

Systematic or Meta-analysis Studies

Genomic profiling in pancreatic ductal adenocarcinoma and a pathway towards therapy individualization: A scoping review



Ritu R. Singh^a, Johanna Goldberg^b, Anna M. Varghese^{c,d,e}, Kenneth H. Yu^{c,d,e}, Wungki Park^{c,d,e}, Eileen M. O'Reilly^{c,d,e,*}

^a Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai St. Luke's and Mount Sinai West, New York, NY 10019, USA

^b MSK Library, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

^c Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

^d Weill Cornell Department of Medicine, Weill Cornell Medicine, New York, NY 10065, USA

^e David M. Rubenstein Center for Pancreatic Research, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

ARTICLE INFO

Keywords:

Pancreatic ductal adenocarcinoma (PDAC)
Genomic alteration (GA)
DNA damage repair
Somatic mutation
Germline mutation
Mismatch repair (MMR)
Microsatellite instability

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. 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.

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

* Corresponding author at: Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA.

E-mail addresses: ritu.singh@mountsinai.org (R.R. Singh), goldbejb@mskcc.org (J. Goldberg), oreillye@mskcc.org (E.M. O'Reilly).

<https://doi.org/10.1016/j.ctrv.2019.03.003>

Received 5 March 2019; Received in revised form 20 March 2019; Accepted 21 March 2019

0305-7372/ © 2019 Elsevier Ltd. All rights reserved.

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 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 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 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 Fig. 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.

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*

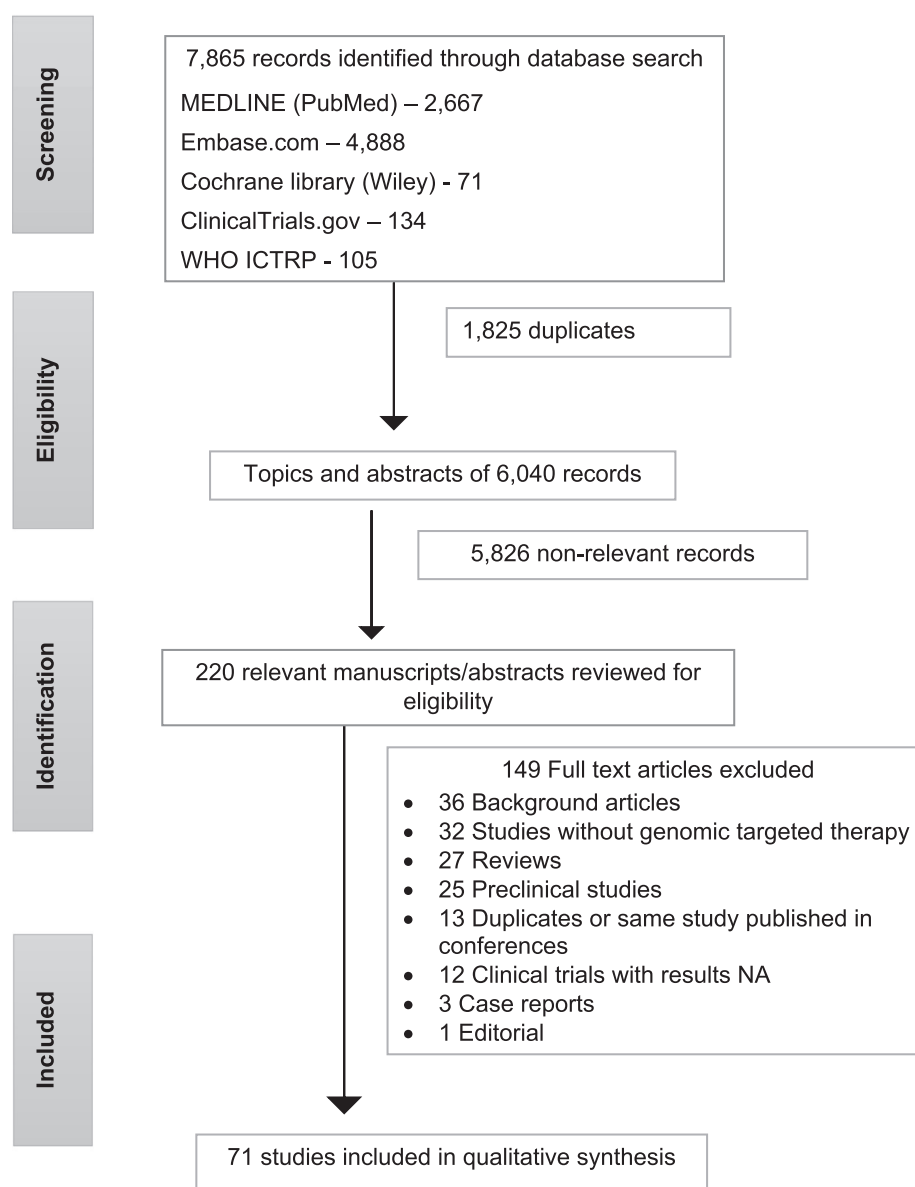


Fig. 1. Flow diagram of literature search and selection of relevant studies.

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* 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].

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

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.

[†] Secondary outcome.

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

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].

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].

