



HAL
open science

Targeting DNA repair in combination with radiotherapy in pancreatic cancer: A systematic review of preclinical studies

Waisse Waissi, Adrien Paix, Anaïs Nicol, Georges Noël, Hélène Burckel

► To cite this version:

Waisse Waissi, Adrien Paix, Anaïs Nicol, Georges Noël, Hélène Burckel. Targeting DNA repair in combination with radiotherapy in pancreatic cancer: A systematic review of preclinical studies. *Critical Reviews in Oncology/Hematology*, 2020, 153, pp.103060 -. 10.1016/j.critrevonc.2020.103060 . hal-03491443

HAL Id: hal-03491443

<https://hal.science/hal-03491443v1>

Submitted on 22 Aug 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Targeting DNA repair in combination with radiotherapy in pancreatic cancer: a systematic review of preclinical studies

Waisse Waissi^{a,b} (Conceptualization) (Investigation) (Writing original draft), Adrien Paix^b (Data curation) (Writing-review & editing), Anaïs Nicol^a (Writing-review & editing) (Visualization), Georges Noël^{a,b,c,d} (Writing-review & editing) (Validation), Hélène Burckel^{a,*} (Conceptualization) (Supervision) (Writing-review & editing) (Validation)

^a Université de Strasbourg, Institut de Cancérologie de Strasbourg, Centre Paul Strauss, 3 rue de la porte de l'Hôpital, 67000 Strasbourg, France

^b Department of Radiotherapy, Institut de Cancérologie Strasbourg, 17 rue Albert Calmette, 67200 Strasbourg, France

^c Université de Strasbourg, CNRS, IPHC UMR 7178, 23 rue du Loess, 67200 Strasbourg, France

^d Université de Strasbourg, Faculté de Médecine de Strasbourg, 4 rue Kirschleger, 67000 Strasbourg, France

* **Corresponding author** at : Université de Strasbourg, Institut de Cancérologie de Strasbourg, Centre Paul Strauss, 3 rue de la porte de l'Hôpital, 67065 Strasbourg Cedex, France, Helene Burckel E-mail address :h.burckel@icans.eu

Keywords Radiotherapy, pancreatic cancer, inhibitors, targeted therapy, DNA repair, radiosensitization

Abstract:

Background: Current research that combines radiation with targeted therapy may dramatically improve prognosis of pancreatic ductal adenocarcinoma (PDAC). We investigated preclinical outcomes of DNA repair inhibitor targeted therapy associated with radiotherapy.

Methods: We searched Pubmed database to identify publications assessing DNA damage targeted therapies in preclinical models of PDAC *in vitro* and *in vivo*. Standard enhancement ratio, median survival and growth delay were extracted.

Results: We identified fourteen publications using DNA repair targeted therapies in preclinical models of PDAC. Ten publications comprising twenty-eight experiments evaluated radiosensitization with different DNA repair inhibitors *in vitro* and displayed cell killing by a factor of 1.35 ± 0.047 . Moreover, 86% (24/28) of *in vitro* experiments showed radiosensitization with DNA damage response inhibitor. However, only 60% (9/15) of the *in vivo* experiments presented radiosensitization effects.

Conclusion: DNA repair targeted therapies use promising radiosensitizers for PDAC and could successfully be translated into clinical trials.

Introduction:

Pancreatic cancer has one of the highest mortality rates among carcinomas. Chemoradiotherapy (CRT) of pancreatic cancer enables unresectable tumors to be resectable and can improve outcomes. Pancreas is an abdominal gland surrounded by many radiosensitive organs such as small bowel, kidneys and liver. Nowadays, delivering appropriate dose to the tumor while minimizing dose to normal tissue is mainly possible, using modern techniques of radiotherapy such as intensity modulated radiotherapy (IMRT) or stereotactic body radiotherapy (SBRT). Another way to optimize cancer cell killing and reduce adverse events to normal tissue is based on the development of targeted radiosensitizers. Targeted therapy differs from chemotherapy as it interferes with a key pathway in tumoral progression, whereas chemotherapy acts on cell growth/division. In the era of personalized medicine, association between radiotherapy and targeted therapy could offer a new perspective for patients with pancreatic cancer. Recently, interest has focused on the understanding of molecular and biological nature of pancreatic cancer (Falasca et al., 2016). Over the last few years, several studies have delivered a large and complete genetic analysis of pancreatic cancers. Indeed, key oncogenes (K-Ras) and tumor suppressor genes (CDKN2A, TP53, SMAD4 and BRCA2) are highly mutated in pancreatic ductal adenocarcinoma (PDAC) and appear early in the tumoral progression involving cell proliferation, differentiation and survival (Witkiewicz et al., 2015). DNA repair has become a major topic of investigation for the treatment of cancer. Mutations involving DNA repair pathways occur in almost 40% of PDAC, as it has recently been confirmed in a whole-exome sequencing study from micro-dissected PDAC cases associated with outcome data (Witkiewicz et al., 2015). Authors observed a high frequency of mutations and deletions in genes that interfere with DNA damage maintenance, such as multiple Fanconi Anemia genes (ATM, CHEK2, BRCA1 and BRCA2). The key determinant of cellular radiosensitivity is

