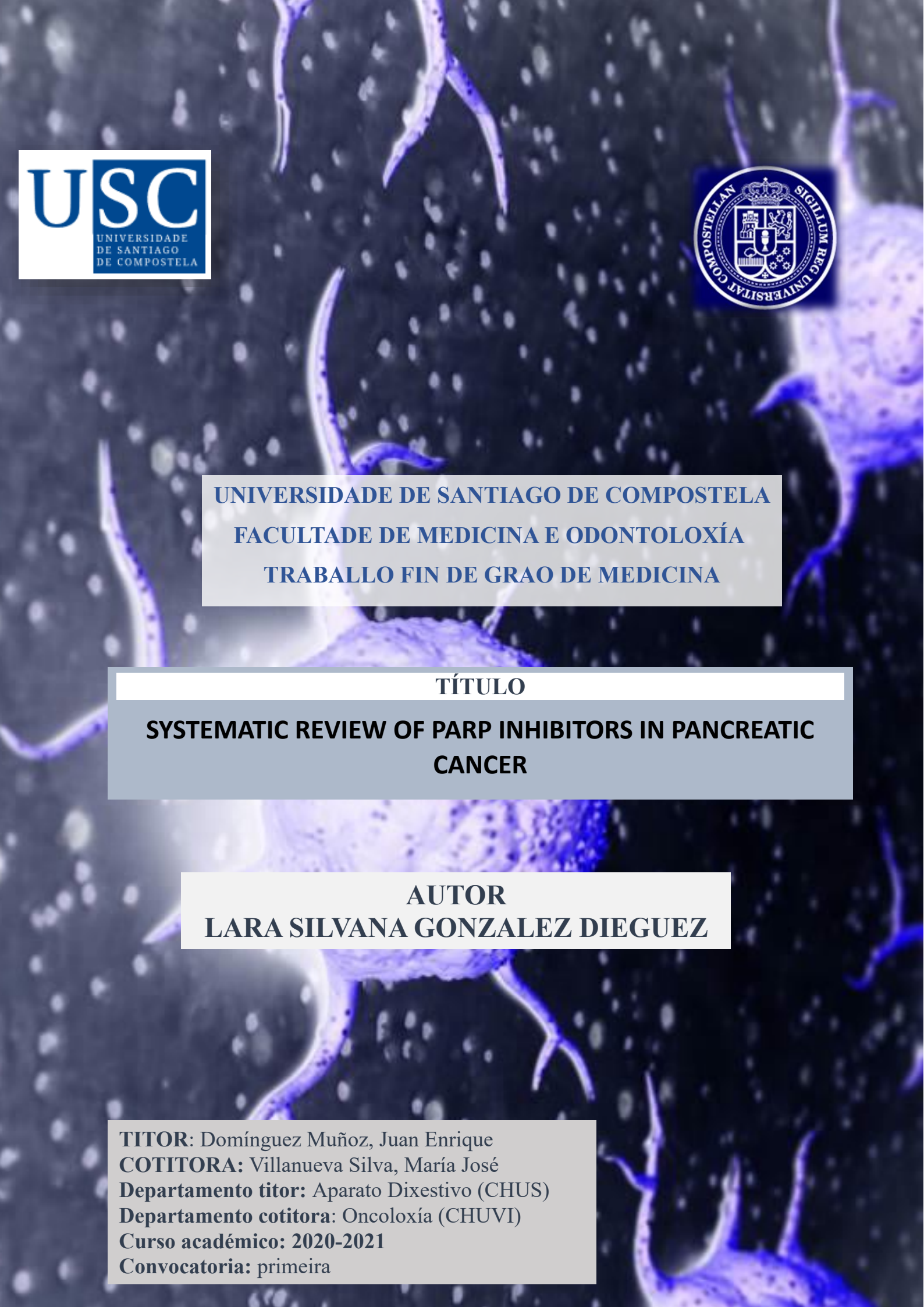


UNIVERSIDADE DE SANTIAGO DE COMPOSTELA
FACULTADE DE MEDICINA E ODONTOLOXÍA
TRABALLO FIN DE GRAO DE MEDICINA

TÍTULO

SYSTEMATIC REVIEW OF PARP INHIBITORS IN PANCREATIC CANCER

AUTOR
LARA SILVANA GONZALEZ DIEGUEZ

TITOR: Domínguez Muñoz, Juan Enrique
COTITORA: Villanueva Silva, María José
Departamento titor: Aparato Dixestivo (CHUS)
Departamento cotitora: Oncoloxía (CHUVI)

Curso académico: 2020-2021
Convocatoria: primeira

ABSTRACT

BACKGROUND: PARP inhibitors (PARPi) have shown activity in epithelial ovarian cancer harbouring homologous recombination repair (HRR) deficiency. A small subgroup of pancreatic cancer (PC) carries HRR deficiencies, being candidates to treatment with PARPi.

OBJECTIVE: To perform a systematic review to summarize all available evidence with PARPi in advanced PC to assess its efficacy and safety.

MATERIAL AND METHODS: An electronic search of clinical trials with HRR deficient advanced PC, published as a research article or in abstract form between 2010 and 2020, was performed. No language restrictions were applied. A predefined protocol was followed in accordance with the PRISMA guidelines. Population was defined as HRR deficient, mBRCA1/2, advanced PC. Intervention was defined as poly(ADP-ribose) polymerase inhibitors, PARPi, olaparib, niraparib, rucaparib, talazoparib, veliparib, clinical trial, advanced PC.

RESULTS: The search identified 135 records, with 14 additional through reference section and grey literature. After screening phase and eligibility process, ten phase I/II-III trials were included for final analysis, namely six monotherapy trials (four as treatment lines and two as maintenance strategy) and four in combination with chemotherapy**.** All but one of the four monotherapy studies were negative trials, specifically the one enrolling patients on progression to gemcitabine. The two PARPi trials as maintenance strategy, showed improved progression free survival (PFS). Combination trials yield severe toxicity in two out of four studies. Interesting data were reported in one trial testing fractionated low dose cisplatin-gemcitabine regimen plus veliparib, whit increased PFS and overall survival (OS) in an exploratory analysis where veliparib was continued as maintenance. Combination of veliparib with FOLFOX also showed a 57% overall response rate (ORR) in platinum naïve patients harboring pathogenic HR-DDR mutations.

CONCLUSION: PARPi showed activity in mBRCA advanced PC as maintenance strategy, some of which being long lasting. Future investigation is needed to circumvent resistance and improve results.

Key Words: pancreatic cancer, poly(ADP-ribose) polymerase inhibitors, PARP inhibitor, homologous recombination repair deficiency/deficient, BRCA 1/2 mutation/mutated.

RESUMEN

INTRODUCCIÓN: Los inhibidores de PARP (PARPi) han mostrado actividad en cánceres de ovario epiteliales con déficit de recombinación homóloga (HRD). Un subgrupo de cáncer de páncreas (CP) también alberga HRD, siendo así candidatos al tratamiento con PARPi.

OBJETIVO: Revisión sistemática para resumir la evidencia disponible sobre el uso de PARPi en CP avanzado y evaluar su eficacia y seguridad.

MATERIAL Y MÉTODOS: Se realizó una búsqueda electrónica, sin restrcción de idioma, de ensayos clínicos de CP avanzado con HRD, publicados como artículos de investigación o resúmenes entre 2010-2020. Se siguió un protocolo predefinido, de acuerdo con la declaración PRISMA. La población fue descrita como HRD, mBRCA1/2 y CP avanzado y la intervención como inhibidores poli(ADP-ribosa) polimerasa, PARPi, olaparib, niraparib, rucaparib, talazoparib, veliparib, ensayo clínico, CP avanzado.

RESULTADOS: Se identificaron 135 registros, con 14 adicionales encontrados en secciones de referencias y literatura gris. Tras fase de cribado y elegibilidad, diez ensayos en fases I/II-III fueron incluidos en el análisis final (seis como monoterapia (cuatro líneas de tratamiento y dos como estrategia de mantenimiento) y cuatro con quimioterapia). Uno de los ensayos de monoterapia, cuyos pacientes no habían progresado con gemcitabina, no era negativo. Los estudios como estrategia de mantenimiento mostraron mejoría de la supervivencia libre de progresión (SLP). Los combinados produjeron toxicidad severa en dos de ellos. Se comunicaron datos relevantes en un ensayo con régimen fraccionado de cisplatino-gemcitabina a dosis bajas más veliparib, observándose aumento de la SLP y la supervivencia global en un análisis en el cual se continuó con veliparib como mantenimiento. La combinación de veliparib-FOLFOX mostró una tasa de respuesta objetiva del 57% en pacientes platino-naïve, portadores de HDR.

CONCLUSIÓN: Los PARPi mostraron actividad en PC avanzado con BRCAm, como terapia de mantenimiento, siendo algunas duraderas. Es necesaria más investigación para evitar resistencias y mejorar resultados.

Palabras clave: cáncer de páncreas, inhibidores poli(ADP-ribosa) polimerasa, inhibidores PARP, déficit/deficiencia recombinación homóloga, BRCA 1/2 mutación/mutado.

RESUMO

INTRODUCCIÓN: Os inhibidores da PARP (PARPi) mostraron actividade en cancros epiteliais de ovario cun déficit de recombinación homóloga (HRD). Un subgrupo de cancro de páncreas (CP) tamén presenta HRD, sendo así candidatos ao tratamento con PARPi.

OBXECTIVO: Levar a cabo unha revisión sistemática para resumir a evidencia dispoñible sobre o uso de PARPi no CP avanzado e avaliar a súa eficacia e seguridade.

MATERIAL E MÉTODOS: Realizouse unha procura electrónica, sen restrición de lingua, de ensaios clínicos de CP avanzado con HRD, publicados como artigos de investigación ou resumos entre 2010 e 2020. Seguiuse un protocolo predefinido, de acordo coa declaración PRISMA. A poboación foi descrita como HRD, mBRCA1/2 e CP avanzado e a intervención como inhibidores poli(ADP-ribosa) polimerasa, PARPi, olaparib, niraparib, rucaparib, talazoparib, veliparib, ensaio clínico, CP avanzado.

RESULTADOS: Identificáronse 135 rexistros, con 14 adicionais atopados en seccións de referencias e literatura gris. Tras fase de cribado e elixibilidade, dez ensaios en fases I/II-III foron incluídos na análise final (seis como monoterapia (catro liñas de tratamento e dous como estratexia de mantemento) e catro con quimioterapia). Un dos ensaios de monoterapia, cuxos pacientes non progresaran con gemcitabina, non era negativo. Os estudos como estratexia de mantemento mostraron melloría da supervivencia libre de progresión (SLP). Os combinados produciron toxicidade severa en dous de eles. Comunicáronse datos relevantes nun ensaio con réxime fraccionado de cisplatino-gemcitabina a doses baixas máis veliparib, observándose aumento da SLP e da supervivencia global nunha análise na cal se continuou con veliparib como mantemento. A combinación de veliparib-FOLFOX mostrou unha taxa de resposta obxectiva (ORR) do 57% en pacientes platino-naïve, portadores de HDR.