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%; $p < 0.001$; mOS 7.2 Vs 4.4 mo; $p < 0.001$ [§]
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 naïve 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%
Fontillas 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 <i>KRAS</i>						
Weden et al. 2010 [32]	Studies on immunologically targeting <i>KRAS</i> KRAS peptide vaccine	NA	Phase 2 non-randomized	Resected PDAC	23	5-year survival 29 Vs 22%; 10-year survival 20 Vs 0%
Dueland et al. 2017 [29]	TG01/GM-CSF	NA	Non-randomized	Resected RAS-mutant PDAC	19	mOS 33.1 mo; DFS 13.9 mo.
Erickson et al. 2017 [30]	TG01/GM-CSF	NA	Observational	Treatment naïve unresectable PDAC	25	mOS 5.1 (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 naïve LA/metastatic PDAC	19	mOS 6.2 mo; PFS 3.9 mo; No objective response
Van Custon et al. 2004 [35]	Tipifarnib + Gem	Gem + placebo	Phase 3	CT naïve advanced PDAC	688	mOS 193 (Tipifarnib) Vs 182 (placebo); $p = 0.75$
Golan et al. 2015 [36]	RNA interference (RNAi) RNAi	NA	Phase 1/2a	LA PDAC	15	mOS 15.4 mo; 18-mo survival 38.5%
Polo-like kinase 1 (<i>PLK1</i>) and phosphoinositide 3-kinase (<i>PI3K</i>) inhibitor						
O'Neil et al. 2015 [37]	Rigosertib + Gem	Gem	Multicenter, phase 2/3 RCT	Metastatic CT naïve PDAC	160	mOS 6.1 Vs 6.4 mo; CI 0.85–1.81
Heining et al. 2018 [50]	ERBB inhibitor Afatinib, pertuzumab, trastuzumab	NA	Retrospective analysis	KRAS-WT PDAC	17 (4/17 KRAS-WT)	Objective partial response (3/3) with POD
Singhi et al. 2017 [51]	ALK inhibitors Crizotinib, ceritinib	NA	Nonrandomized (case-series)	PDAC	5	SD = 3/4
Oncolytic virus						
Noonan et al. 2016 [47]	Pelareorep + paclitaxel/carboplatin	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 naïve advanced PDAC	34	mOS 10.2 mo; SD = 23/34
Weekes et al. 2017 [49]	ERK inhibitor Cobimetinib	NA	Phase 1b, dose escalation	Advanced solid tumors	23	55% (6/11) SD [*]

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.

[§] *KRAS* status did not affect response.

^{||} Compared to nonvaccinated cohort.

^{*} High cumulative toxicity.

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.

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 *BRCA*2 (*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 *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

Table 3
Studies Targeting *BRCA*/*PALB2* Mutations.

Author, Year	Drug tested	Study design	Population	N	Outcomes (Primary/secondary)
O'Reilly et al. 2018 [111]	Velparib + Gem/Cis	Phase 1, dose escalation	Untreated <i>BRCA</i> / <i>PALB2</i> mutated PDAC or strong FH	17	DLT, RP2D; mOS 23.3 Vs 11 mo (<i>BRCA</i> + Vs <i>BRCA</i> -)
Kauffman et al. 2015 [99]	Olaparib	Nonrandomized phase 2	≥ 2 prior therapies, <i>BRCA</i> mutated	23 PC ^a	5/23 (21%) CR + PR; mOS 9.8 mo; PFS 4.6 mo; 8/23 SD
Yardhoan 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	<i>BRCA</i> mutated LA/metastatic PDAC (≥ 1 prior treatment)	19 [†]	ORR 3/19 (16%); DCR 6/19 (31.6%)
Lowery et al. 2018 [10]	Velparib	Single-arm phase 2 nonrandomized	<i>BRCA</i> / <i>PALB2</i> mutated previously treated PDAC	16	RECIST 1.1; PFS 1.7 mo.; mOS 3.1 mo.%
Aung et al. 2016 [100]	Platinum-based CT	Prospective database	<i>BRCA</i> mutated PDAC	57	mOS 15.3 (platinum) Vs 8.3 mo (other CT)
Golan et al. 2017 [72]	Platinum-based CT	Retrospective analysis	<i>BRCA</i> mutated stage 3/4 PDAC	71	mOS 22 (platinum) Vs 9 mo. (other CT), <i>p</i> = 0.039

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; gBRCA germline *BRCA*; NA not available.

^a Stable disease on platinum agent.

[†] 17 *BRCA2*, 5 *BRCA1*, 1 both *BRCA2*/*BRCA1*.

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

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 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 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-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.

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

Table 4
Ongoing Clinical Trials.

Clinical trial	Drug tested	Control	Study design	Population	N [†]	Primary outcome
NCT02184195	Agents targeting DNA damage repair (DDR) – PARP inhibitors Olaparib (maintenance)	Placebo	Phase 3, double blind RCT	<i>gBRCA</i> mutant metastatic PDAC	154	PFS
NCT01585805	Gem/cis + Veliparib	Gem/Cis	Phase 2 RCT	<i>BRCA/PALB2</i> 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 + NaI-IRI + FU + leucovorin CDK inhibitors	NA	Phase 1/1b, open label	Metastatic GI cancers [§]	110	DLT, ORR
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
NCT03637491	MEK inhibitor talazoparib + Binimetinib + avelumab	Binimetinib + avelumab	Phase 1b/2 open label, RCT	LA/metastatic RAS mutant solid tumors	127	DLT, ORR (CR + PR)
NCT02340117	<i>P53</i> targeting SGT53 + Gem/nab-P	NA	Phase 2, single arm	Metastatic PDAC	28	PFS at 5.5 month
NCT01676259	Other targets/Immunotherapy Gem/nab-P ± siG12D-LODER	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

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.