based on the capacity of cells to repair highly lethal DNA double-strand breaks. Therefore, targeting proteins involved in DNA damage response to ionizing radiation may be an appropriate alternative strategy. Indeed, a recent whole-genome sequencing study assessing structural variations among pancreatic cancers identified four structural variations based on translocations, copy number variations, deletions and amplifications (Waddell et al., 2015). Tumors with an “unstable” subtype were harbouring BRCAness signature with BRCA1/2 or PALB2 deleterious mutations and were sensitive to platinum-based therapy. Radiosensitivity is highly depend on the capacity of cells to repair DNA damages and using agents that inhibit DNA repair may enhance number and/or complexity of strand breaks, leading to cell death. Therefore, the goal of the present systematic review was to retrieve publications regarding *in vitro* and *in vivo* assessments of DNA repair targeted therapies used as radiosensitizers for pancreatic cancer (2007–2020). We aimed to investigate whether *in vitro* and *in vivo* combination of DNA repair targeted therapy with irradiation are affected by types of targeted therapies and/or by types of cell lines.

Materials and methods:

1. Data sources and study selection. PubMed database was searched with the following search string: "Pancreatic cancer"[All Fields] AND ("radiosensitization"[All Fields] OR "chemoradiation"[All Fields] OR "radiochemotherapy"[All Fields] OR "chemoradiotherapy"[All Fields] OR "radiation"[All Fields]) AND ("2007/01/01"[PDAT] : "2020/01/11"[PDAT]). Then, all titles or abstracts containing DNA damage response terms (ATM/ATR, CHK1/2, Wee1, PARP, DNA-PK, and PP2A) were identified. References of all included studies were reviewed for more eligible studies. The last search was run on January 11th 2020. Each study was screened and reviewed for eligibility independently by two authors. For *in vitro* assessment, studies were excluded if they did not report colony forming assay with multiple dose assessment.

2. Outcomes. The primary outcome was the standard enhancement ratio (SER) evaluating the *in vitro* radiosensitization effect of DNA damage response inhibitor on colony forming assay. For studies which did not specify SER in their manuscript, data were extracted from published plots using Web Plot Digitizer (<https://automeris.io/WebPlotDigitizer>) to convert datapoints into numerical values. Then SER was determined by calculating the ratio of doses in treated and control conditions for a given isoeffect (SF=0.1).

Secondary outcomes included the *in vivo* radiosensitization effect of DNA damage response inhibitors, the *in vitro/in vivo* radiosensitization effects of DNA damage response inhibitors on normal cell lines and the *in vitro/in vivo* effects of DNA damage response inhibitors on gemcitabine-based chemoradiotherapy.

3. Data extraction. Data were extracted independently and verified by two authors (WW and AP) using a predefined data extraction form. For each study, we extracted the type of cell line and the type of targeted therapy used. Concerning *in vivo* studies, the type of graft (xenotopic/orthotopic), the radiotherapy schedule (fractionation/single dose) and the criteria for assessing drug activity (tumor doubling time/tumor growth delay) were also reported.

Results:

1. Identified studies

PubMed database searches yielded 2794 unique citations. All abstracts from PubMed were retrieved and using pubmed.mineR package we selected 96 abstracts containing one of the following terms: “ATM”, “ATR”, “PARP”, “Wee1”, “PP2A”, “CHK”, and “DNA-PK”. After full-text review and evaluation of appropriate references, 14 unique citations were included in this review (Figure 1).