CONCLUSIÓN: Os PARPi mostraron actividade no PC avanzado con BRCAm, como terapia de mantemento, sendo algunhas delas duradeiras. É necesaria máis investigación para evitar resistencias e mellorar os resultados.

Palabras chave: cancro de páncreas, inhibidores poli(ADP-ribosa) polimerasa, inhibidores PARP, déficit/deficiencia recombinación homóloga, BRCA 1/2 mutación/mutado.

INDEX

BACKGROUND

In the past, the medical community has categorized cancer by reason of the tissue origin, assuming that tumors from different patients arising from the same organ shared similar traits and should be treated similarly, in contrast to tumors of different organs, irrespective of cellular similarities.

As diagnostic technologies advanced, more insight on immunochemistry and molecular pathology of cancer has been achieved, showing that cancers with the exact same histopathology, can harbor important differences in molecular pathways which are responsible for different prognosis. Even more, malignancies from different kind not only can share molecular pathways but also driver mutations which are essential for cancer survival. The identification of those actionable genomic alterations has paved the way for an unprecedented era of precision medicine, in which targeted treatment is driven by the presence of mutation in key pathway for tumor survival .(1)

These new pieces of evidence have identified different attributes in most cancer types that gave rise to new classifications based on biological and clinical coincidences and discrepancies among cancers of the same origin, thus enabling better patient subclassification according to prognostic stratification, optimized management by predictive subgroups, as well as further risk stratification.(1)

The identification of mutations shared by tumors of different origin, and subsequent specific treatment according to the mutation identified, is a growing trend in the field of oncology. Pioneering clinical trials, known as basket trials, have been designed involving patients with tumors of different origin that share the same molecular alterations, and positive results have been reported that have given rise to a concept kwon as tumor-agnostic treatment, which is the one directed by molecular features, irrespective of tumor origin (2).

Pancreatic cancer (PC), predicted to be the second deadliest cancer type in the next ten years, has not been an exception. From a histological point of view, PC can be divided into endocrine and exocrine subtypes, the latter being by far the most common, which can be further subdivided into several subgroups. Of these, pancreatic ductal adenocarcinoma (PDAC) accounts for more than 90% of exocrine PCs and arises from precursors known as pancreatic intraepithelial neoplasia (PIN). Most PDACs are referred to as "not otherwise specified" (NOS). Other rare variants of PDAC include adeno-squamous carcinoma (a mixture of squamous and glandular differentiation), acinar cell carcinoma and carcinomas with mixed histology and pancreatoblastoma, to mention a few. Finally, a minority subgroup of exocrine carcinomas originates from cysts, such as cystic mucinous neoplasm and intraductal papillary mucinous neoplasm (IPMN). (3)

PC molecular classification was particularly challenging due to the fact that pancreatic tumors contain a relatively low percentage of malignant cells, with prominent desmoplastic reaction with a dense fibrotic stroma (4), with barely 5%–20% neoplastic cellularity (5), making mutational analysis and gene expression features difficult on neoplastic cells. The Cancer Genome Atlas (TCGA), a landmark cancer genomics program derived from a joint effort, beginning in 2006, between the National Human Genome Research Institute and the National Cancer Institute, to molecularly characterize different cancer types, took the challenge to

develop a molecular classification of PC. (6). After developing special bioinformatic methods, the TCGA analysis revealed a complex molecular landscape, with a small group of tumors harboring multiple KRAS mutations, the rest being KRAS wild-type PDACs and carrying random alterations in other oncogenic drivers. Interestingly enough, somatic and germline mutations in DNA repair genes (*BRCA1/2, PALB2 and ATM* mutations) were identified in up to 6 % of patients in this series.(7). It should be note that only 4% of the patients in the TCGA analysis had stage 4 diseases, due to the challenge of obtaining a good tumor sample in advanced pancreatic cancer.

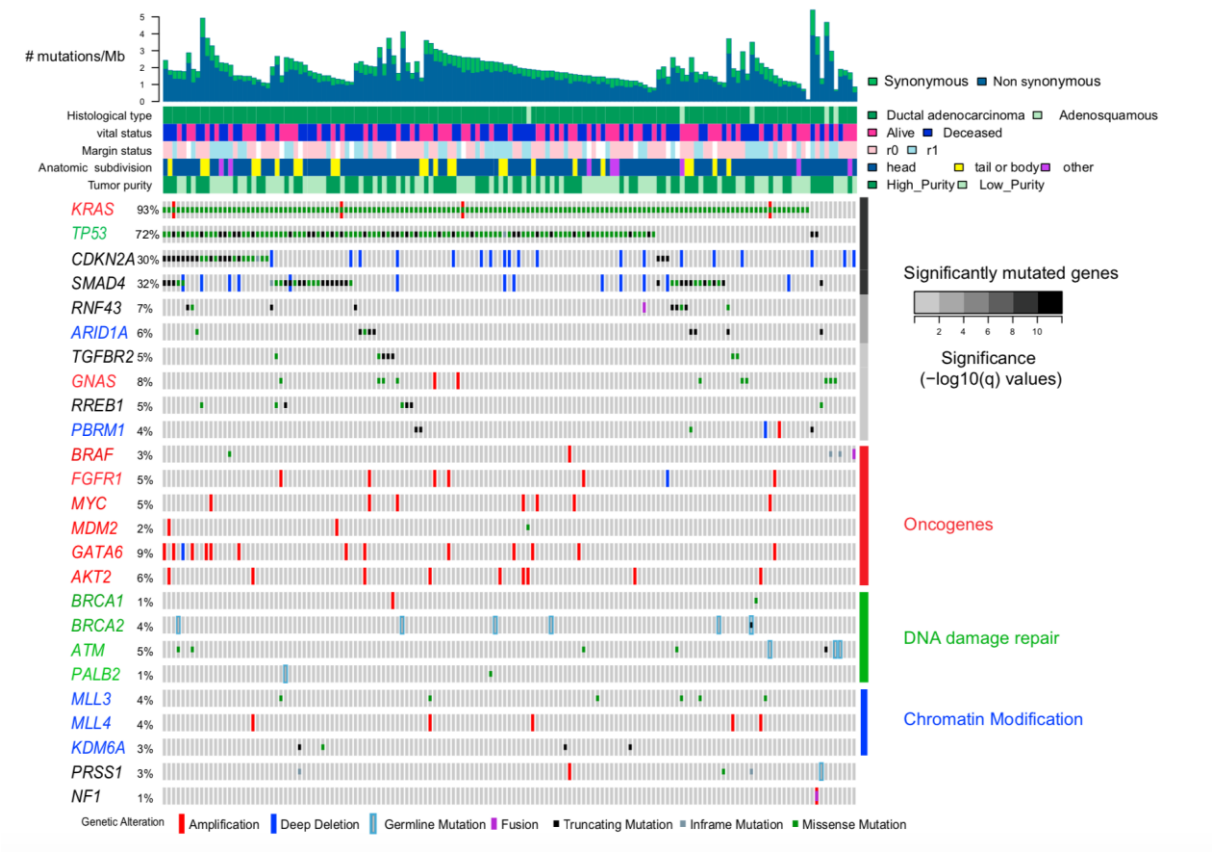


Figure 1. TCGA molecular findings in 150 pancreatic cancer samples, with only 4 cases with stage IV disease (7)

The presence of mutations in DNA damage repair genes, such as BRCA1, BRCA2 and PALB2 in PC, is of utmost importance owing the reported activity of poly(ADP-ribose) polymerase (PARP) inhibitors in tumors harboring homologous recombination repair (HRR) gene deficiency. PARP is a sensor of DNA damage, being key in the repair of single strand DNA breaks (SSBs). Accordingly, PARP inhibition leads to the accumulation of single- strand breaks, which become double-strand breaks (DSB) during replication. In absence of proper BRCA function (BRCA1 and BRCA2 proteins are critical for DSB repair) o with dysfunction in other HRR gen pathways, DSB cannot be repaired, triggering cell death by means of damaged cells disposal (8–10). Thus, cells harboring defects in BRCA genes or other deficiencies in homologous recombination DNA damage repair (HR-DDR) genes are prone to be hypersensitive to PARP inhibition, a process termed synthetic lethality.(11,12)

Such strategy has already been successfully applied in several cancer types, with platinum-sensitive BRCA-mutated epithelial ovarian cancer being the paradigm of treatment with PARP inhibitors (PARPi), not only in first line where improved results have been reported, with niraparib (PRIMA trial) (13) and olaparib (SOLO 1 trial) (14) achieving statistically and clinically meaningful increase in overall response rate and progression free survival, but also in second lines and beyond with the same drugs (15,16) as well as with other PARPi such as rucaparib (17) and veliparib (18). It should be noted that some ovarian cancer patients treated with PARPi as maintenance therapy experience long-lasting disease free survival, with years on treatment.

Increased progression free survival has also been reported in BRCA carriers breast cancer patients with olaparib (19) and talazoparib (20), as well in BRCA mutant prostate cancer (21)

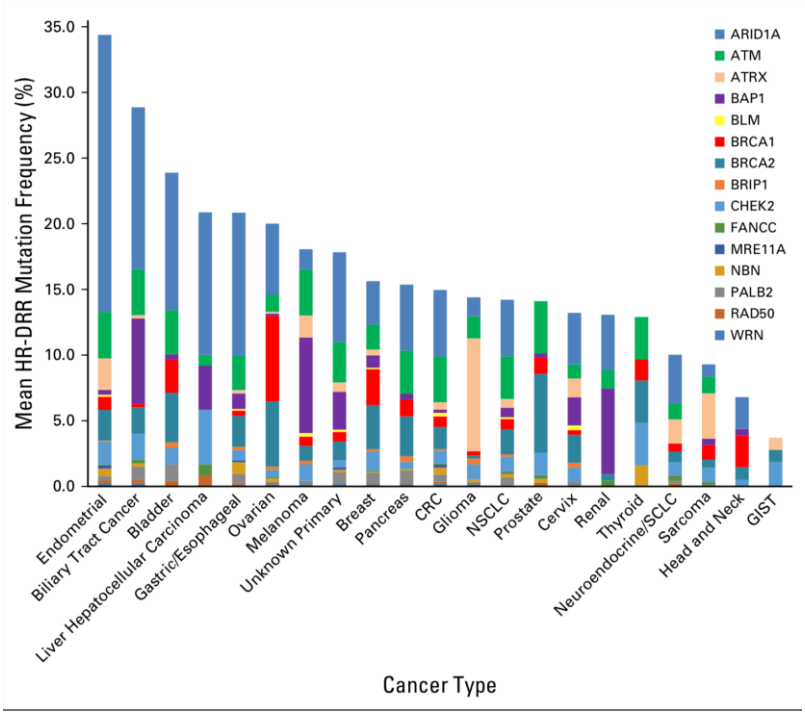


Figure 2. Results of Next generation sequencing (NGS) of HR-DDR genes in solid tumors, including 2162 pancreatic cancers.