§ Pancreatic, colorectal, gastroesophageal and biliary tract cancers.

[†] Estimated sample size.

^{||} (PDAC, NSCLC, other RAS mutant solid tumors).

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

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].

Funding support

Cancer Center Support Grant P30 -17 CA008748.

Declaration of interest

A.M. Varghese: Research funding to MSK: Lilly, Taiho Pharmaceuticals, Bristol Myers Squibb, Silenseed.

K.H. Yu: Research funding to MSK: Halozyne, BMS. Consulting/Advisory: Halozyne, Ipsen.

E.M. O'Reilly: Research funding to MSK: Genentech, Roche, BMS, Halozyne, Celgene, MabVax Therapeutics, ActaBiologica, OncoMed, Momenta Pharmaceuticals, Parker Institute, AstraZenica, Silenseed, Incyte, Pfizer, Polaris, Lustgarten Foundation, NCI-CTEP. Consulting/Advisory: Cytomx, BioLineRx, Targovax, Halozyne, Celgene, Bayer, Loxo, Polaris, Sobi.

All other authors have no conflicts to declare.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctrv.2019.03.003>.

References

- [1] Institute NC. Cancer stat facts: pancreatic cancer. April 2018 ed: surveillance, Epidemiology and End Results Program; 2018.
- [2] Kondo T, Kanai M, Kou T, Sakuma T, Mochizuki H, Kamada M, et al. Association