2. *In vitro* radiosensitization

Thirteen publications evaluated *in vitro* radiosensitization with DDRi. As irradiation with photons is the standard of care for locally advanced/borderline PDAC, we focused on

publication assessing radiosensitization with DDRi after photons irradiation. Ten publications using nine different cell lines were included in the review (Table 1). They presented therapies targeting PARP1/2, CHK1/2, ATR, Wee1, PP2A and DNA-PK in respectively three, three, two, two, one and one studies. Radiosensitization level differed from type of cell lines and type of targeted therapy (Figures 2 and 3). Depending on the type of DNA damage response (DDR) inhibitor, SER ranged from 1.14 to 1.48. For BRCA-WT cell lines, all DDR inhibitors (DDRi) induced radiosensitization, except for Wee1 inhibitor which radiosensitized only 40% of experiments (2/5). As MIA PaCa-2 was the most studied cell line, we analyzed the level of radiosensitization and showed that radiosensitization was enhanced from 30 to 75% depending on DDRi. In two studies using CAPAN-1 (BRCA2 mutated) cell line, there was no radiosensitization with either Wee1 or CHK1 inhibitors. Taken together, the pooled analysis of *in vitro* studies indicated that DNA targeting therapy radiosensitized pancreatic cancer cell lines in a large majority of studies (24/28), with a mean standard enhancement ratio of 1.35 ± 0.047 .

3. *In vivo* radiosensitization

Eight studies with fifteen different experiments were included in this review (Table 2). Almost all experiments were performed on subcutaneous xenografts, except one which used orthotopic xenograft. Most *in vivo* experiments were based on commercial cell lines derived xenograft models (10/15), the others on patient-derived xenografts (PDX) (5/15). For both survival and volume experiments, the reporting amount of pancreatic tumor cells injected gave a median of $5 \cdot 10^6$ cells (range: $1 \cdot 10^6$ - $5 \cdot 10^6$). One-third of the experiments reported single dose schedule (5/15) from 5 to 12 Gy, whereas the remaining ten experiments reported fractionated irradiation (from 1 to 2 Gy per fraction, for a total dose of 9 to 18 Gy). Radiosensitization effects were reported in 60% experiments (9/15), by enhancing tumor doubling time or increasing growth delay, compared to irradiation alone.

4. Potentialized gemcitabine-based chemoradiotherapy

As gemcitabine-based chemoradiotherapy is part of treatment for patients with locally advanced PDAC, we aimed to analyze the capacity of DDRi to enhance chemoradiosensitization. Two *in vitro* studies assessed gemcitabine-based chemoradiotherapy (GB-CRT) sensitization with DNA repair targeted therapies on five different cell lines for a total of seven experiments (Table 3). Five among seven experiments showed a significant enhancement of GB-CRT with DDRi, compared to radiosensitization with gemcitabine alone. CAPAN-1 cell line was the only one that could not be radiosensitized with DDRi when treated with GB-CRT. Three *in vivo* studies assessed gemcitabine-based chemoradiotherapy sensitization with DNA repair targeted therapies on subcutaneous xenografts (Table 4). One study used PDX. The addition of DDRi to the combination of gemcitabine and irradiation extended substantially tumor growth delay (survival) and time required for tumor doubling in two out of three experiments and trend to enhance tumor growth delay in the latter.

5. Effect on normal cell radiosensitivity

Given that the dose-limiting toxicity for radiation treatment of the pancreas is duodenum, two studies also evaluated the effect of DDRi on the radiosensitization of normal intestinal epithelial cells. Vance *et al.* showed that neither olaparib (PARP inhibitor, PARPi) nor AZD7762 (CHK1 inhibitor) radiosensitized normal cells (Vance et al., 2011). However, their association enhanced cytotoxicity compared to each inhibitor alone. Fokas *et al.* evaluated the radiosensitizing effect of VE-822 (ATR inhibitor, ATRi) on intestinal morphology, after mice abdominal X-ray irradiation (XRT). Authors indicated that in mice treated with VE-822 and XRT, number of apoptotic intestinal cells, jejunal morphology and weight loss were not significantly different compared to mice treated with XRT alone (Fokas et al., 2012).