Bearing in mind the dismal prognosis of advanced PC (APC), which overall survival with current standard treatments is less than one year (22), there is a crucial need to improve those results with new treatment strategies. Taking into account that roughly 9% of unselected PC patients are associated with a somatic or a germline mutation in *BRCA1* or *BRCA2* (*BRCA1/2*) (23,24) not to mention a heightened frequency of somatic mutations in HR-DDR genes by modern sequencing techniques (up to 15.4% (95% CI, 13.0%-18.0%), as reported in recent sequencing of 833 pancreatic tumors (Figure 2) (25), as well as the aforementioned meaningful significant improvement in survival with PARPi in several tumors, these agents might become a milestone for APC patients. Therefore, conducting a systematic review on available evidence with PARPi in APC may shed light into the optimal use of PARPi in these patients, as well as provide insight on the management of adverse effects.

OBJECTIVE

To perform a systematic review of clinical trials in order to identify and summarize all available evidence with PARPi in BRCA mutated or other homologous recombination deficiency (HRD) in advanced pancreatic cancer (APC) patients, to evaluate efficacy and safety of those agents in the aforementioned patients.

MATERIAL AND METHODS

Clinical trials with PARPi that included advanced pancreatic cancer patients published as a research article or in abstract form between January 2010 and December 2020 were scoured. A predefined protocol was designed and followed in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guideline for systematic review. Population was defined as advanced pancreatic ductal adenocarcinoma (PDAC) with special focus on BRCA and/or HD-DDR mutations. Intervention was defined as PARPi, olaparib, niraparib, rucaparib, veliparib, talazoparib, clinical trial. In order to assess efficacy, overall response rate (ORR, as the sum of complete response rate plus partial response rate, defined by RECIST criteria as per protocol trial), clinical benefit rate (CBR, as the sum of complete response rate, partial response rate and long lasting stable disease defined as per protocol trial), duration of response (DoR, as the time elapsed from response assessment to progression o last follow up, which ever came first) were retrieved as outcomes in addition to survival data in form of progression free survival (PFS, defined as the time elapsed from treatment initiation to progression, last follow-up or death, whichever came first) and overall survival (OS, defined as the time elapsed from the start of treatment to death or last follow-up, whichever came first), where available. Adverse events (AE) were also collected and assessed.

Trial selection was performed by author of the present graduation work with double check with the librarian, supervised by the cotutor. No language restriction was applied.

SEARCH STRATEGY

An electronically search was performed in PubMed, Embase, Web of Science for articles, clinicaltrial.gov database as well as ASCO, ESMO, and ECCO meetings for abstracts reporting the use of PARPi in advanced /recurrent pancreatic cancer, using a combination of broad terms related to pancrea* cancer, *carcinoma and PAPR inhibitors, olaparib, niraparib, rucaparib, velaparib, talazoparib, BRCA*, HRD*, clinical trial. The ClinicalTrial.gov website was also

scrutinized for trials. A comprehensive manual search of the Appendix as well as the Reference section of published trials was undertaken.

TRIAL SELECTION

Inclusion criteria were clinical trials involving advanced PDCA, focusing on or including BRCA mutations and/or other HR-DDR genes mutations, treated with PARPi and published in abstract form or as research articles between January 2010 and December 2020 (Table 1). No restriction as to type of prior treatment or number of previous lines was applied. Ongoing studies with published results were included as well. In addition to monotherapy trials, combination therapies studies were also included, although evaluated in a separate section. Trial selection was performed by author of the present graduation work, double-checked with the librarian, all supervised by the co-tutor. There was no restriction on the language used in the publications.

Table 1. Search criteria for the selection process

Type of study	Clinical trial with PARP inhibitors (olaparib, rucaparib, veliparib, talazoparib and others)
Condition or domain being studied	Advanced pancreatic ductal adenocarcinoma (PDAC)
Participants/Population	Adult population (>18 years of age), including but not limited to BRCA and HD-DDR mutated populations.
Timeline criteria	Clinical trial published between January 2010 and December 2020
Linguistic criteria	Any language

Exclusion criteria were: (i) patients with no advanced/recurrent pancreatic cancer, (ii) clinical trials in BRCA or HRD status not reported, (iii) studies that matched different databases, (iv) completed trials with no published results, (v) ongoing trials with no published results, (vi) case reports, narrative reviews, editorials, news articles, commentaries or letters. (vii) In the event of multiple publications reporting the same trial, only the most recent data were considered. (viii) Preference of phase II o III over phase I of the same drug was applied.

(viii) Clinical trials whose studied treatment option did not involve PARP inhibitors were excluded

DATA EXTRACTION

The studies retrieved during the search were screened for relevance. Those defined as being potentially eligible were fully evaluated to find out whether they met the requirements for inclusion criteria. They were accepted or rejected based on the predefined inclusion and exclusion criteria.

From each included study the following information was extracted, with close attention to AMSTAR checklist for systematic review evaluation, including demographics, efficacy and safety data. Regarding demographics, number of patients enrolled, clinical trial design, median age of participants, stage, performance status, sample size, type of PARPi delivered, other drugs if applied, were assessed. As per efficacy data, median follow-up (defined as the time from the start of treatment to last follow-up or death), response type according to response criteria in solid tumors (RECIST) criteria (complete response, partial response, stable disease, and, progression), overall response rate (ORR, including partial response plus complete response), clinical benefit rate (CBR, namely complete response plus partial response plus long lasting stable disease), duration of response (DoR, defined as the time elapsed from the first cycle to progression in the responding population), progression free survival (PFS, defined as the time elapsed from the first cycle to progression, last follow-up or death, whichever came first), overall survival (OS, defined as the time elapsed from the inclusion in the study to death or last follow-up), were retrieved. Regarding safety, Adverse Events (AEs) and Serious Adverse events (SAEs) were retrieved and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

RESULTS

A search on three major medical and scientific databases articles as well on oncology meeting abstracts and clinical trial data base, yielded 135 records. Additional 14 trials were identified through further reference section of published articles and grey literature. After the identification phase, 69 were rejected, 32 based on title, and 37 for being case reports, narrative reviews, editorials or letters. Of the 80 remaining for the screening phase, 61 were excluded either on the basis of abstract (10), for being an ongoing trial without published efficacy and safety data (18), or for duplication (33). Nineteen trials were assessed for the eligibility phase, 9 of which were rejected in view of this systematic review exclusion criteria ii (4) and due to lack of specific results in PC (5), leaving a final selection of 10 trials meeting inclusion criteria in which efficacy data (tumor response rate, survival - overall or progression-free survival) and safety data (adverse events) were reported. Six monotherapy trials (4 with PARPi as treatment lines per se and 2 in which PARPi was administered as maintenance therapy provided there was no tumor progression after a set time on platinum-based therapy) and 4 combinations trials with PARPi in combinations with chemotherapy in advanced PDCA and reporting data on efficacy

tumor response, survival (overall or progression-free survival), or adverse events, meeting the inclusion criteria, were retrieved (Table 2) and results will be assessed in this systematic review for final analysis.

Figure 3 represents a diagram of this systematic review, starting with the identification of articles, subsequent screening, and assessment for eligibility, showing the abstract and research articles definitively included that met all inclusion criteria and none of the exclusion criteria.

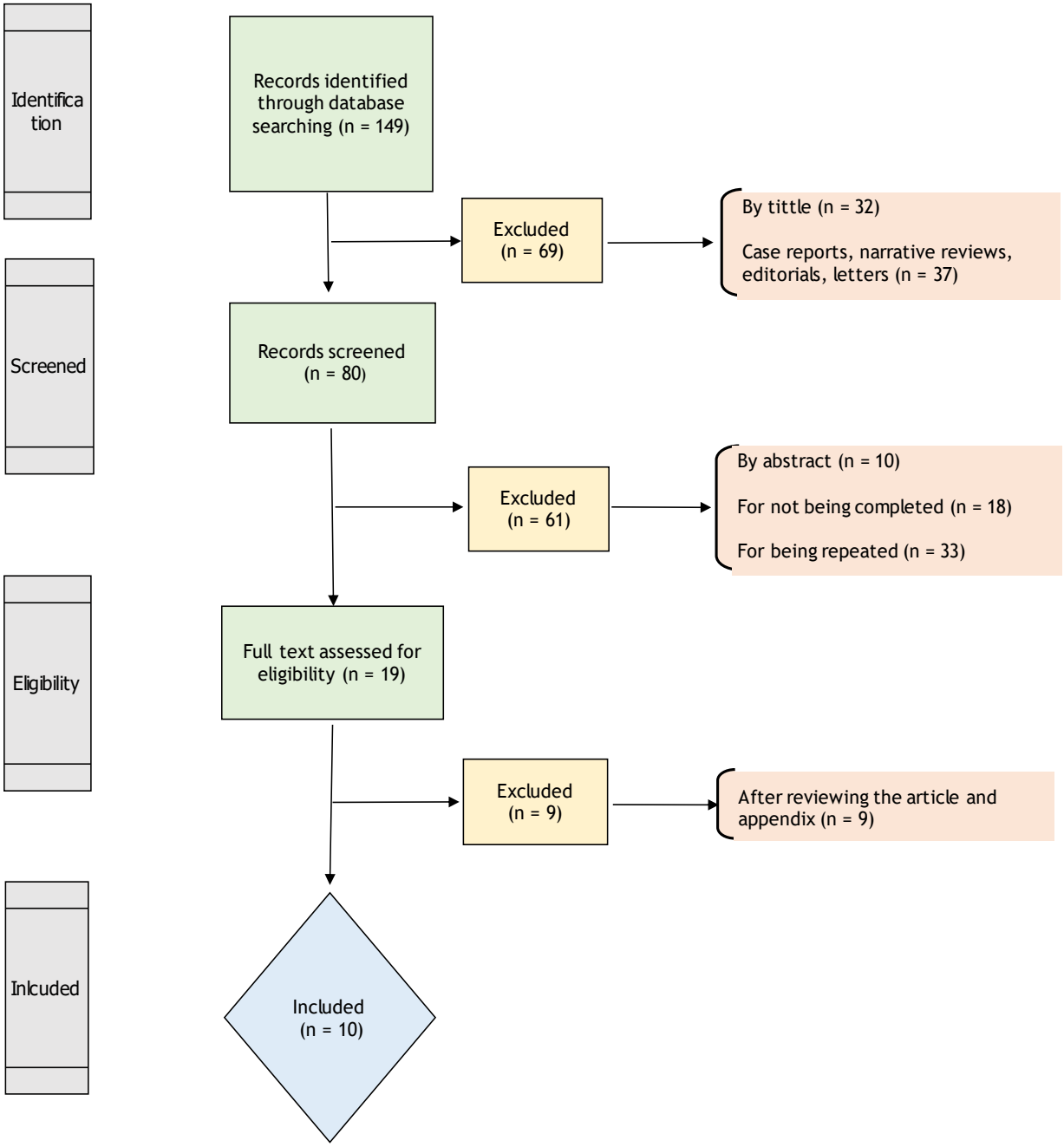


Figure 3. FLOWCHART ACCORDING TO PROSPERO-LIKE PROTOCOL (PRISMA GUIDELINES).