- between homologous recombination repair gene mutations and response to oxaliplatin in pancreatic cancer. *Oncotarget* 2018;9:19817–25. <https://doi.org/10.18632/oncotarget.24865>.
- [3] Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014;74:2913–21. <https://doi.org/10.1158/0008-5472.CAN-14-0155>.
 - [4] Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2013;369:1817–25. <https://doi.org/10.1056/NEJMoa1011923>.
 - [5] Paulson AS, Tran Cao HS, Tempero MA, Lowy AM. Therapeutic advances in pancreatic cancer. *Gastroenterology* 2013;144:1316–26. <https://doi.org/10.1053/j.gastro.2013.01.078>.
 - [6] Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013;369:1691–703. <https://doi.org/10.1056/NEJMoa1304369>.
 - [7] Wang-Gillam A, Li C-P, Bodoky G, Dean A, Shan Y-S, Jameson G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet* 2016;387:545–57. [https://doi.org/10.1016/S0140-6736\(15\)00986-1](https://doi.org/10.1016/S0140-6736(15)00986-1).
 - [8] Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review, 1975–2015. Bethesda, MD: National Cancer Institute; 2018. https://seer.cancer.gov/csr/1975_2015/ based on November 2017 SEER data submission, posted to the SEER web site, April 2018.
 - [9] Domchek SM, McWilliams R, Hendifar A, Shroff RT, Leichman L, Epelbaum R, et al. A phase 2, open-label study of the PARP inhibitor rucaparib in patients with pancreatic cancer and a known deleterious BRCA mutation. In: Cancer research conference: AACR special conference on pancreatic cancer: innovations in research and treatment 2014 New Orleans, LA United States conference start: 20140518 conference end: 20140521 Conference publication: (varpagings); 2015. p. 75. 10.1158/1538-<http://doi.org/7445.panca2014-b102>.
 - [10] Lowery MA, Kelsen DP, Capanu M, Smith SC, Lee JW, Stadler ZK, et al. Phase II trial of veliparib in patients with previously treated BRCA-mutated pancreas ductal adenocarcinoma. *Eur J Cancer* 2018;89:19–26. <https://doi.org/10.1016/j.ejca.2017.11.004>.
 - [11] O'Reilly EM, Lee JW, Lowery MA, Capanu M, Stadler ZK, Moore MJ, et al. Phase I trial evaluating cisplatin, gemcitabine, and veliparib in 2 patient cohorts: germline BRCA mutation carriers and wild-type BRCA pancreatic ductal adenocarcinoma. *Cancer* 2018;124:1374–82. <https://doi.org/10.1002/cncr.31218>.
 - [12] Yarchoan M, Myzak MC, Johnson 3rd BA, De Jesus-Acosta A, Le DT, Jaffee EM, et al. Olaparib in combination with irinotecan, cisplatin, and mitomycin C in patients with advanced pancreatic cancer. *Oncotarget* 2017;8:44073–81. <https://doi.org/10.18632/oncotarget.17237>.
 - [13] Chiaravalli M, Reni M, O'Reilly EM. Pancreatic ductal adenocarcinoma: state-of-the-art 2017 and new therapeutic strategies. *Cancer Treat Rev* 2017;60:32–43. <https://doi.org/10.1016/j.ctrv.2017.08.007>.
 - [14] O'Kane G, Fischer S, Denroche R, Ho Jang G, Zhang A, Dodd A, et al. Integrative molecular profiling and response to chemotherapy on the COMPASS trial; 2019. http://doi.org/10.1200/JCO.2019.37.4_suppl.188.
 - [15] Puleo F, Nicolle R, Blum Y, Cros J, Elarouci N, Franchimont D, et al. Clinical application and potential usefulness of targeted next-generation sequencing on resected pancreatic ductal adenocarcinoma; 2018. p. 78.
 - [16] Qian ZR, Robinson DA, Nowak JA, Morales-Oyarvide V, Dunne RF, Kozak MM, et al. Association of alterations in main driver genes with outcomes of patients with resected pancreatic ductal adenocarcinoma. *JAMA Oncol* 2018;4.
 - [17] Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada clinical trials group. *J Clin Oncol* 2007;25:1960–6. <https://doi.org/10.1200/jco.2006.07.9525>.
 - [18] Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* 2015;372(26):2509–20. <https://doi.org/10.1056/NEJMoa1500596>.
 - [19] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097. <https://doi.org/10.1371/journal.pmed.1000097>.
 - [20] Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. *J Med Libr Assoc JMLA* 2016;104:240–3. <https://doi.org/10.3163/1536-5050.104.3.014>.
 - [21] Infante JR, Somer BG, Park JO, Li CP, Scheulen ME, Kasubhai SM, et al. A randomised, double-blind, placebo-controlled trial of trametinib, an oral MEK inhibitor, in combination with gemcitabine for patients with untreated metastatic adenocarcinoma of the pancreas. *Eur J Cancer* 2014;50:2072–81. <https://doi.org/10.1016/j.ejca.2014.04.024>.
 - [22] Van Cutsem E, Hidalgo M, Canon JL, Macarulla T, Bazin I, Poddubskaya E, et al. Phase I/II trial of pimasertib plus gemcitabine in patients with metastatic pancreatic cancer. *Int J Cancer* 2018. <https://doi.org/10.1002/ijc.31603>.
 - [23] Van Laethem JL, Riess H, Jassem J, Haas M, Martens UM, Weekes C, et al. Phase I/II study of refametinib (BAY 86–9766) in combination with gemcitabine in advanced pancreatic cancer. *Target Oncol* 2017;12:97–109. <https://doi.org/10.1007/s11523-016-0469-y>.
 - [24] Bodoky G, Timcheva C, Spigel DR, La Stella PJ, Ciuleanu TE, Pover G, et al. A phase II open-label randomized study to assess the efficacy and safety of selumetinib (AZD6244 [ARRY-142886]) versus capecitabine in patients with advanced or metastatic pancreatic cancer who have failed first-line gemcitabine therapy. *Invest New Drugs* 2012;30:1216–23. <https://doi.org/10.1007/s10637-011-9687-4>.
 - [25] Ko AH, Bekaii-Saab T, Van Ziffle J, Mirzoeva OM, Joseph NM, Talasz AA, et al. A multicenter, open-label phase II clinical trial of combined MEK plus EGFR inhibition for chemotherapy-refractory advanced pancreatic adenocarcinoma. *Clin Cancer Res* 2016;22:61–8. <https://doi.org/10.1158/1078-0432.CCR-15-0979>.