Discussion:

Patients with PDAC have a poor prognosis and improving local control is mandatory. Indeed,

in LAP07 trial, 32% of patients had locoregional tumor progression after 5-fluorouracil (5-FU) based chemoradiotherapy and 58% had locoregional progression after chemotherapy alone (Hammel et al., 2016). In ESPAC-4 trial comparing two regimens (gemcitabine vs gemcitabine + 5-FU) of adjuvant chemotherapy after resection of localized PDAC, 60% of patients had marginal resection (R1), impacting overall survival (Neoptolemos et al., 2017). These data emphasized the rational of improving local control in PDAC. Although many chemotherapeutic agents have been evaluated for radiosensitization of pancreatic cancer, 5-fluorouracil and gemcitabine are the most used in current daily practice. Lately, non-chemotherapeutic agents such as DNA damage response inhibitors are under development as single agents or in association with chemotherapy. In this review, we aimed to define the potential radiosensitizing role of DDRi for pancreatic cancer. To the best of our knowledge, this is the first systematic review assessing published preclinical radiosensitization data, through DDR inhibition in pancreatic cancer. We identified that DNA repair targeted therapies enhanced by one-third radiosensitization *in vitro*. As a result of the small number of studies, we could not fully establish that radiosensitization was influenced by the type of DNA repair inhibitor or the type of cell line. As the therapeutic effect depends on the difference between efficacy on tumor cells and toxicity on normal cells, we submitted in this review that only two studies out of fourteen assessed the effect of two targeted therapies (PARPi and ATRi) on both epithelial intestinal and pancreatic tumor cells. These studies emphasized that neither PARPi nor ATRi enhanced radiation effect on intestinal cells *in vitro* (PARPi) and *in vivo* (ATRi) (Fokas et al., 2012; Vance et al., 2011). Whereas gemcitabine-based chemoradiotherapy can increase local control rates and improve progression-free survival, local recurrence remains a matter of concern (Zhu et al., 2011). DDRi may radiosensitize and also enhance gemcitabine-based chemoradiotherapy. Three publications presented that targeting DDR proteins (CHK1, ATR and Wee1) is an effective strategy for

sensitizing pancreatic cancers to gemcitabine-based chemoradiation (Engelke et al., 2013; Fokas et al., 2012; Kausar et al., 2015).

Irradiation induces different types of DNA damage such as single-strand breaks (SSB), double-strand breaks (DSB), DNA crosslinks and base modifications. The type of DNA damage triggers different response pathway. It is well known that PARP-1 is a major SSB sensor, allowing the recruitment of DNA repair proteins such as XRCC1, DNA ligase III and polymerase- β , thus inducing DNA repair (Vyas et al., 2013). As a single agent, PARPi are particularly used for treatment of homologous recombination (HR) deficient cells, based on the concept of synthetic lethality (Chalmers et al., 2010). However, only a small fraction of pancreatic cancers (15.4%) is HR deficient (Heeke et al., 2018). In this subset of patient, a recent phase III trial compared olaparib as a maintenance therapy in patients with metastatic PDAC with germline BRCA1 or BRCA2 mutation that had not progressed after first line platinum-based chemotherapy. Authors, showed that progression-free survival was higher in maintenance group compared to placebo (7.4 months vs. 3.8 months; HR = 0.53; 95% CI = 0.35 to 0.82; P = 0.004) (Golan et al., 2019). As a fundamental component of DDR, PARP-1 can be inhibited in cancer cells, thus explaining the rationale for combination with irradiation (Curtin and Szabo, 2013). In this review, we pointed out that three studies presented an increase of *in vitro* radiosensitization with PARPi from 20 to 50% (Karnak et al., 2014; Tuli et al., 2014; Vance et al., 2011). However, two of these studies evaluated radiosensitization *in vivo* (Karnak et al., 2014; Tuli et al., 2014) and only one showed radiosensitization (Tuli et al., 2014). Based on preclinical data, authors conducted a phase I study evaluating gemcitabine-based chemoradiotherapy with PARPi (veliparib) and indicated that the association was well-tolerated and emphasized that PARP3 and RBX1 expressions were associated with improved overall survival (Tuli et al., 2019).