Table 2. PARPi trials in advanced PDAC

	TRIAL TYPE	STUDY TYPE AND REFERENCE	PARPi used
MONOTHERAPY TRIALS	PARPi AS TREATMENT LINE PER SE	PHASE II NCT01078662 PHASE II (27) PAHSE I NCT01286987 PHASE II NCT02042378	OLAPARIB CAPSULES VELIPARIB TALAZOPARIB RUCAPARIB
	PARPi AS MAINTENANCE STRATEGY	PHASE II NCT02042378 PHASE III NCT02184195)	RUCAPARIB OLAPARIB TABLETS
COMBINATION TRIALS	PARPi COMBINED WITH CT	PHASE I/II NCT00515866 PHASE I NCT01296763 PHASE II NCT01585805 Phase I/II NCT01489865	OLAPARIB (CAPSULE FORMULATIONS P.II) OLAPARIB + CPT-11-CDDP-MITC VELIPARIB + CDDP + GEM VELIPARIB +FOLFOX

CDDP: CISPLATIN; CPT-11: IRINOTECAN; CT: chemotherapy; FOLFOX: 5-FU CONTINOUS INFUSION + FOLINIC ACID + OXALIPLATIN; GEM: GEMCITABINE; MITC: MITOMYCIN C; PARPi: PARP inhibitor; PDAC: pancreatic ductal adenocarcinoma

Of note, olaparib was initially available as capsule form, and later tablet formulations became available, with different dosing schedule. Accordingly, in early olaparib clinical trials, the capsule formulation was administered, and, in more recent olaparib trials, tablet formulation was employed. Therefore, the dose and formulation of olaparib is highlighted in each olaparib trial for interpretation purposes.

MONOTHERAPY TREATMENT TRIALS

Olaparib monotherapy (400 mg twice daily, capsule formulation) was tested in a multicenter phase II trial (NCT01078662) (26)**,** in patients with advanced cancer and germline BRCA1/2 mutation, including pancreatic cancer patients who had progressed on prior gemcitabine chemotherapy. The primary efficacy end point was objective response rate. In this trial, the percentage of BRCA1 and BRCA2 mutation in advanced pancreatic cancer was 21.7% and 73.9%, respectively.

The ORR in the 23 pancreatic cancer cases, who had undergone an average of 2 prior treatment lines, was 21.7% (five out of 23; 95% CI, 7.5 to 43.7), with 4% CR and 17% PR. Stable disease ≥ 8 weeks was observed in 35% of patients (95% CI, 16.4 to 57.3). No apparent differences in response rate were observed based upon prior treatment type (platinum-based treatment, ORR of 20%, or non-platinum regimen, ORR 25%), albeit acknowledging the fact that all responses occurred in patients who had not progressed on prior platinum regimen.

The median PFS and median OS in the pancreatic cohort were 4.6 months and 9.8 months, respectively. The proportion of patients alive at 12 months was 40.9% in this cohort.

Most commonly reported grade ≥ 3 adverse events (AEs) in the pancreatic group were anemia (17.4%), fatigue (13%), vomiting (4%) and abdominal pain (4%), with 30% of patients with pancreatic cancer requiring dose reduction. Across all cancer types, 9 patients had grade 5 SAE, with 2 events, sepsis and myelodysplastic syndrome (MDS), considered to be related to olaparib.

Veliparib monotherapy was tested in stage III/IV, germline BRCA1/2m or PALB2m pancreatic ductal adenocarcinoma with 1-2 prior treatment lines, in a prospective, multicenter, non-randomized phase II trial, which results were reported in 2018 (27). Veliparib was given at an initial dose of 300 mg twice-daily (N = 3), increased subsequently to 400 mg twice-daily (N = 15) days 1-28. The primary end-point was ORR. Secondary end-points included PFS, duration of response (DoR), overall survival (OS) and safety.

Sixteen patients were enrolled; five participants (31%) had a BRCA1 mutation and 11 (69%), BRCA2 mutation. All but two patients (88%) had received previous platinum-based chemotherapy (64% of whom had progressed on that treatment). One of the two platinum naïve cases had undergone prior DNA damaging agents (irinotecan and mitomycin C). More than half of patients in this study (56%) had received 2 prior lines.

There was no response to treatment (ORR 0%), with one unconfirmed PR. Stable disease was observed in 31% of cases (5 patients), with 25% SD lasting 8 weeks or longer (4 patients, all of whom had been exposed to platinum), and 69% progressions were reported. The accrual was closed due to lack of activity. Median PFS was 1.7 months (95% confidence interval [CI] 1.57-1.83 months) and median OS, 3.1 months (95% CI 1.9-4.1)

In terms of toxicity, 6 patients (38%) experienced grade III toxicity, the most commonly reported being fatigue (25%), hyperbilirubinemia (19%), thrombocytopenia (13%), alkaline phosphatase increase (13%), dehydration (13%), and, hyponatremia (13%).

A phase I dose-escalation and dose-expansion clinical trial (NCT01286987) (28) studied the use of talazoparib (0.025-1.1 mg daily) in patients with advanced BRCAm as well as selected sporadic cancer. The primary endpoints consisted of ORR, PFS, best overall response, duration of response, SD and MTD. The secondary endpoints were SAEs and PK parameters.

Median prior regimens were 4 and 2 in the dose-escalation and in the two-part study, respectively. Thirteen advanced pancreatic patients (3 in the escalation part and 10 in the expansion cohort) were treated. The maximum tolerated dose (MTD) was 1 mg per day. In pancreatic cancer patients, ORR with 1 mg per day dose was 25.28% (2 partial responders, one carrying a BRCA2 mutation and the remaining one, a PALB2 mutation), with a CBR (SD lasting over 16 weeks) of 31%. Median PFS and duration of response were not released for pancreatic cancers. Most common grade 3-4 AE were anemia (23%), thrombocytopenia (18%), neutropenia (10%) and fatigue (3%).

Shroff et al, reported results of RUCAPANC (29), a phase II trial (NCT02042378, completed in 2016) in patients with locally advanced or metastatic pancreatic cancer with deleterious germline o somatic BRCA mutation, treated with rucaparib 600 mg twice daily as monotherapy after relapse or progression to one or two prior chemotherapy lines, no previous PARPi was allowed. The primary endpoint of this trial was ORR. Sixteen of the 19 patients borne a germline BRCAm and 3 had a somatic mutation. Regarding mutational type, 78.9% were BRCA 2 mutations. Previous platinum-based chemotherapy had been delivered in 78.9% of patients, and 42.1% of patients had progressed to platinum therapy. Response was seen in 3 of the last 4 patients recruited, accounting for an ORR of 15.8% (95% CI, 3.4% - 39.6%), with 2 PR and 1 a CR. Of note, ORR was 33.3% in those patients with only one prior line and 2 out of 3 tumors bearing a somatic mutation had a confirmed objective response. None of the four responding patients had experienced disease progression on prior platinum-based chemotherapy (one of them being platinum naïve). The disease control rate, which includes PR, CR or stable disease (SD) lasting more than 12 weeks, was 31.6% (6/19), increasing to 44.4% (4/9) in patients who had received just 1 chemotherapy regimen before the trial. As prespecified in the protocol, accrual was stopped due to absence of response after assessment of the first 15 recruited patients, with 13 of them presenting radiological or clinical progression, 2 discontinuing due to AEs, 1 having SD and 1 showing radiological progression. Most common Grade $\geq$ 3 AE were anemia (31.6%), fatigue (15.8%), and ascites (15.8%), with Grade $\geq$ 3 nausea, vomiting, abdominal pain, thrombocytopenia and transaminitis, being 10.5% each.

MAINTENANCE MONOTHERAPY TRIALS

Reiss et al. reported interim results of an ongoing phase II trial (NCT03140670) (30), assessing rucaparib (600mg bid) as maintenance therapy, in patients with metastatic pancreatic cancer and somatic or germline BRCA1/2 or PALB2 mutations, whose cancer had not progressed on or following at least four months of platinum-containing chemotherapy. Patients could also have received 2 prior lines of chemotherapy, but no other PARP inhibitor. The treatment was delivered until progression or unacceptable toxicity. The primary endpoint was ORR (RECIST 1.1 criteria) and the second endpoints consisted of PFS, DoR, and OS.

The interim analysis was presented in 2019, at the AACR (American Association for Cancer Research) Annual Meeting, with data cutoff as of December 31st 2018, having enrolled 24 patients of the 42 initially planned patients, 19 of whom were available for PFS assessment. Distribution by mutational type was 84%, 10.5% and 5.3% for BRCA1/2 germline mutations, PALB2 germline mutations and somatic BRCA 2 mutations, respectively.

The median PFS was 9.1 months from the start of rucaparib therapy. The estimated OS was not reached. With seven responding patients out of 19, the ORR was 36.8%, accounting for 6 PR and 1 CR. Disease control rate (CR + PR + SD lasting for at least eight weeks) was 89.5%. Eight patients had been on treatment for over 6 months and two patients remained on rucaparib for over a year (13 months and 15 months) (28).

The phase III POLO (31) (NCT02184195) was a randomized 3:2, double-blind, multicenter, international clinical trial, evaluating Olaparib (300 mg twice a day, tablets formulation, in 92 patients) versus placebo (62 patients), as maintenance therapy, starting 4-8 weeks after last chemotherapy cycle, in patients with germline BRCA-mutated metastatic pancreatic cancer, without progression on at least 16 weeks of first line platinum-containing chemotherapy regimen. The treatment was delivered until progression or unacceptable toxicity. Crossover was not permitted. The primary endpoint of this trial was Progression Free Survival (PFS), defined as the time from randomization until radiological disease progression or death. Secondary endpoints were Overall Survival (OS), Second Progression Free Survival (PFS2), Time to Second Subsequent Therapy (TSST), Time First Subsequent Therapy (TFST), Treatment Discontinuation Time (TDT), Objective Response Rate (ORR), Disease Control Rate (DCR), Quality of Life (QoL) and Adverse Events (AEs).

Roughly one-third and two third of patients carried BRCA1 and BRCA 2 mutations, respectively. Most commonly used chemotherapy regimen was FOLFIRINOX (86% and 81% in the olaparib and placebo group, respectively. With regard to PFS, Olaparib showed a significantly higher PFS versus placebo (7.4 versus 3.8 months, respectively; hazard ratio (HR): 0.53, 95% confidence interval [CI], 0.35 to 0.82; P=0.004), the percentage of patients alive after 6 months, being double in the Olaparib group. At an interim analysis, with data maturity of 46%, the analysis of OS showed no statistically significant difference (median, 18.9 months versus 18.1 months; HR, 0.91; 95% CI, 0.56 to 1.46; P=0.68), and the analysis of PFS2 differed from 13.2 versus 9.2 months (HR: 0.76) in favor of the olaparib group.

All in all, ORR was 20% in the Olaparib group and 10% in the placebo arm, with 2 patients in the Olaparib arm achieving a complete response (CR), both ongoing at the time of data cutoff. Response in the olaparib group was independent of response o stabilization to the first line platinum-based regimen. The median time until response was 5.4 and 3.6 months and the median duration of the response (DoR) was 24.9 and 14.8 months in the Olaparib and the placebo group, respectively. The median duration on treatment was 6.0 months (range, 0.8 to 45.3) and 3.7 months (range, 0.1 to 30.1) in the olaparib versus placebo group, respectively. Interestingly enough, 30 patients in the olaparib group versus 8 patients in the placebo group were still on treatment at the time of data cutoff. Nine patients (15%) in the placebo group went on to receive a PARP inhibitor after disease progression during the trial (8 olaparib, 1 rucaparib, 1 veliparib) (32).