 - [26] Chung V, McDonough S, Philip PA, Cardin D, Wang-Gillam A, Hui L, et al. Effect of selumetinib and MK-2206 vs oxaliplatin and fluorouracil in patients with metastatic pancreatic cancer after prior therapy: SWOG S1115 study randomized clinical trial. *JAMA Oncol* 2017;3:516–22. <https://doi.org/10.1001/jamaoncol.2016.5383>.
 - [27] Le Tourneau C, Delord JP, Gonçalves A, Gavoille C, Dubot C, Isambert N, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncol* 2015;16:1324–34. [https://doi.org/10.1016/S1470-2045\(15\)00188-6](https://doi.org/10.1016/S1470-2045(15)00188-6).
 - [28] Kundranda MN, Donald Peter B, Kramer K, Ai J, Tan BA, Kilmant E, et al. Next-generation sequencing (NGS) to identify potential therapeutic targets in advanced pancreatic cancer. *J Clin Oncol* 2015;33. https://doi.org/10.1200/jco.2015.33.3_suppl.357.
 - [29] Infante JR, Fecher LA, Falchook GS, Nallapareddy S, Gordon MS, Becerra C, et al. Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial. *Lancet Oncol* 2012;13:773–81. [https://doi.org/10.1016/S1470-2045\(12\)70270-x](https://doi.org/10.1016/S1470-2045(12)70270-x).
 - [30] Adjei AA, Richards DA, El-Khoueiry A, Becerra CHR, Stephenson JJ, Leffingwell DP, et al. Pharmacodynamic results of BAY 86–9766, an oral MEK inhibitor, in combination with sorafenib, an oral multikinase inhibitor, in advanced cancer patients. *Mol Cancer Ther* 2011;10. <https://doi.org/10.1158/1535-7163.TARG-11-A88>.
 - [31] Bedard PL, Tabernero J, Janku F, Aw Z, Paz-Ares L, Vansteenkiste J, et al. A Phase Ib dose-escalation study of the oral pan-P13K inhibitor buparlisib (BKM120) in combination with the oral MEK1/2 inhibitor trametinib (GSKI120212) in patients with selected advanced solid tumors. *Clin Cancer Res* 2015;21:730–8. <https://doi.org/10.1158/1078-0432.CCR-14-1814>.
 - [32] Weekes CD, Lockhard A, Lorusso P, Murray E, Park E, Tagen M, et al. A Phase Ib study to evaluate the MEK inhibitor cobimetinib in combination with the ERK1/2 inhibitor GDC-0994 in patients with advanced solid tumors. AACR annual meeting. 2017.
 - [33] Dueland S, Valle JW, Bell K, Faluyi O, Staiger H, Gjertsen TJ, et al. TG01/GM-CSF and adjuvant gemcitabine in patients with resected RAS-mutant adenocarcinoma of the pancreas. *Ann Oncol* 2017;28:v227–8.
 - [34] Eriksen JA, Gladhaug IP, Rosseland A, Risberg Handeland K, Buanes T. An observational clinical study with RAS peptide vaccine TG01 evaluating immune response, safety and overall survival in patients with non-resectable pancreatic cancer. *Ann Oncol* 2017;28:v409–10.
 - [35] Richards D, Muscarella P, Bekaii-Saab T, Wilfong L, Rosemurgy A, Ross S, et al. A phase 2 adjuvant trial of GI-4000 plus gemcitabine vs. Gemcitabine alone in ras+ patients with resected pancreas cancer: R1 subgroup analysis. *Ann Oncol* 2012;23:iv5. <https://doi.org/10.1093/annonc/mds151>.
 - [36] Weden S, Klemp M, Gladhaug IP, Moller M, Eriksen JA, Gaudernack G, et al. Long-term follow-up of patients with resected pancreatic cancer following vaccination against mutant K-ras. *Int J Cancer* 2011;128:1120–8. <https://doi.org/10.1002/ijc.25449>.
 - [37] Yutani S, Komatsu N, Yoshitomi M, Matsueda S, Yonemoto K, Mine T, et al. A phase II study of a personalized peptide vaccination for chemotherapy-resistant advanced pancreatic cancer patients. *Oncol Rep* 2013;30:1094–100. <https://doi.org/10.3892/or.2013.2556>.
 - [38] Laheru D, Shah P, Rajeshkumar NV, McAllister F, Taylor G, Goldsweig H, et al. Integrated preclinical and clinical development of S-trans, trans-Farnesylthiosalicylic Acid (FTS, Salirasib) in pancreatic cancer. *Invest New Drugs* 2012;30:2391–9. <https://doi.org/10.1007/s10637-012-9818-6>.
 - [39] Van Cutsem E, van de Velde H, Karasek P, Oettle H, Vervenne WL, Szawlowski A, et al. Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. *J Clin Oncol* 2004;22:1430–8. <https://doi.org/10.1200/JCO.2004.10.112>.
 - [40] Golan T, Khvalevsky EZ, Hubert A, Gabai RM, Hen N, Segal A, et al. RNAi therapy targeting KRAS in combination with chemotherapy for locally advanced pancreatic cancer patients. *Oncotarget* 2015;6:24560–70. <https://doi.org/10.18632/oncotarget.4183>.
 - [41] O'Neil BH, Scott AJ, Ma WW, Cohen SJ, Leichman L, Aisner DL, et al. A phase II/III randomized study to compare the efficacy and safety of rigosertib plus gemcitabine versus gemcitabine alone in patients with previously untreated metastatic pancreatic cancer. *Ann Oncol* 2015;26:1923–9. <https://doi.org/10.1093/annonc/mdv264>.
 - [42] Assenat E, Mineur L, Mollevi C, Lombard-Bohas C, Mazard T, Samalin E, et al. Phase II study evaluating the association of gemcitabine, trastuzumab, and erlotinib as first-line treatment in patients with metastatic pancreatic adenocarcinoma (GATE 1). *J Clin Oncol* 2015;18. https://doi.org/10.1200/jco.2015.33.3_suppl.379.
 - [43] Chiramel J, Backen AC, Pihlak R, Lamarca A, Frizziero M, Tariq NU, et al. Targeting the epidermal growth factor receptor in addition to chemotherapy in patients with advanced pancreatic cancer: a systematic review and meta-analysis. *Int J Mol Sci* 2017;18. <https://doi.org/10.3390/ijms18050909>.
 - [44] Fountzilas G, Bobos M, Kalogera-Fountzila A, Xiros N, Murray S, Linardou H, et al. Gemcitabine combined with gefitinib in patients with inoperable or metastatic pancreatic cancer: a phase II study of the Hellenic Cooperative Oncology Group with biomarker evaluation. *Cancer Invest* 2008;26:784–93. <https://doi.org/10.1080/07321830701481111>.