Single-strand breaks can also activate ATR/CHK1 pathway, thus triggering S and G2/M-

phase checkpoints. It is worth noting that ATR is also involved into the stabilization of stalled forks replication preventing their collapse (Qiu et al., 2018). Thus, inhibiting ATR may enhance stress replication. Two studies evaluated ATRi as radiosensitizer and presented a SER from 1.3 to 2.1, depending on cell lines (Fokas et al., 2012; Prevo et al., 2012). This *in vitro* radiosensitization was confirmed *in vivo* (Fokas et al., 2012).

Double-strand breaks remain the major lethal type of DNA damage after irradiation. DSBs repair requires histone H2AX phosphorylation, recruitment of MRN complex (MRE11-Rad50-Nbs1) and ATM. Two main mechanisms are involved in DSBs repair: homologous recombination (HR) and non-homologous end-joining (NHEJ). DDRi were evaluated in proficient and deficient HR cell lines. It is stressed that DDRi did not radiosensitize BRCA2 mutated and HR deficient cell line CAPAN-1 (Engelke et al., 2013; Karnak et al., 2014). Indeed, HR deficient cells are sensitive to both DDRi and irradiation alone. Thus, the expected benefit of their combination would be very small and not clinically significant. In comparison to HR, DSB ligation through NHEJ pathway is active throughout the cell cycle and has faster kinetic. Li et al. showed that PDAC developed a reliance on NHEJ and as major component of NHEJ, DNA-PK inhibition enhanced radiosensitization *in vitro* (Li et al., 2012).

In past few years, radiotherapy technical advances such as protontherapy, allowed to increase physical dose to the tumor, while decreasing dose to normal tissue. Thanks to physical characteristic of Bragg Peak (BP), protons demonstrate a good dose distribution. The biological effectiveness of charged particles is mostly dependent on the linear energy transfer (LET) of the particles. Indeed, it has been postulated that multiple damage within a short DNA segment, known as clustered damage sites, is the major lethal type of damage induced by high-LET particles (Hada and Georgakilas, 2008). Thus, one would argue that enhancing the number or complexity of DNA damage through DDR inhibition could improve biological

effectiveness (Calugaru et al., 2014). Thus, three studies investigated the effect of PARP inhibition on the response of high-LET irradiation and showed that *in vitro* enhancement ratio ranged from 1.4 to 2.5, depending on LET and PARPi concentrations (Hirai et al., 2016, 2012; Wéra et al., 2019). Authors implied that PARPi sensitized cells with high-LET irradiation by enhancing the number of sub-lethal oxidative clustered DNA damage, thus leading to a delay in DNA damage repair (Hirai et al., 2016). Recently, one study showed that a RAD51 inhibitor enhanced radiosensitization after protontherapy (Wéra et al., 2019). Moreover, authors showed that PDAC cell lines (PANC-1 and KP4) could be radiosensitized with combination of PARPi and RAD51 inhibitor (B02) in fast cycling cells. This approach suggests that fast cycling tumors surrounded by non-proliferating healthy tissue could benefit from this combination.

The potential of increased toxicity is also a matter of concern. In a recent phase I/II study, Tuli *et al.* assessed gemcitabine-based chemoradiotherapy associated with a PARPi, veliparib, for patients with locally advanced or borderline PDAC (Tuli et al., 2019). Authors stated a high rate of grade ≥ 3 adverse events such as lymphopenia (96%). Although, haematological toxicity is known to be specifically associated with PARP inhibition, gastro-intestinal (GI) toxicity is related to the combination of radiotherapy and PARPi. In this case, authors indicated that 11% of patients had GI grade ≥ 3 adverse events. In the recently published POLO study, authors described 40% of grade ≥ 3 adverse events with olaparib PARPi treatment (Golan et al., 2019). This emphasizes the potential tolerance difference between the various available PARPi.

Locally advanced pancreatic cancer (LAPC) is associated with poor prognosis and generally considered incurable. Radiosensitizing PDAC with DDRi may be successful in downsizing tumor, thus impacting on surgical outcomes such as resection status in order to convert unresectable LAPC into resectable disease. Indeed, DDRi based radiotherapy may impact on

surgical outcomes such as resection status. Recently, the phase III randomized clinical trial, PREOPANC, showed that R0 resection was significantly higher in gemcitabine based chemoradiotherapy (71%) compared to immediate surgery (40%) for borderline PDAC(Versteijne et al., 2020) In our review, we investigate preclinical data of radiosensitization with DDRi and showed that when DDRi radiosensitization was higher than gemcitabine based radiosensitization. Moreover, DDR inhibition could enhance gemcitabine based chemoradiotherapy. Thus, downsizing tumor and improving resection status could be better with DDRi based radiosensitization. However, the impact of the association radiotherapy with DDRi on tumor shrinking and subsequent better resection status can only be speculated and need to be validated in clinical trial.