Severe adverse events (grade 3-4) appeared in 24% of the Olaparib and in 15% in the Placebo patients, with anemia, asthenia and decrease appetite being the most common among olaparib patients. No grade 5 side effect was reported. Dose interruption, dose reduction and treatment discontinuation occurred in 35% vs 5%, 16% vs 3%, and 5% vs 2% in the olaparib versus placebo arm, respectively. There was no significant variation in global quality-of-life scale between both groups.

Table 3 summarizes the results of monotherapy trials by endpoint trial.

Pooled efficacy analysis could not have been carried out because of both, the immaturity of data of the rucaparib trial coupled with the fact that patients in that study could have had received up to two prior lines compared with the first line pf the POLO trial.

COMBINATION TRIALS

A dose-escalation trial followed by an dose-expansion phase I/II trial (NCT00515866), in patients with advanced solid tumors with olaparib in combination with gemcitabine, including locally advanced/metastatic pancreatic cancer, was reported in 2015 (33). In the capsule dose-escalation trial, patients with up to two prior chemotherapy lines were included. No prior chemotherapy was allowed in the tablet dose-escalation phase, nor in the expansion phase (capsule formulation only). Trial treatment during the escalation phase consisted of olaparib capsules (50-200 mg capsules, twice daily) continuously or intermittently (days 1-14 of a 28-day cycle) and Gemcitabine (600-800 mg/m^2 weekly for 3 weeks of a 4 weeks cycle) or olaparib tablets (100 mg daily, day 1-14) plus gemcitabine 600 mg/m^2, to establish the MTD. Once the suitable dose was determined, patients with locally advanced or metastatic pancreatic cancer, irrespective of mutational status, underwent an unblinded randomization, in a 2:1 ratio, to either the combination arm (Olaparib capsule + gemcitabine, at tolerated combination dose) or gemcitabine monotherapy (1000 mg/m^2).

The primary endpoint of this trial was to determine safety and tolerability, establishing MTD of Olaparib + Gemcitabine. Secondary endpoints were identification of DLT, assessment of antitumoral activity (ORR, PFS, OS and change of tumor size in percentage determined by imaging) and pharmacokinetics (PK) determination in the plasma of those patients treated with Olaparib and Gemcitabine, alone or in combination.

Table 3. Efficacy results with PARP inhibitor monotherapy in advanced pancreatic cancer

TRIAL TYPE AND REFERENCE	TREATMENT INTERVENTION	POPULATION TYPE	SIZE	PRIMARY ENDPOINTS	SECONDARY ENDPOINTS	OTHER OUTCOMES
PHASE II multicenter single arm trial. NCT01078662 (26)	Olaparib average of 2 prior lines Capsule formulation	gBRCAm APC BRCA1m: 21.7% BRCA2m: 73.9%	N = 23	ORR 21.7%, 4% CR and 17% PR All response in absence of progression on platinum	PFS 4.6m; OS 9.8m; > grade 3 Aes: Anemia (17.4%), Fatigue (13%), Vomiting (4%) and Abdominal Pain (4%).	Response Rate with prior platinum-based or non-platinum-based regimen NSS
PHASE II non-randomized trial (27)	Veliparib as 2nd or 3rd line	gBRCAm / PALB2 APC BRCA1m: 31%; BRCA2m: 69%	N = 16 64% progressed on platinum	ORR 0% 31% SD 25% long lasting	PFS 1.7m (95% CI 1.57-1.83); OS 3.1m (95% CI 1.9-1.4)	
PHASE I dose- escalation and dose-expansion NCT01286987 (28)	Talazoparib	g/s BRCAm /PALB2 APC	N = 13	ORR 25.28%, 2 PR. CBR 31%	Grade 3-4 AEs: Anemia (23%), Thrombocytopenia (18%), Neutropenia (10%) and Fatigue (3%).	No information on platinum resistance
PHASE II single arm NCT02042378 (29)	Rucaparib as 2nd or 3rd line	g/s BRCAm, APC (16g + 3s) BRCA2m: 78.9%	N = 19	ORR 15.8% (3/19), 2 PR and 1 CR		42.1% of patients had progressed to platinum therapy
PHASE II single arm NCT03140670 (30)	Rucaparib maintenance after 1st or 2nd CT line	g/s BRCAm 1/2 /PALB2 APC	N = 42planned, 24 enrolled, 19 available for ORR and PFS	ORR: 36.8% (7/19) 6 PR and 1 CR DCR 89.5%	PFS 9m (interim analysis, 19 p)	No progression or at least 4 months on platinum regimen
PHASE III randomized, double blind Polo trial. NCT02184195 (31)	Olaparib maintenance vs placebo, following first line platinum-based CT Tablet formulation	gBRCAm 1/2 APC BRCA1 m !/3 BRCA2m 2/3	N = 154 (olaparib: 92 p, placebo: 62 p)	PFS 7.4 vs 3.8 m, (HR): 0.53, 95% CI, 0.35 - 0.82	OS 18.9 vs 18.1 m, NSS (immature data) ORR 20% (2 CR) vs 10%	DOR 24.9 m (95% CI, 14.8-NC) vs 3.7 months (95% CI, 2.1 to NC)

APC: advanced pancreatic cancer; BRCAm: BRCA mutation; CT: chemotherapy; g: germline mutation; g/s: germline or somatic mutation; HR: hazard ratio; m: months; NC: could not be calculated; NSS: not statistically significant; ORR: overall response rate (complete response + partial response); OS: overall survival; p: patients; PFS: progression free survival;

In terms of safety, continuous dosing of olaparib capsules in combination with a gemcitabine dose >600 mg/m^2 was deemed to be non-tolerable following two DLTs [grade 3 neutropenia with persistent fatigue and grade 3 increased alanine aminotransferase (ALT)] in patients treated with continuous olaparib capsules 100 mg twice daily and gemcitabine 800 mg/m^2. Olaparib capsules (100 mg twice daily, day 1-14) plus gemcitabine 600 mg/m^2, was found to be the MTD in both phase of the trial. Overall, 81% of patients (38 out of 47) treated with olaparib capsule and gemcitabine reported grade ≥3 AEs, with twenty-nine patients (44%) reporting serious AEs (SAEs), the most common being dyspnea (14%), abdominal pain (10%), vomiting (10%) and deep vein thrombosis (10%). No SAEs was considered to be related to olaparib alone and 6 of the SAES were attributed to the combination Olaparib/Gemcitabine. There were 2 grade 5 SAEs in the combination arm, one due to neutropenic sepsis, being the other one secondary to bacterial peritonitis and renal failure.

The phase I clinical trial evaluated Olaparib in association with irinotecan, cisplatin, and mitomycin C in patients with advanced pancreatic cancer (NCT01296763) (34). The primary endpoint was to study the number of participants who experience Dose-Limiting Toxicities (DLT), in order to determine the Maximum Tolerated Dose (MTD) and the second endpoint was to analyze the number of years from cycle 1/ day 1 On-Study to date of death. The patients had to have an unresectable PDAC diagnosed in order to be eligible and a life expectancy greater than 12 weeks. The study did not exclude individuals without a BRCAm but prioritized Jewish individuals (about 6% cases carried a BRCAm), patients with familial pancreatic cancer (associated to HRR deficiencies) and patients with diagnosed BRCAm (n=2). There was no limit on the number of prior chemotherapy regimens allowed; however, treatment with a PARP inhibitor or more than one drug of the Irinotecan-Cisplatin-Mitomycin C (IMC) regimen was an exclusion criterion. This trial enrolled 18 patients in 6 different dose-escalations (-1 to 5). Dose level -1: Olaparib (50mg m2) on days 1 and 8 plus Irinotecan (70mg/m^2) and Cisplatin (25mg/m^2) (IC). Dose level 1 consisted of Olaparib (100 mg twice-daily) on days 1 and 8 plus IC, and enrolled six patients. Dose level 2: Olaparib on days 1-3 and 8-10 plus IC, enrolled six patients. Dose level 3: Olaparib (200 mg twice-daily) on days 1-3 and 8-10 plus IC. Dose level 4: Olaparib on days 1-12 and IC on days 1 and 8. Dose level 5: Olaparib (MTD from dose escalation -1 to 4) on days 1 and 8 plus ICM (5mg/m^2 on day 1), enrolled six patients. 22% of the enrolled patients discontinued treatment because of AEs, and 56% required a dose reduction or delay due to toxicity. 4 patients had to leave the study because of toxicity and 1 due to clinical progression, leaving 13 patients for the clinical activity evaluation. 3 patients had a PR (1 in dose level 5 and 1 in dose level 1) and there was no CR. ORR in the evaluated patients was 23% and the disease control rate was 62%. The 2 patients with a known BRCAm had a PR, one lasting 4 years and another lasting 3 months.

An Open-label, randomized, multicenter, two-arm phase II trial (NCT01585805) of first line gemcitabine (600 mg/m2) and cisplatin (25 mg/m2) with (arm A) or without (Arm B) veliparib (80 mg orally twice per day on days 1-12) in 21 day cycles, in patients with pancreas adenocarcinoma carrying germline *BRCA/PALB2* mutation, was reported in 2020.(35) No prior platinum agent or PARPi was allowed. The primary endpoint was ORR and the secondary end points were PFS, OS, disease control rate (DCR), safety, and correlative analyses.

Fifty patients were evaluated, with 27 patients (54%) in arm A, and 23 patients (46%) in arm B. Twelve (24%) harbored BRCA1 mutations, 35 (70%) carried BRCA2 mutations, and 3

(6%) tested positive for PALB2 mutations The ORR for the veliparib combination arm was 74.1% and 65.2% in the veliparib free group (P = 0.55); with both arms exceeding the prespecified activity threshold. DCR was 100% and 78.3% in the veliparib combination arm and the veliparib-free group, respectively (P = 0.02). Median PFS did not statistically differed between arms, with 10.1 months (95% CI, 6.7 to 11.5 months) and 9.7 months (95% CI, 4.2 to 13.6 months; P = .73), respectively. The same was true for median OS, being 15.5 months (95% CI, 12.2 to 24.3 months) and 16.4 months (95% CI, 11.7 to 23.4 months; P = 0.6), respectively. Exploratory analyses of patients who received 4 or more months of platinum-containing regimen and, in the absence of disease progression, continued or received a PARPi as the immediate next line of therapy. Ten patients, 8 with stage IV, combined from both trial arms, fulfilling those criteria, had a median OS of 23.4 months (95% CI, 6.5 to 53.9 months). Exploratory analyses by BRCA mutational type yielded a median PFS for BRCA1 (n = 12) of 6.8 months (95% CI, 2.8 to 10.1 months) and for BRCA2 (n = 35), 11.3 months (95% CI, 9.8 to 12.8 months). Median OS for BRCA1 was 14 months (95% CI, 8.1 to 18.5 months) and 20.2 months (95% CI, 12.3 to 24.4 months) for BRCA2.

Even though Arm A reported more myelotoxicity and more dose reductions, nonhematologic toxicities were similar in both arms. Grade 3 to 4 hematologic toxicities in veliparib-containing regimen compared with veliparib free group were as follows: neutropenia was seen in 13 participants (48%) versus seven (30%), thrombocytopenia in 15 (55%) versus two cases (9%), and anemia in 14 (52%) versus eight patients (35%).