- 1080/07357900801918611.
- [45] Kim GP, Foster NR, Salim M, Flynn PJ, Moore DF, Zon R, et al. Randomized phase II trial of panitumumab, erlotinib, and gemcitabine (PGE) versus erlotinib-gemcitabine (GE) in patients with untreated, metastatic pancreatic adenocarcinoma. *J Clin Oncol* 2011;29. <https://doi.org/10.1200/jco.2011.29.15.suppl.4030>.
 - [46] Kullmann F, Hartmann A, Stohr R, Messmann H, Dollinger MM, Trojan J, et al. KRAS mutation in metastatic pancreatic ductal adenocarcinoma: results of a multicenter phase II study evaluating efficacy of cetuximab plus gemcitabine/oxaliplatin (GEMOXCT) in first-line therapy. *Oncology* 2011;81:3–8. <https://doi.org/10.1159/000330194>.
 - [47] Philip PA, Benedetti J, Corless CL, Wong R, O'Reilly EM, Flynn PJ, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: southwest oncology group-directed intergroup trial S0205. *J Clin Oncol* 2010;28:3605–10. <https://doi.org/10.1200/jco.2009.25.7550>.
 - [48] Wang JP, Wu CY, Yeh YC, Shyr YM, Wu YY, Kuo CY, et al. Erlotinib is effective in pancreatic cancer with epidermal growth factor receptor mutations: a randomized, open-label, prospective trial. *Oncotarget* 2015;6:18162–73. <https://doi.org/10.18632/oncotarget.4216>.
 - [49] Perez-Soler R, Delord JP, Halpern A, Kelly K, Krueger J, Sureddi BM, et al. HER1/EGFR inhibitor-associated rash: future directions for management and investigation outcomes from the HER1/EGFR inhibitor rash management forum. *Oncologist* 2005;10:345–56. <https://doi.org/10.1634/theoncologist.10.5.345>.
 - [50] Mahalingam D, Goel S, Aparo S, Patel Arora S, Noronha N, Tran H, et al. Phase II study of pelareorep (REOLYSIN(R)) in combination with gemcitabine for patients with advanced pancreatic adenocarcinoma. *Cancers (Basel)* 2018;10. <https://doi.org/10.3390/cancers10060160>.
 - [51] Noonan AM, Farren MR, Geyer SM, Huang Y, Tahiri S, Ahn D, et al. Randomized phase 2 trial of the oncolytic virus pelareorep (Reolysin) in upfront treatment of metastatic pancreatic adenocarcinoma. *Mol Ther* 2016;24:1150–8. <https://doi.org/10.1038/mt.2016.66>.
 - [52] Varga A, Soria JC, Hollebecque A, LoRusso P, Vaishampayan U, Okrah K, et al. A first-in-human phase I study to evaluate the ERK1/2 inhibitor GDC-0994 in patients with advanced solid tumors. *Eur J Cancer* 2016;69:S11. [https://doi.org/10.1016/S0959-8049\(16\)32624-7](https://doi.org/10.1016/S0959-8049(16)32624-7).
 - [53] Weekes CD, Lockhart AC, LoRusso P, Murray ER, Park E, Tagen M, et al. A Phase Ib study to evaluate the MEK inhibitor cobimetinib in combination with the ERK1/2 inhibitor GDC-0994 in patients with advanced solid tumors. *AACR annual meeting*. 2017.
 - [54] Heining C, Horak P, Uhrig S, Codo PL, Klink B, Hutter B, et al. NRG1 Fusions in KRAS wild-type pancreatic cancer. *Cancer Discov* 2018. <https://doi.org/10.1158/2159-8290.cd-18-0036>.
 - [55] Singhi A, Ali SM, Greenbowe J, Ross JS, Nguyen K, Nikiforova M, et al. A clinicopathologic study of ALK rearrangements in pancreatic ductal adenocarcinoma. *Lab Invest* 2016;96:448A–9A.
 - [56] Singhi AD, Ali SM, Lacy J, Hendifar A, Nguyen K, Koo J, et al. Identification of targetable ALK rearrangements in pancreatic ductal adenocarcinoma. *J Natl Compr Canc Netw* 2017;15:555–62. <https://doi.org/10.6004/jnccn.2017.0058>.
 - [57] Pishvaian MJ, Rolfo CD, Liu SV, Multani PS, Maneval EC, Garrido-Laguna I. Clinical benefit of entrectinib for patients with metastatic pancreatic cancer who harbor NTRK and ROS1 fusions. 2018;36:521. <http://doi.org/10.1200/JCO.2018.36.4.suppl.521>.
 - [58] Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med* 2018;378:731–9. <https://doi.org/10.1056/NEJMoa1714448>.
 - [59] Crane CH, Varadhachary GR, Yordy JS, Staerkel GA, Javle MM, Safran H, et al. Phase II trial of cetuximab, gemcitabine, and oxaliplatin followed by chemoradiation with cetuximab for locally advanced (T4) pancreatic adenocarcinoma: correlation of Smad4(Dpc4) immunostaining with pattern of disease progression. *J Clin Oncol* 2011;29:3037–43. <https://doi.org/10.1200/JCO.2010.33.8038>.
 - [60] Bachet JB, Marechal R, Demetter P, Bonnetain F, Couvelard A, Svrcek M, et al. Contribution of CXCR4 and SMAD4 in predicting disease progression pattern and benefit from adjuvant chemotherapy in resected pancreatic adenocarcinoma. *Ann Oncol* 2012;23:2327–35. <https://doi.org/10.1093/annonc/mdr617>.
 - [61] Herman JM, Fan KY, Wild AT, Wood LD, Blackford AL, Donehower RC, et al. Correlation of Smad4 status with outcomes in patients receiving erlotinib combined with adjuvant chemoradiation and chemotherapy after resection for pancreatic adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2013;87:458–9. <https://doi.org/10.1016/j.ijrobp.2013.06.2039>.
 - [62] Shin SH, Kim HJ, Hwang DW, Lee JH, Song KB, Jun E, et al. The DPC4/SMAD4 genetic status determines recurrence patterns and treatment outcomes in resected pancreatic ductal adenocarcinoma: a prospective cohort study. *Oncotarget* 2017;8:17945–59.
 - [63] Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the conko-001 randomized trial. *JAMA* 2013;310:1473–81. <https://doi.org/10.1001/jama.2013.279201>.
 - [64] Strieler JK, Sinn M, Pelzer U, Juhling A, Wislocka L, Bahra M, et al. P53 overexpression and Ki67-index are associated with outcome in ductal pancreatic adenocarcinoma with adjuvant gemcitabine treatment. *Pathol Res Pract* 2016;212:726–34. <https://doi.org/10.1016/j.prp.2016.06.001>.
 - [65] Yang SH, Lee JC, Guo JC, Kuo SH, Tien YW, Kuo TC, et al. Association of MDM2 expression with shorter progression-free survival and overall survival in patients with advanced pancreatic cancer treated with gemcitabine-based chemotherapy. *PLoS ONE* 2017;12. <https://doi.org/10.1371/journal.pone.0180628>.