In our review, we showed that all *in vivo* experiences assessed radiosensitization with PDAC xenografts mouse model. To better assess tumor and microenvironment responses to radiation and DDRi association, future *in vivo* studies should be performed in genetically engineered mouse models (GEMMs). In contrast to cancer cell inoculation models, GEMMs acquire *de novo* tumors in immune-proficient mice and have close histopathological and molecular features of human cancer (Castle et al., 2017; Kersten et al., 2017).

Conclusions

In past decades, many advances have been made for most of cancer subtypes. However, there was no substantial change for patients diagnosed with pancreatic cancers. In the same time, the understanding of pancreatic cancer biology generated considerable interest. The major challenge is now to translate this biological knowledge into clinical applications. For this purpose, targeting DNA damage response in combination with radiotherapy is of great potential and needs to be confirmed with clinical data. Phase I trials are currently enrolling patients with various DDRi associated with radiotherapy. Lastly, future clinical trials should also assess the potential of biomarkers of response for each drug, thus identifying patients that

could benefit from each type of radiosensitizers.

Declarations of Competing Interest: no conflict of interest to declare for all authors.

References

- Calugaru, V., Nauraye, C., Cordelières, F.P., Biard, D., De Marzi, L., Hall, J., Favaudon, V., Mégnin-Chanet, F., 2014. Involvement of the Artemis Protein in the Relative Biological Efficiency Observed With the 76-MeV Proton Beam Used at the Institut Curie Proton Therapy Center in Orsay. *Int. J. Radiat. Oncol.* 90, 36–43. <https://doi.org/10.1016/j.ijrobp.2014.05.018>
- Castle, K.D., Chen, M., Wisdom, A.J., Kirsch, D.G., 2017. Genetically engineered mouse models for studying radiation biology. *Transl. Cancer Res.* 6, S900–S913. <https://doi.org/10.21037/tcr.2017.06.19>
- Chalmers, A.J., Lakshman, M., Chan, N., Bristow, R.G., 2010. Poly(ADP-Ribose) Polymerase Inhibition as a Model for Synthetic Lethality in Developing Radiation Oncology Targets. *Semin. Radiat. Oncol., Harnessing DNA Repair to Improve Radiotherapy Outcome* 20, 274–281. <https://doi.org/10.1016/j.semradonc.2010.06.001>
- Curtin, N.J., Szabo, C., 2013. Therapeutic applications of PARP inhibitors: Anticancer therapy and beyond. *Mol. Aspects Med., Biological roles and medical implications of Poly-ADP ribosylation* 34, 1217–1256. <https://doi.org/10.1016/j.mam.2013.01.006>
- Engelke, C.G., Parsels, L.A., Qian, Y., Zhang, Q., Karnak, D., Robertson, J.R., Tanska, D.M., Wei, D., Davis, M.A., Parsels, J.D., Zhao, L., Greenson, J.K., Lawrence, T.S., Maybaum, J., Morgan, M.A., 2013. Sensitization of Pancreatic Cancer to Chemoradiation by the Chk1 Inhibitor MK8776. *Clin. Cancer Res.* 19, 4412–4421. <https://doi.org/10.1158/1078-0432.CCR-12-3748>
- Falasca, M., Kim, M., Casari, I., 2016. Pancreatic cancer: Current research and future directions. *Biochim. Biophys. Acta BBA - Rev. Cancer.* <https://doi.org/10.1016/j.bbcan.2016.01.001>
- Fokas, E., Prevo, R., Pollard, J.R., Reaper, P.M., Charlton, P.A., Cornelissen, B., Vallis, K.A., Hammond, E.M., Olcina, M.M., Gillies McKenna, W., Muschel, R.J., Brunner, T.B., 2012. Targeting ATR in vivo using the novel inhibitor VE-822 results in selective