Pishvaian and colleagues reported results of a single-arm, open-label Phase I/II study (NCT01489865) of veliparib along with infusional 5-FU and oxaliplatin (FOLFOX, no 5FU bolus) in patients with metastatic pancreatic cancer (mPDAC) (34). The dose escalation phase consisted of veliparib (40 mg-250 mg twice per day, for 7 days of a 14-day cycle), in order to identify the recommended dose for phase II part. Preselection criteria for the phase 2 part were either a pathogenic somatic or germline *BRCA1/2, PALB2, ATM* mutation, and/or a family history compatible with breast or ovarian cancer syndrome. The phase II part was divided into two cohorts, namely, treatment naïve patients or with those who had received prior treatment. When available, somatic or germline data were collected. The primary objective of the Phase II cohorts was the ORR with key secondary endpoints being median PFS and OS.

Thirty-one participants were enrolled in the dose escalation phase. The veliparib dose for FOLFOX combination was deemed to be 200 mg twice daily. Additional 33 participants were included in the phase II part, 15 treatment-naïve and 18 pretreated, with 78% of patients being platinum-naïve. 69% of participants had family history and 27%, a known HR-DDR mutation. The ORR was 26%, with heightened activity in platinum-naïve participants (33%) as well as in those carriers of a pathogenic HR-DDR mutation (50%), achieving an ORR 57% when both criteria were met. Overall, the median PFS and median OS were 3.7 and 8.5 months, respectively. Most frequently observed grade 3-4 AE were hematologic toxicity (16%) and nausea/vomiting (6%).

Table 4 displays the retrieved results from the combination trials included in this systematic review, showing clinical trial type and reference, treatment intervention, population type, primary and secondary endpoints, and other outcomes, when available.

Table 4. Efficacy results with PARP inhibitor in combination therapy in advanced pancreatic cancer

TRIAL TYPE AND REFERENCE	TREATMENT INTERVENTION	POPULATION TYPE	SIZE	PRIMARY ENDPOINTS	SECONDARY ENDPOINTS	OTHER OUTCOMES
PHASE I dose-escalation and dose-expansion two arm trial. NCT00515866 (33) Capsule and table formulation	Olaparib + Gemcitabine (arm A) vs Gemcitabine alone (arm B); After 1st or 2nd CT line (capsule dose-escalation); No prior CT in tablet phase.	Locally advanced/metastatic PC Irrespective of mutational status	N = 46 (dose-escalation) and N = 23 (dose-expansion)	MTD: Olaparib (100mg twice daily) + Gemcitabine (600mg/m^2) Capsule formulation	Dose-escalation: ORR 10%; Dose-expansion 27% (arm A) and 14% (arm B). 81% (arm A) grade >3 AEs, 44% SAEs.	**Prolongs PFS and OS in BRCAm patients**
PHASE I dose-escalation NCT01296763 (34)	Olaparib + irinotecan + cisplatin + mitomycin C No limit prior lines	Unresectable PDAC Irrespective mutational status, prioritizing Jews, family history and BRCAm	N = 18	ORR 23% (13 evaluable patients)		
PHASE II two-arm randomized trial. NCT01585805 (35)	Gemcitabine + Cisplatin + Veliparib (arm A) vs Gemcitabine + Cisplatin (arm B); No prior platinum agent allowed	gBRCAm (47p)/ PALB2 (3p), PDAC	N = 50 (arm A: 27p, arm B: 23p)	ORR arm A 74.1%, arm B 65.2%; Non hematologic toxicities similar in both arms; Arm A more dose reductions and myelotoxicity	DCR 100% (A)/ 78.3% (B); PFS and OS NSS; PFS BRCA1 6.8m / BRCA2 12.8m; OS BRCA1 14m / BRCA2 20.2m	
PHASE I/II one-arm trial. NCT01489865 (36)	Veliparib + infusional 5-FU and Oxaliplatin (FOLFOX)	g/s BRCAm/ PALB2/ ATM…, metastatic PDAC	N = 31	MTD (phase I): Veliparib 200mg twice daily ORR (Phase II) 26% (50% in mutated)	PFS 3.7m; OS 8.5m; Grade >3 AEs: hematological toxicity (16%) and nausea/vomiting (6%)	ORR heightened in naïve-treatment group (33%) and in HR-DDRm (50%)

PC: pancreatic cancer; PDAC: pancreatic ductal adenocarcinoma BRCAm: BRCA mutation; CT: chemotherapy; g: germline mutation; g/s: germline or somatic mutation; HR: hazard ratio; m: months; ORR: overall response rate; MTD: maximum tolerated dose; DCR: disease control rate; AEs: adverse events; SAEs: serious AEs; OS: overall survival; p: patients; PFS: progression free survival;

SIDE-EFFECTS ASSOCIATED WITH PARP INHIBITORS

Despite the clinical benefits of PARP inhibitor therapy, undesirable side effects do occur during treatment. Even though they are flavors of the same class drug, each molecule has its own nuances as far as side effects are concerned.

From all studies included in this systematic review, toxicities associated with each treatment have been extracted, as specified in the protocol. Four agents have been assessed in the monotherapy trials in this systematic review (olaparib, veliparib, rucaparib and talazoparib). Results are displayed trough Figures 4-7, by monotherapy agent showing the highest toxicity level as well as its percentage.

Figure 4 - AEs Olaparib

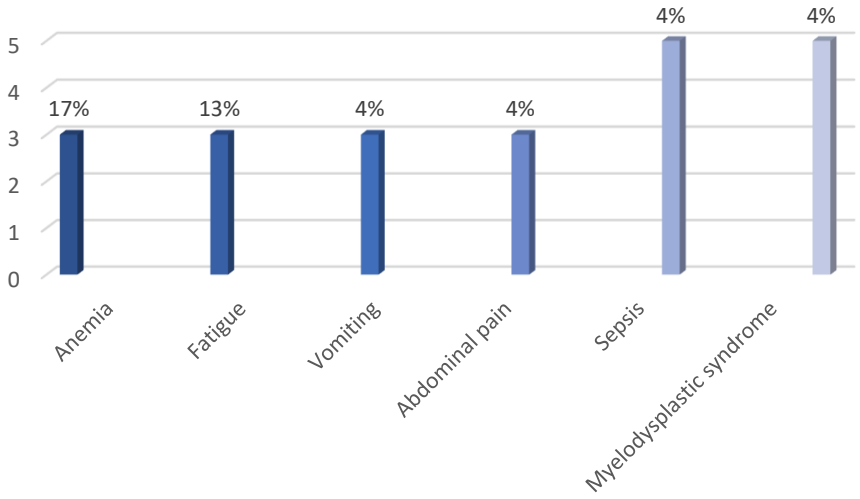
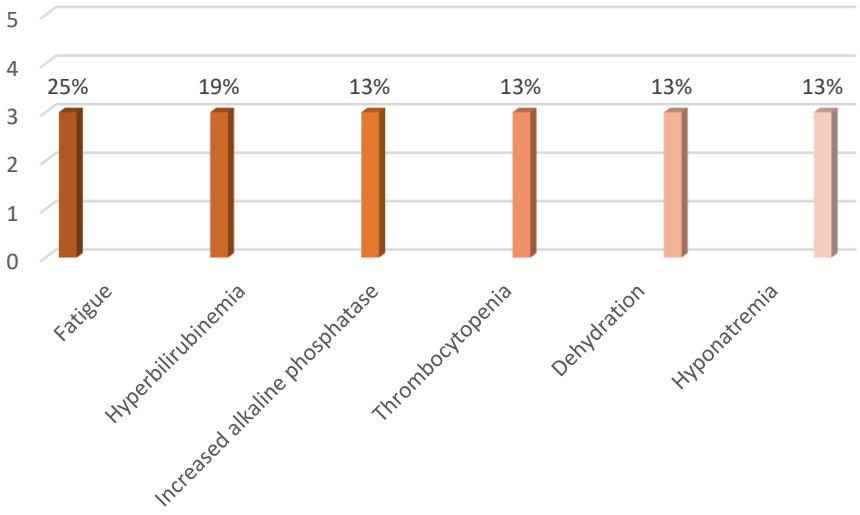
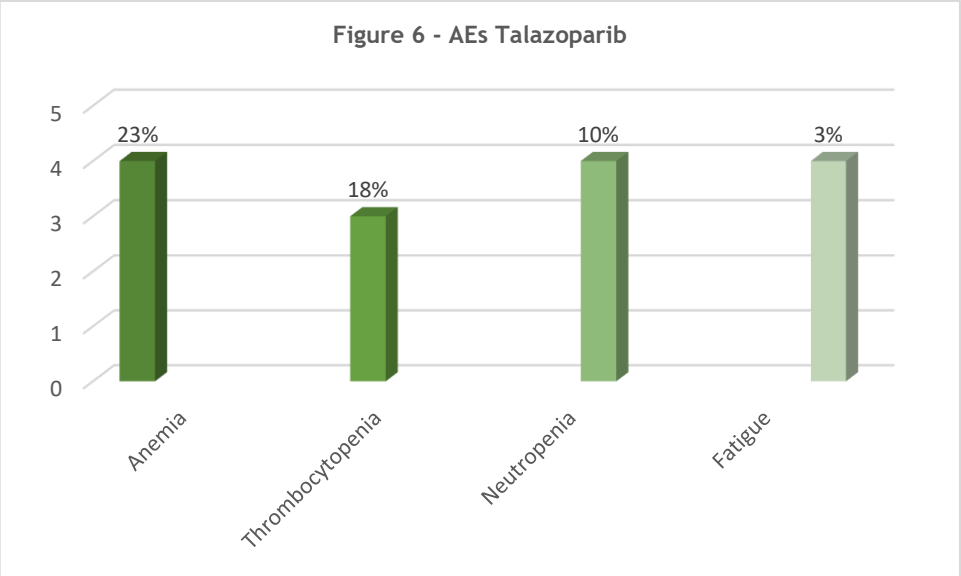
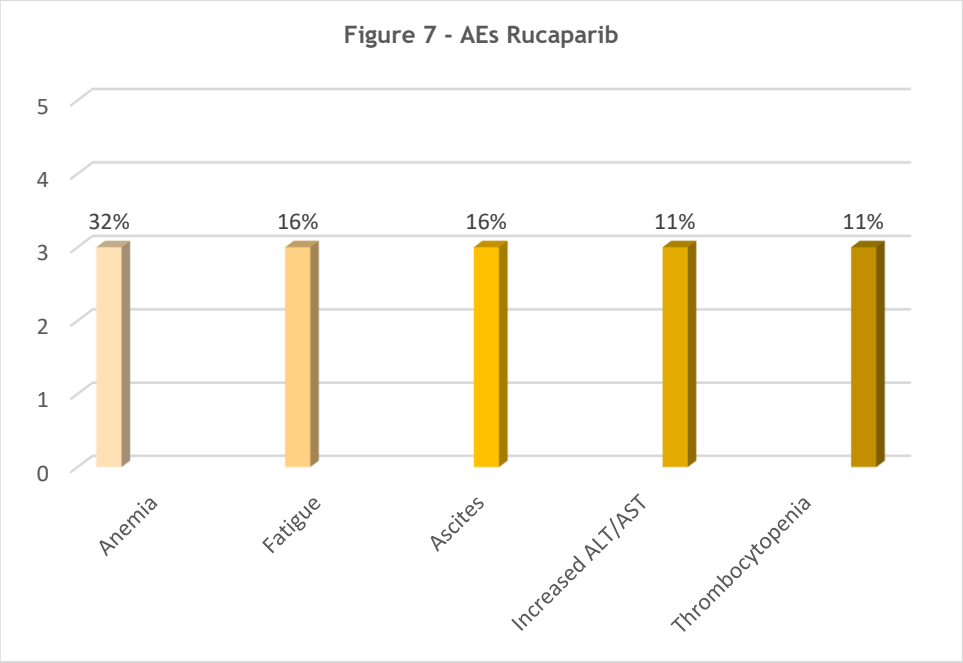


Figure 5 - AEs Veliparib







Figures 4-7 show most common side effects and grades reported in the different trials grouped by agents, when available. Each diagram shows the most frequent adverse effects, as well the most severe, reported in the trials and grouped by drug.

