	Phase 2 RCT	Metastatic PDAC	73	mOS 6.1 Vs 6.3 mo; p=0.6
Mahalingam, et al 2018[46]	Pelareorep + Gem	NA	Single-arm, Phase 2, non-randomized	CT naive advanced PDAC	34	mOS 10.2 mo; SD=23/34
			ERK inhibitor			
Weekes, et al 2017[49]	Cobimetinib	NA	Phase 1b, dose escalation	Advanced solid tumors	23	55% (6/11) SD $^{\neq}$

§ *KRAS* status did not affect response;

$^{//}$ compared to nonvaccinated cohort;

$^{\neq}$ high cumulative toxicity.

Gem gemcitabine; RCT randomized controlled trial; CT chemotherapy; DCR disease control rate; Vs versus; mo month; mOS median overall survival; LA locally advanced; EGFR epidermal growth factor receptor; PFS progression free survival; NA not applicable; TG01 mixture of synthetic RAS peptides; GM-CSF granulocyte monocyte-colony stimulating factor; DFS disease-free survival; DLT delayed-type hypersensitivity; GI-4000 tarmogen (targeted molecular immunogen); RFS recurrence free survival; wk week; FTS S-trans, trans-farnesylthiosalicylic acid; WT wild-type; POD progression of disease; SD stable disease.

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Table 3.

Studies Targeting *BRCA/PALB2* Mutations

Author, Year	Drug tested	Study design	Population	N	Outcomes (Primary/secondary)
O'Reilly, et al. 2018[11]	Veliparib + Gem/Cis	Phase 1, dose escalation	Untreated *BRCA/PALB2* mutated PDAC or strong FH	17	DLT, RP2D; mOS 23.3 Vs 11 mo *(BRCA+* Vs *BRCA-)*
Kauffman, et al. 2015[99]	Olaparib	Nonrandomized phase 2	≥2 prior therapies, *BRCA* mutated	23 PC[¶]	5/23 (21%) CR+PR; mOS 9.8 mo; PFS 4.6 mo; 8/23 SD
Yarchoan, et al. 2017[12]	Olaparib + Cis/mitomycin/Irinotecan	Phase 1, dose escalation	Unresectable PDAC	18	MTD; Grade ≥3 AE=89%
Domcheck, et al. 2014[9]	Rucaparib	Open label, phase 2 RCT	*BRCA* mutated LA/metastatic PDAC (≥1 prior treatment)	19[†]	ORR3/19(16%); DCR6/19(31.6%)
Lowery, et al. 2018[10]	Veliparib	Single-arm phase 2 nonrandomized	*BRCA/PALB2* mutated previously treated PDAC	16	RECIST 1.1; PFS1.7 mo.; mOS 3.1 mo.%
Aung, et al 2016[100]	Platinum-based CT	Prospective database	*BRCA* mutated PDAC	57	mOS 15.3 (platinum) Vs 8.3 mo (other CT)
Golan, et al 2017[72]	Platinum-based CT	Retrospective analysis	*BRCA* mutated stage 3/4 PDAC	71	mOS 22 (platinum) Vs 9 mo. (other CT), p=0.039

[¶]17 BRCA2, 5 BRCA1, 1 both BRCA2/BRCA1;

[§]stable disease on platinum agent;

[†]enrollment pre-terminated after an insufficient response rate as prespecified in the trial protocol.

FH family history; DLT dose limited toxicity; RP2D recommended phase 2 dose; mOS median overall survival; mo month; CR complete response; PR partial response; SD stable disease; MTD maximum tolerated dose; AE adverse event; RCT randomized controlled trial; ORR overall response rate; DCR disease control rate; RECIST Response Evaluation Criteria In Solid Tumors; CT chemotherapy; PFS progression free survival; g*BRCA* germline *BRCA*; NA not available

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Table 4.