- sensitization of pancreatic tumors to radiation. *Cell Death Dis.* 3, e441–e441. <https://doi.org/10.1038/cddis.2012.181>
- Golan, T., Hammel, P., Reni, M., Van Cutsem, E., Macarulla, T., Hall, M.J., Park, J.-O., Hochhauser, D., Arnold, D., Oh, D.-Y., Reinacher-Schick, A., Tortora, G., Algül, H., O'Reilly, E.M., McGuinness, D., Cui, K.Y., Schlienger, K., Locker, G.Y., Kindler, H.L., 2019. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. *N. Engl. J. Med.* 381, 317–327. <https://doi.org/10.1056/NEJMoa1903387>
- Hada, M., Georgakilas, A.G., 2008. Formation of Clustered DNA Damage after High-LET Irradiation: A Review. *J. Radiat. Res. (Tokyo)* 49, 203–210. <https://doi.org/10.1269/jrr.07123>
- Hammel, P., Huguet, F., van Laethem, J.-L., Goldstein, D., Glimelius, B., Artru, P., Borbath, I., Bouché, O., Shannon, J., André, T., Mineur, L., Chibaudel, B., Bonnetain, F., Louvet, C., LAP07 Trial Group, 2016. Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib: The LAP07 Randomized Clinical Trial. *JAMA* 315, 1844–1853. <https://doi.org/10.1001/jama.2016.4324>
- Heeke, A.L., Pishvaian, M.J., Lynce, F., Xiu, J., Brody, J.R., Chen, W.-J., Baker, T.M., Marshall, J.L., Isaacs, C., 2018. Prevalence of Homologous Recombination-Related Gene Mutations Across Multiple Cancer Types. *JCO Precis. Oncol.* 2018.
- Hirai, T., Saito, S., Fujimori, H., Matsushita, K., Nishio, T., Okayasu, R., Masutani, M., 2016. Radiosensitization by PARP inhibition to proton beam irradiation in cancer cells. *Biochem. Biophys. Res. Commun.* 478, 234–240. <https://doi.org/10.1016/j.bbrc.2016.07.062>
- Hirai, T., Shirai, H., Fujimori, H., Okayasu, R., Sasai, K., Masutani, M., 2012. Radiosensitization effect of poly(ADP-ribose) polymerase inhibition in cells exposed to low and high linear energy transfer radiation. *Cancer Sci.* 103, 1045–1050. <https://doi.org/10.1111/j.1349-7006.2012.02268.x>
- Karnak, D., Engelke, C.G., Parsels, L.A., Kausar, T., Wei, D., Robertson, J.R., Marsh, K.B., Davis, M.A., Zhao, L., Maybaum, J., Lawrence, T.S., Morgan, M.A., 2014. Combined Inhibition of Wee1 and PARP1/2 for Radiosensitization in Pancreatic Cancer. *Clin. Cancer Res.* 20, 5085–5096. <https://doi.org/10.1158/1078-0432.CCR-14-1038>
- Kausar, T., Schreiber, J.S., Karnak, D., Parsels, L.A., Parsels, J.D., Davis, M.A., Zhao, L., Maybaum, J., Lawrence, T.S., Morgan, M.A., 2015. Sensitization of Pancreatic Cancers to Gemcitabine Chemoradiation by WEE1 Kinase Inhibition Depends on