DISCUSSION

Treatment for advanced PDAC is continuously evolving and increasingly being guided by genomic analysis and identification enriched subtypes which can benefit from a specific treatment strategy; with HR-DDR being a prime example in PDAC. As such, PARP inhibitors

have been tested in advanced PDAC with diverse inclusion criteria, most focusing in BRCA 1 / 2, HR-DDR deficient tumors, not only as monotherapy but also in combination strategy.

Germline *BRCA* mutations, inherited in an autosomal dominant fashion, do not always translate into cancer, i.e. if they are incompletely penetrant. *BRCA1 and BRCA2* I are estimated to convey a 2-4-fold, and 3- to 8-fold increase, respectively, in the risk of PDAC development (37).

Monotherapy results with PARPi as second or further lines has yielded modest results (26–29) and response based on sensitivity to prior platinum treatment has yielded opposite results, with no response in platinum-refractory disease in a rucaparib monotherapy trial (29) and no difference in ORR stratified by prior platinum therapy in olaparib monotherapy trial, albeit acknowledging the fact that all responses occurred in patients who had not progressed on prior platinum regimen (26). Lowery and colleagues reporting results with veliparib single agent showed no objective responses, suggesting that its effectiveness not as maintenance but rather as true monotherapy line is inadequate in late lines, at the studied dose and schedule (27).

It was not until population selection through platinum sensitivity and the use of PARPi as immediate maintenance treatment in non-progressors, as compared with second or further lines upon progression, that clinical significant benefit begun to emerge (30,31).

Interestingly enough, the need of and subsequent choice of the platinum regimen is matter of debate. PDAC arising in the setting of a BRCA mutation are thought to show increased sensitivity to platinum compounds, such as cisplatin and oxaliplatin, due to induced double-strand breaks and secondary inability to repair those because of ineffective BRCA-associated DNA repair. Nonetheless, no randomized trials comparing platinum versus nonplatinum-based regimens in this PDAC subgroup have been published to date. Superior OS was reported in a retrospective cohort of patients with advanced BRCA-mutated PDAC who received platinum-based therapy (22 patients) compared with 21 patients treated with nonplatinum regimen (22 vs 9 months, respectively; $p = 0.04$), although the retrospective nature of the study must be kept in mind (38). Smaller series have reported similar outcomes with platinum agents (39,40). A systematic review and metanalysis on this subject concluded in the need of further investigation with randomized trials in homogenous clinical settings (41).

Impressed by the exceedingly good result of the randomized phase II veliparib trial, with 2-year (30.6%) and 3-year (17.8%) survival rates of the entire cohort, among the longest reported in any randomized trial in PDAC to date, one could be prone to establish cisplatin-gemcitabine as the new standard in BRCAm PDCA (35). However, gemcitabine plus cisplatin did not show statistical OS improvement over gemcitabine monotherapy in similar phase III trials (42,43), albeit not being HDDR-selected population. As a consequence, in absence of randomized, prospective trials comparing different platinum-based chemotherapies, it is unknown whether FOLFIRINOX, a standard platinum-based first line regimen in advanced PDAC, can be safely replaced by less toxic regimens such as gemcitabine with cisplatin or FOLFOX (with irinotecan omission), with subsequent toxicity reduction while maintaining efficacy, in BRCA-mutated patients.

The impressive ORR results by O'Reilly et al trial are of particular importance in the locally advanced irresectable setting, where cytoreduction could lead to potentially beneficial salvage surgery, another subject matter of debate which would need randomization (44).

As far as combination treatment is concerned, association between PARP inhibitors and chemotherapy not only do not appear to increase efficacy but increases toxicity, mainly hematologic, with death related to infection due to myelotoxicity.

PARP inhibitors are not devoid of AE, with the AE profile of maintenance being similar to that reported in other tumor types. Most commonly reported AE were myelotoxicity and fatigue across all studied agents, similar to chemotherapy.

Myelodysplastic Syndrome, another feared AE, has been inconsistently related to PARP inhibitors, frequently in the context of heavily pretreated patients.

Maintenance treatment with PARP inhibitors are aimed to prolong PFS, and ideally OS, without impairment in quality of life, with maintenance being a new concept in PDAC. Of interesting note, responses can be slow and take months to occur (30). However, a subset of patients with advanced PDAC performed exceptionally well with platinum-based chemotherapy, with prolong period on treatment, although allergic reactions with increasing cycles as well as neurotoxicity are the rule of thumb, so toxicity must be taken into account when it comes to maintenance treatment choice.

Ultimately, patients progressed on PARP inhibitors due to secondary resistance. Several mechanisms of PARP resistance in *BRCA1/2*-m tumors have been proposed, such as stabilization of mutant protein, genetic reversion of truncating mutations in *BRCA1* or *BRCA2*, presence of hippomorphic *BRCA1* or *BRCA2* function (including *BRCA1* C61G mutation), and loss of *53BPI* (43–46).

When compared with ovarian cancer trials, results with maintenance PARPi are much less impressive in pancreatic cancer, with fewer long-term responders, probably due to their different tumor microenvironment, with fibrosis outnumbering cancer cell in pancreatic cancer (accounting of 90 to 95% of the tumor bulk) and the fact that PARPi have no effect on tumor microenvironment. That could be a plausible explanation for the different results achieved when addressing the same altered pathway, in which the microenvironment and/or other site-specific features could ultimately module efficacy. The predominance of BRCA2 mutations over BRCA1 mutations in pancreatic cancer (the reverse situation to that of ovarian cancer) do not seem to influence results, since the response rate and efficacy do not differ between the two.

As far are side effects are concerned, a review of side effects in different PARPi (45) displayed that a very common side effect of PARP inhibitors are hematological toxicities. These effects, occur promptly after starting treatment and disappear after a few months. Anemia is the most common and severe AE in this group, being the percentage of patients affected higher in the niraparib trials than in the other PARPi and leading to dose reduction or even discontinuation. Thrombocytopenia and neutropenia (second and third most common AEs in this group) are also more common with Niraparib.

Gastrointestinal AEs (45) are seeing commonly on PARPi, with nausea being the main one. This side effect is prevented with prophylaxis or treated with daily prokinetic and antihistamine, in order to reduce the symptoms. Other frequent gastrointestinal symptoms reported by patients are constipation, vomiting, and diarrhea. Fatigue is an almost universal toxicity for all PARPi and is thought of as a class effect. Most of the patients show a mild grade of fatigue which can be prevented by exercise, massage therapy, etc. Increased cholesterol levels and serum aminotransferase are some of the abnormalities found in laboratory tests, being this last one mostly self-limiting and not associated to other liver toxicity signs. Increased in creatinine levels, or other renal toxicities have been reported as well, mostly seen with Rucaparib and Veliparib.

Less common toxicities are emerging as the use of PARPi is growing. Neurological, such as headaches and insomnia, as well as respiratory, cardiovascular (hypertension, tachycardia, etc.), musculoskeletal and cutaneous have been observed. These are rare events, and some, like the cardiovascular toxicities, linked mostly to Niraparib, an agent not been tested in PC. The literature also describes "secondary malignancies" like myelodysplastic syndrome and acute myeloid leukemia, which are severe adverse events that have a high impact on the patient's life and usually lead to discontinuation of the treatment.

A study by Berek et al. published results in 2018 comparing AEs in Niraparib vs Placebo (46). It showed that the use of Niraparib led to more dose modifications, more hematological side effects in the first months of treatment. Some side effects were dose related, but others had similar grades of toxicity with a different PARPi dose. In this study a low baseline platelet counts and baseline body weight (<58 kg) were determined risk factors for severe thrombocytopenia and other serious AEs.

WAYS OF IMPROVEMENT

Results from undergoing early phase trials of drug development targeting DDRP targets other than PARP (e.g., MK1775 for *WEE-1,* AZD0156 for *ATM*, LY2603618 for *CHK1*, and), are awaited.

High stromal infiltration is a hallmark of PC, where neoplastic cells account for only 5%-20% of the tumor bulk. Developing a strategy to address PC microenvironment might improve results. A randomized phase II trial of niraparib with immunotherapy (either antiCTLA4 agent ipilimumab or anti-PD1 nivolumab in advanced PC patients not progressing on platinum based regimen is ongoing (47)

CONCLUSION

PARPi showed significant activity in terms of prolonged PFS when used as maintenance strategy in BRCAm advanced PDAC patients, with some sporadic long-lasting survival. Nonetheless, progression rapidly occurred in the majority of cases, secondary to the development of resistance pathways as well as to the strong microenvironment influence in PC. Further studies are underway to circumvent these issues.

ACKNOWLEDGEMENTS

First and foremost, I have to thank my cotutor Dr. María José Villanueva Silva. Without her assistance, knowledge and dedication in every step of the process, this systematic review would never have been accomplished.

I would also like to acknowledge my tutor Dr. J. Enrique Domínguez Múñoz, for his support with this work, and I am very grateful for his invaluable wisdom.

I also want to show my gratitude to Yolanda Sanmartín, for her helping hand throughout the research and process.

I take this opportunity to express my appreciation to all of the Department faculty members for their impact and teaching in the last six years. It is my privilege to also thank my parents, my partner and my friends for the unceasing encouragement and support throughout my years of study and through the process of researching and writing this systematic review.

Lastly I would like to place on record my sense of gratitude to one and all, who directly or indirectly, have lent their hand in this work, highlighting the Alvaro Cunqueiro Hospital (Vigo) who opened its doors and whose employees have always been ready to lend a helping hand.