Ongoing Clinical Trials

Clinical trial	Drug tested	Control	Study design	Population	N ¶	Primary outcome
Agents targeting DNA damage repair (DDR) - PARP inhibitors						
NCT02184195	Olaparib (maintenance)	Placebo	Phase 3, double blind RCT	*gBRCA* mutant metastatic PDAC	154	PFS
NCT01585805	Gem/cis + Veliparib	Gem/Cis	Phase 2 RCT	*BRCA/PALB2* mutant PDAC	107	Response rate by RECIST
NCT02890355	mFOLFIRI + Veliparib	mFOLFIRI	Phase 2 RCT	Metastatic PDAC	143	mOS
NCT01489865	Veliparib + mFOLFOX	NA	Phase 1/2	Metastatic PDAC	79	DLT
NCT03553004	Niraparib	NA	Phase 2, single arm	Previously treated metastatic PDAC	18	ORR (PR+SD)
NCT03337087	Rucaparib + Nal-IRI + FU + leucovorin	NA	Phase 1/1 b, open label	Metastatic GI cancers §	110	DLT, ORR
CDK inhibitors						
NCT02501902	Pablociclib + nab-P	NA	Phase 1, dose escalation trial	Metastatic PDAC	77	DLT
NCT02897375	Palbociclib + Cis or Carboplatin	NA	Phase 1, dose escalation	Advanced solid tumors	90	RP2D, DLT
NCT02703571	Ribociclib + Trametinib	NA	Phase 1/2, nonrandomized	Advanced PDAC/CRC	150	ORR, DLT
NCT02985125	Ribociclib + everolimus	NA	Phase 1/2, nonrandomized	Metastatic CT resistant PDAC	44	PFS at 8 weeks
MEK inhibitor						
NCT03637491	talazoparib + Binimetinib + avelumab	Binimetinib + avelumab	Phase 1b/2 open label, RCT	LA/metastatic RAS mutant solid tumors //	127	DLT, ORR (CR+PR)
P53 targeting						
NCT02340117	SGT53 + Gem/nab-P	NA	Phase 2, single arm	Metastatic PDAC	28	PFS at 5.5 month
Other targets/Immunotherapy						
NCT01676259	Gem/nab-P ± siG12D-L0DER	Gem/nab-P	Phase 2 RCT	LA PC	80	PFS
NCT02243371	GVAX + CY + nivolumab Vs GVAX + CY	GVAX + CY + CRS-207	Phase 2 RCT	Previously treated metastatic PDAC	96	mOS
NCT01896869	Ipilimumab + GVAX	NA	Phase 2 RCT	Metastatic PDAC	83	mOS
NCT02383433	Regorafenib + Gem	NA	Phase 2, single group	Previously treated metastatic PDAC	2	PFS
NCT01652976	Dasatinib + FOLFOX	NA	Phase 2, single group	Metastatic PDAC	58	PFS
NCT02699749	TAK-931 †	NA	Phase 1, dose escalation	Advanced solid tumors	100	DLT

¶ Estimated sample size;

§ Pancreatic, colorectal, gastroesophageal and biliary tract cancers;

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[//](PDAC, NSCLC, other RAS mutant solid tumors;

[†]CDC7 (cell division cycle 7-related protein kinase).

RCT randomized controlled trial; gBRCA germline BRCA; PFS progression free survival; RECIST Response Evaluation Criteria in Solid Tumors; mFOLFIRI modified regimen containing Folic acid, Fluorouracil, Irinotecan; mOS median overall survival; mFOLFOX modified regimen containing Folic acid, Fluorouracil, Oxaliplatin; CRS-207 live attenuated Listeria monocytogenes strain; FOLFIRINOX Folic acid, Fluorouracil, Irinotecan, Oxaliplatin; NA not applicable; DLT dose limited toxicity; ORR objective response rate; CR complete response; PR partial response; NaI-IRI liposomal irinotecan; FU fluorouracil; GI gastrointestinal; nab-P nanoparticle albumin&-bound paclitaxel; SGT53 Study of Combined Targeted p53 Gene Therapy; RP2D recommended phase 2 dose; LA locally advanced.

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