 - [66] Sinn M, Budczies J, Damm F, Lohneis P, Schmuck R, Treue D, et al. TP53 mutation predicts sensitivity to adjuvant gemcitabine in pancreatic cancer: results from the CONKO-001 study. *Ann Oncol* 2017;28:v251. <https://doi.org/10.1093/annonc/mdx369>.
 - [67] Aung KL, Fischer SE, Denroche RE, Jang GH, Dodd A, Creighton S, et al. Genomics-driven precision medicine for advanced pancreatic cancer: early results from the COMPASS trial. *Clin Cancer Res* 2018;24:1344–54. <https://doi.org/10.1158/1078-0432.CCR-17-2994>.
 - [68] Pishvaian MJ, Bender RJ, Halverson D, Rahib L, Hendifar AE, Mikhail S, et al. Molecular profiling of patients with pancreatic cancer: initial results from the know your tumor initiative. *Clin Cancer Res* 2018;24:5018–27. <https://doi.org/10.1158/1078-0432.CCR-18-0531>.
 - [69] Egeli U, Tezcan G, Cecener G, Tunca B, Demirdogen Sevinc E, Kaya E, et al. miR-216b targets FGFR1 and confers sensitivity to radiotherapy in pancreatic ductal adenocarcinoma patients without EGFR or KRAS mutation. *Pancreas* 2016;45:1294–302. <https://doi.org/10.1097/mpa.0000000000000640>.
 - [70] Cheng DT, Mitchell TN, Zehir A, Shah RH, Benayed R, Syed A, et al. Memorial Sloan Kettering-integrated mutation profiling of actionable cancer targets (MSK-IMPACT): a hybridization capture-based next-generation sequencing clinical assay for solid tumor molecular oncology. *J Mol Diagn* 2015;17:251–64. <https://doi.org/10.1016/j.jmoldx.2014.12.006>.
 - [71] Lowery MA, Jordan EJ, Basturk O, Ptashkin RN, Zehir A, Berger MF, et al. Real-time genomic profiling of pancreatic ductal adenocarcinoma: potential actionability and correlation with clinical phenotype. *Clin Cancer Res* 2017;23:6094–100. <https://doi.org/10.1158/1078-0432.CCR-17-0899>.
 - [72] Kondo T, Kanai M, Kou T, Sakuma T, Mochizuki H, Kamada M, et al. Impact of BRCAness on the efficacy of oxaliplatin-based chemotherapy in patients with unresectable pancreatic cancer. *J Clin Oncol* 2017;35. <https://doi.org/10.1200/JCO.2017.35.4.suppl.250>.
 - [73] Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature* 2015;518:495–501. <https://doi.org/10.1038/nature14169>.
 - [74] Vyas O, Leung K, Ledbetter L, Kaley K, Rodriguez T, Garcon MC, et al. Clinical outcomes in pancreatic adenocarcinoma associated with BRCA-2 mutation. *Anticancer Drugs* 2015;26:224–6. <https://doi.org/10.1097/CAD.0000000000000178>.
 - [75] Sehdev A, Gbolahan O, Hancock BA, Stanley M, Shahda S, Wan J, et al. Germline and somatic DNA damage repair gene mutations and overall survival in metastatic pancreatic adenocarcinoma patients treated with FOLFIRINOX. *Clin Cancer Res* 2018;24:6204–11. <https://doi.org/10.1158/1078-0432.CCR-18-1472>.
 - [76] O'Kane GM, Borgida A, Dodd A, Aung KL, Holter S, Knox J, et al. Prognosis of familial pancreatic cancer (FPC): a matched case analysis. *Ann Oncol* 2017;28:v249. <https://doi.org/10.1093/annonc/mdx369>.
 - [77] Lowery MA, Stadler ZK, Ludwig E, Salo-Mullen E, D'Adamo DR, Allen PJ, et al. Clinical outcomes in pancreatic adenocarcinoma (PAC) associated with a known BRCA mutation. *J Clin Oncol* 2011;29. <https://doi.org/10.1200/jco.2011.29.4.suppl.268>.
 - [78] Golan T, Sella T, O'Reilly EM, Katz MH, Epelbaum R, Kelsen DP, et al. Overall survival and clinical characteristics of BRCA mutation carriers with stage I/II pancreatic cancer. *Br J Cancer* 2017;116:697–702. <https://doi.org/10.1038/bjc.2017.19>.
 - [79] Golan T, Kanji ZS, Epelbaum R, Devaud N, Dagan E, Holter S, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. *Br J Cancer* 2014;111:1132–8. <https://doi.org/10.1038/bjc.2014.418>.
 - [80] Blair AB, Groot VP, Gemenetis G, Wei J, Cameron JL, Weiss MJ, et al. BRCA1/BRCA2 germline mutation carriers and sporadic pancreatic ductal adenocarcinoma. *J Am Coll Surg* 2018;226(630–7):e1. <https://doi.org/10.1016/j.jamcollsurg.2017.12.021>.
 - [81] Shroff RT, Hendifar A, McWilliams RR, Geva R, Epelbaum R, Rolfe L, et al. Rucaparib monotherapy in patients with pancreatic cancer and a known deleterious BRCA mutation. *JCO Precision Oncology*. 2018:1–15. <https://doi.org/10.1200/po.17.00316>.
 - [82] Lowery MA, Kelsen DP, Stadler ZK, Yu KH, Janjigian YY, Ludwig E, et al. An emerging entity: pancreatic adenocarcinoma associated with a known BRCA mutation: clinical descriptors, treatment implications, and future directions. *Oncologist* 2011;16:1397–402. <https://doi.org/10.1634/theoncologist.2011-0185>.
 - [83] Lucas AL, Shkya R, Lipsyc MD, Mitchel EB, Kumar S, Hwang C, et al. High prevalence of BRCA1 and BRCA2 germline mutations with loss of heterozygosity in a series of resected pancreatic adenocarcinoma and other neoplastic lesions. *Clin Cancer Res* 2013;19:3396–403. <https://doi.org/10.1158/1078-0432.CCR-12-3020>.
 - [84] Hu ZI, Varghese AM, Shia J, Zervoudakis A, Lowery MA, Yu KH, et al. Clinical characterization of pancreatic ductal adenocarcinomas (PDAC) with mismatch repair (MMR) gene mutations. *J Clin Oncol* 2017;35. <https://doi.org/10.1158/1078-0432.CCR-17-3099>.
 - [85] Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015;372:2509–20. <https://doi.org/10.1056/NEJMoa1500596>.
 - [86] Cavalieri CC, Swanson E, Whisenant JR, Weis JR, Gilcrease GW, Stenehjem DD, et al. Pembrolizumab in gastrointestinal (GI) malignancies with defective DNA mismatch repair (dMMR): a single institution experience. *J Clin Oncol* 2017;35:792. <https://doi.org/10.1200/JCO.2017.35.4.suppl.792>.
 - [87] Jardim DL, Groves ES, Breitfeld PP, Kurzrock R. Factors associated with failure of oncology drugs in late-stage clinical development: a systematic review. *Cancer Treat Rev* 2017;52:12–21. <https://doi.org/10.1016/j.ctrv.2016.10.009>.
 - [88] Seruga B, Ocana A, Amir E, Tannock IF. Failures in phase III: causes and