REFERENCES

1. Carbone A. Cancer Classification at the Crossroads. Cancers. 2020 Apr 15;12(4):980.
2. Offin M, Liu D, Drilon A. Tumor-Agnostic Drug Development. Am Soc Clin Oncol Educ Book Am Soc Clin Oncol Annu Meet. 2018 May 23;38:184–7.
3. Collisson EA, Bailey P, Chang DK, Biankin AV. Molecular subtypes of pancreatic cancer. Nat Rev Gastroenterol Hepatol. 2019 Apr;16(4):207–20.
4. Iacobuzio-Donahue CA, Ryu B, Hruban RH, Kern SE. Exploring the Host Desmoplastic Response to Pancreatic Carcinoma. Am J Pathol. 2002 Jan;160(1):91–9.
5. Wood LD, Hruban RH. Pathology and Molecular Genetics of Pancreatic Neoplasms: Cancer J. 2012;18(6):492–501.
6. The Cancer Genome Atlas Program - National Cancer Institute [Internet]. [cited 2021 Mar 28]. Available from: https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga
7. Raphael BJ, Hruban RH, Aguirre AJ, Moffitt RA, Yeh JJ, Stewart C, et al. Integrated Genomic Characterization of Pancreatic Ductal Adenocarcinoma. Cancer Cell. 2017 Aug;32(2):185-203.e13.
8. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. 2005;434:6.
9. Li ML, Greenberg RA. Links between genome integrity and BRCA1 tumor suppression. Trends Biochem Sci. 2012 Oct;37(10):418–24.
10. Watkins JA, Irshad S, Grigoriadis A, Tutt AN. Genomic scars as biomarkers of homologous recombination deficiency and drug response in breast and ovarian cancers. Breast Cancer Res. 2014 Jun;16(3):211.
11. Rottenberg S, Jaspers JE, Kersbergen A, van der Burg E, Nygren AOH, Zander SAL, et al. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. Proc Natl Acad Sci. 2008 Nov 4;105(44):17079–84.
12. Ashworth A. A Synthetic Lethal Therapeutic Approach: Poly(ADP) Ribose Polymerase Inhibitors for the Treatment of Cancers Deficient in DNA Double-Strand Break Repair. J Clin Oncol. 2008;26(22):3785–90.
13. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2019 Dec 19;381(25):2391–402.
14. Moore K, Colombo N, Scambia G, Kim B-G, Oaknin A, Friedlander M, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2018 Dec 27;379(26):2495–505.
15. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016 Dec;375(22):2154–64.
16. Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017 Sep 1;18(9):1274–84.
17. Dal Molin GZ, Omatsu K, Sood AK, Coleman RL. Rucaparib in ovarian cancer: an update on safety, efficacy and place in therapy. Ther Adv Med Oncol. 2018 Jan 1;10:175883591877848.

18. Burki TK. Veliparib for advanced ovarian cancer. Lancet Oncol. 2019 Nov 1;20(11):e616.
19. Robson M, Im S-A, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation. N Engl J Med. 2017 Aug 10;377(6):523–33.
20. Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee K-H, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation. N Engl J Med. 2018 Aug 23;379(8):753–63.
21. Hussain M, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2020;383(24):2345–57.
22. Thierry C, Françoise D, Marc Y, Olivier B, Rosine G, Yves B, et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. N Engl J Med. 2011;9.
23. Australian Pancreatic Cancer Genome Initiative, Bailey P, Chang DK, Nones K, Johns AL, Patch A-M, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 2016 Mar;531(7592):47–52.
24. Australian Pancreatic Cancer Genome Initiative, Waddell N, Pajic M, Patch A-M, Chang DK, Kassahn KS, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015 Feb;518(7540):495–501.
25. Heeke AL, Pishvaian MJ, Lynce F, Xiu J, Brody JR, Chen W-J, et al. Prevalence of Homologous Recombination–Related Gene Mutations Across Multiple Cancer Types. JCO Precis Oncol. 2018 Nov;(2):1–13.
26. Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmaña J, et al. Olaparib Monotherapy in Patients With Advanced Cancer and a Germline *BRCA1/2* Mutation. J Clin Oncol. 2015 Jan 20;33(3):244–50.
27. 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 Jan;89:19–26.
28. de Bono J, Ramanathan RK, Mina L, Chugh R, Glaspy J, Rafii S, et al. Phase I, Dose-Escalation, Two-Part Trial of the PARP Inhibitor Talazoparib in Patients with Advanced Germline *BRCA1/2* Mutations and Selected Sporadic Cancers. Cancer Discov. 2017 Jun;7(6):620–9.
29. 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 Precis Oncol. 2018 Nov;(2):1–15.
30. Binder KAR, Mick R, O'Hara M, Teitelbaum U, Karasic T, Schneider C, et al. Abstract CT234: A Phase II, single arm study of maintenance rucaparib in patients with platinum-sensitive advanced pancreatic cancer and a pathogenic germline or somatic mutation in BRCA1, BRCA2 or PALB2. Cancer Res. 2019;79(13 Supplement):CT234–CT234.
31. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Maintenance Olaparib for Germline *BRCA* -Mutated Metastatic Pancreatic Cancer. N Engl J Med. 2019 Jul 25;381(4):317–27.
32. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Maintenance Olaparib for Germline *BRCA* -Mutated Metastatic Pancreatic Cancer. N Engl J Med. 2019 Jul 25;381(4):317–27.
33. Bendell J. Phase I study of olaparib plus gemcitabine in patients with advanced solid tumours and comparison with gemcitabine alone in patients with locally advanced/metastatic pancreatic cancer. Ann Oncol. 2015;26(4):8.

34. Yarchoan M, Myzak MC, Iii BAJ, Jesus-Acosta AD, Le DT, Jaffee EM, et al. Olaparib in combination with irinotecan, cisplatin, and mitomycin C in patients with advanced pancreatic cancer. :9.
35. O'Reilly EM, Lee JW, Zalupski M, Capanu M, Park J, Golan T, et al. Randomized, Multicenter, Phase II Trial of Gemcitabine and Cisplatin With or Without Veliparib in Patients With Pancreas Adenocarcinoma and a Germline BRCA/PALB2 Mutation. J Clin Oncol. 2020;38(13):1378–88.
36. Pishvaian MJ, Wang H, Zhuang T, He AR, Hwang JJ, Hankin A, et al. A phase I/II study of ABT-888 in combination with 5-fluorouracil (5-FU) and oxaliplatin (Ox) in patients with metastatic pancreatic cancer (MPC). J Clin Oncol. 2013;31(4_suppl):147–147.
37. Pilarski R. The Role of BRCA Testing in Hereditary Pancreatic and Prostate Cancer Families. Am Soc Clin Oncol Educ Book. 2019;(39):79–86.
38. 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 Sep;111(6):1132–8.
39. 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. The Oncologist. 2011 Oct;16(10):1397–402.
40. 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 [Internet]. 2015;26(2). Available from: https://journals.lww.com/anti-cancerdrugs/Fulltext/2015/02000/Clinical_outcomes_in_pancreatic_adenocarcinoma.10.aspx
41. Rebelatto TF, Falavigna M, Pozzari M, Spada F, Cella CA, Laffi A, et al. Should platinum-based chemotherapy be preferred for germline BReast CAncer genes (BRCA) 1 and 2-mutated pancreatic ductal adenocarcinoma (PDAC) patients? A systematic review and meta-analysis. Cancer Treat Rev [Internet]. 2019 Nov 1 [cited 2021 Jan 3];80. Available from: https://doi.org/10.1016/j.ctrv.2019.101895
42. Heinemann V, Quietzsch D, Gieseler F, Gonnermann M, Schönekäs H, Rost A, et al. Randomized Phase III Trial of Gemcitabine Plus Cisplatin Compared With Gemcitabine Alone in Advanced Pancreatic Cancer. J Clin Oncol. 2006;24(24):3946–52.
43. Colucci G, Labianca R, Di Costanzo F, Gebbia V, Cartenì G, Massidda B, et al. Randomized Phase III Trial of Gemcitabine Plus Cisplatin Compared With Single-Agent Gemcitabine As First-Line Treatment of Patients With Advanced Pancreatic Cancer: The GIP-1 Study. J Clin Oncol. 2010;28(10):1645–51.
44. Fazio N. Cisplatin Plus Gemcitabine as Standard of Care for Germline BRCA/PALB2-Mutated Pancreatic Adenocarcinoma: Are We Moving Too Fast? J Clin Oncol. 2020;38(21):2466–7.
45. LaFargue CJ, Dal Molin GZ, Sood AK, Coleman RL. Exploring and comparing adverse events between PARP inhibitors. Lancet Oncol. 2019 Jan;20(1):e15–28.
46. Berek JS, Matulonis UA, Peen U, Ghatage P, Mahner S, Redondo A, et al. Safety and dose modification for patients receiving niraparib. Ann Oncol. 2018 Aug;29(8):1784–92.
47. Reiss KA, Mick R, O'Hara MH, Teitelbaum UR, Karasic TB, Schneider CJ, et al. A randomized phase II trial of niraparib plus either nivolumab or ipilimumab in patients with advanced pancreatic cancer whose cancer has not progressed on platinum-based therapy. J Clin Oncol. 2019;37(15_suppl):TPS4161–TPS4161.

APPENDIX

Prospero like protocol according to PRISMA guidelines

ADMINISTRATIVE INFORMATION

Tittle	Systematic review on PARP inhibitors in advanced pancreatic cancer.
Registration	The protocol of this systematic review will not be recorded.
Authors	Lara Silvana González Diéguez supervised by the cotutor, María José Villanueva Silva.
INTRODUCCTION	
Rationale	PARP is a family of nuclear enzymes which contribute to single strand DNA repair. The PARP inhibitors bind to the PARP-DNA complex preventing DNA repair, leaving cells prone to double strand breaks. Tumors with BRCA mutations, such as a subgroup of pancreatic cancer, are unable to repair double strand breaks, being therefore good candidates to PARP inhibitors, to achieve tumor control.
Objectives	To perform a systematic review of clinical trials to identify and summarize all available evidence with PARP inhibitors in BRCA mutated or other homologous recombination deficiency (HRD) in advanced pancreatic cancer.
METHODS	
Eligibility criteria	Inclusion criteria will be clinical trials with PARP inhibitors that include BRCA mutated and HRD in advanced pancreatic cancer patients, published in abstract form or as a research article between January 2010 and December 2020. There will be no restrictions on the language used in the publication.
Information sources	An electronically search will be performed in PubMed, Embase, Clinicaltrials.gov, Web of Science for articles as well as ASCO and ESMO meeting database for abstracts. ClinicalTrail.gov website was also scrutinized for trials.
Search strategy	Search strategy will include a combination of broad terms related to pancreatic cancer, carcinoma and PARP inhibitors, clinical trial, BRCA, HRD, olaraprib, niraparib, rucaparib, veliparib, talazoparib.
Exclusion criteria	Exclusion criteria will be: (i) patients with no advanced/recurrent pancreatic cancer, (ii) clinical trials with BRCA or HRD tumors reported, (iii) studies that matched different databases, (iv) completed trials with no published results, (v) ongoing trials with no published results, (vi) case reports, narrative reviews, editorials, news articles, commentaries or letters.

DATA

Data items	For each included study we will extract the following data: number of patients enrolled, design, type of trial, stage, median participant age, performance status, sample size, type of PARP inhibitor used, other drugs if applied, primary outcome, secondary outcome, objectives, median follow-up, response type (complete response, partial response, progression or stable disease), overall response rate (ORR) (partial (PR) plus complete response rate (CR)), clinical benefit rate (CBR), duration of response, time to progression (TTR), progression free survival (PFS), overall survival (OS) and toxicity.