- consequences. *Clin Cancer Res* 2015;21:4552–60. <https://doi.org/10.1158/1078-0432.Ccr-15-0124>.
- [89] Jardim DL, Schwaederle M, Wei C, Lee JJ, Hong DS, Eggermont AM, et al. Impact of a biomarker-based strategy on oncology drug development: a meta-analysis of clinical trials leading to FDA approval. *J Natl Cancer Inst* 2015;107:djv253. <https://doi.org/10.1093/jnci/djv253>.
- [90] Integrated Genomic Characterization of Pancreatic Ductal Adenocarcinoma. *Cancer Cell*. 2017;32:185–203.e13. Doi: 10.1016/j.ccell.2017.07.007.
- [91] Holter S, Borgida A, Dodd A, Grant R, Semotiuk K, Hedley D, et al. Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. *J Clin Oncol* 2015;33:3124–9. <https://doi.org/10.1200/jco.2014.59.7401>.
- [92] Salo-Mullen EE, O'Reilly EM, Kelsen DP, Ashraf AM, Lowery MA, Yu KH, et al. Identification of germline genetic mutations in patients with pancreatic cancer. *Cancer* 2015;121:4382–8. <https://doi.org/10.1002/cncr.29664>.
- [93] Chantrill LA, Nagrial AM, Watson C, Johns AL, Martyn-Smith M, Simpson S, et al. Precision medicine for advanced pancreas cancer: the individualized molecular pancreatic cancer therapy (IMPACT) trial. *Clin Cancer Res* 2015;21:2029–37. <https://doi.org/10.1158/1078-0432.Ccr-15-0426>.
- [94] Witkiewicz AK, McMillan EA, Balaji U, Baek G, Lin WC, Mansour J, et al. Whole-exome sequencing of pancreatic cancer defines genetic diversity and therapeutic targets. *Nat Commun* 2015;6:6744. <https://doi.org/10.1038/ncomms7744>.
- [95] Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443–54. <https://doi.org/10.1056/NEJMoa1200690>.
- [96] Taube JM, Klein A, Brahmer JR, Xu H, Pan X, Kim JH, et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. *Clin Cancer Res* 2014. <https://doi.org/10.1158/1078-0432.CCR-13-3271>.
- [97] Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature* 2013;503:548–51. <https://doi.org/10.1038/nature12796>.
- [98] Patricelli MP, Janes MR, Li LS, Hansen R, Peters U, Kessler LV, et al. Selective inhibition of oncogenic KRAS output with small molecules targeting the inactive state. *Cancer Discov* 2016;6:316–29. <https://doi.org/10.1158/2159-8290.Cd-15-1105>.
- [99] Mai TT, Lito P. A treatment strategy for KRAS-driven tumors. *Nat Med* 2018;24:902–4. <https://doi.org/10.1038/s41591-018-0111-x>.
- [100] Chen YN, LaMarche MJ, Chan HM, Fekkes P, Garcia-Fortanet J, Acker MG, et al. Allosteric inhibition of SHP2 phosphatase inhibits cancers driven by receptor tyrosine kinases. *Nature* 2016;535:148–52. <https://doi.org/10.1038/nature18621>.
- [101] Belmont PJ, Jiang P, McKee TD, Xie T, Isaacson J, Barylak NE, et al. Resistance to dual blockade of the kinases PI3K and mTOR in KRAS-mutant colorectal cancer models results in combined sensitivity to inhibition of the receptor tyrosine kinase EGFR. *Sci Signaling* 2014;7:ra107. <https://doi.org/10.1126/scisignal.2005516>.
- [102] NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian. 2018; Version 1; 2019.