- Homologous Recombination Repair. *Neoplasia* 17, 757–766.
<https://doi.org/10.1016/j.neo.2015.09.006>
- Kersten, K., de Visser, K.E., van Miltenburg, M.H., Jonkers, J., 2017. Genetically engineered mouse models in oncology research and cancer medicine. *EMBO Mol. Med.* 9, 137–153. <https://doi.org/10.15252/emmm.201606857>
- Li, Y.-H., Wang, X., Pan, Y., Lee, D.-H., Chowdhury, D., Kimmelman, A.C., 2012. Inhibition of Non-Homologous End Joining Repair Impairs Pancreatic Cancer Growth and Enhances Radiation Response. *PLoS ONE* 7, e39588.
<https://doi.org/10.1371/journal.pone.0039588>
- Lohse, I., Kumareswaran, R., Cao, P., Pitcher, B., Gallinger, S., Bristow, R.G., Hedley, D.W., 2016. Effects of Combined Treatment with Ionizing Radiation and the PARP Inhibitor Olaparib in BRCA Mutant and Wild Type Patient-Derived Pancreatic Cancer Xenografts. *PLOS ONE* 11, e0167272. <https://doi.org/10.1371/journal.pone.0167272>
- Morgan, M.A., Parsels, L.A., Zhao, L., Parsels, J.D., Davis, M.A., Hassan, M.C., Arumugarajah, S., Hylander-Gans, L., Morosini, D., Simeone, D.M., Canman, C.E., Normolle, D.P., Zabludoff, S.D., Maybaum, J., Lawrence, T.S., 2010. Mechanism of Radiosensitization by the Chk1/2 Inhibitor AZD7762 Involves Abrogation of the G2 Checkpoint and Inhibition of Homologous Recombinational DNA Repair. *Cancer Res.* 70, 4972–4981. <https://doi.org/10.1158/0008-5472.CAN-09-3573>
- Neoptolemos, J.P., Palmer, D.H., Ghaneh, P., Psarelli, E.E., Valle, J.W., Halloran, C.M., Faluyi, O., O'Reilly, D.A., Cunningham, D., Wadsley, J., Darby, S., Meyer, T., Gillmore, R., Anthoney, A., Lind, P., Glimelius, B., Falk, S., Izbicki, J.R., Middleton, G.W., Cummins, S., Ross, P.J., Wasan, H., McDonald, A., Crosby, T., Ma, Y.T., Patel, K., Sherriff, D., Soomal, R., Borg, D., Sothi, S., Hammel, P., Hackert, T., Jackson, R., Büchler, M.W., 2017. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *The Lancet* 389, 1011–1024. [https://doi.org/10.1016/S0140-6736\(16\)32409-6](https://doi.org/10.1016/S0140-6736(16)32409-6)
- Prevo, R., Fokas, E., Reaper, P.M., Charlton, P.A., Pollard, J.R., McKenna, W.G., Muschel, R.J., Brunner, T.B., 2012. The novel ATR inhibitor VE-821 increases sensitivity of pancreatic cancer cells to radiation and chemotherapy. *Cancer Biol. Ther.* 13, 1072–1081. <https://doi.org/10.4161/cbt.21093>
- Qiu, Z., Oleinick, N.L., Zhang, J., 2018. ATR/CHK1 inhibitors and cancer therapy. *Radiother. Oncol.* 126, 450–464. <https://doi.org/10.1016/j.radonc.2017.09.043>

- Tuli, R., Shiao, S.L., Nissen, N., Tighiouart, M., Kim, S., Osipov, A., Bryant, M., Ristow, L., Placencio-Hickok, V.R., Hoffman, D., Rokhsar, S., Scher, K., Klempner, S.J., Noe, P., Davis, M.J., Wachsman, A., Lo, S., Jamil, L., Sandler, H., Piantadosi, S., Hendifar, A., 2019. A phase 1 study of veliparib, a PARP-1/2 inhibitor, with gemcitabine and radiotherapy in locally advanced pancreatic cancer. *EBioMedicine*. <https://doi.org/10.1016/j.ebiom.2018.12.060>
- Tuli, R., Surmak, A.J., Reyes, J., Armour, M., Hacker-Prietz, A., Wong, J., DeWeese, T.L., Herman, J.M., 2014. Radiosensitization of Pancreatic Cancer Cells In Vitro and In Vivo through Poly (ADP-ribose) Polymerase Inhibition with ABT-888. *Transl. Oncol.* 7, 439–445. <https://doi.org/10.1016/j.tranon.2014.04.003>
- Vance, S., Liu, E., Zhao, L., Parsels, J.D., Parsels, L.A., Brown, J.L., Maybaum, J., Lawrence, T.S., Morgan, M.A., 2011. Selective radiosensitization of p53 mutant pancreatic cancer cells by combined inhibition of Chk1 and PARP1. *Cell Cycle* 10, 4321–4329. <https://doi.org/10.4161/cc.10.24.18661>
- Versteijne, E., Suker, M., Groothuis, K., Akkermans-Vogelaar, J.M., Besselink, M.G., Bonsing, B.A., Buijsen, J., Busch, O.R., Creemers, G.-J.M., van Dam, R.M., Eskens, F.A.L.M., Festen, S., de Groot, J.W.B., Groot Koerkamp, B., de Hingh, I.H., Homs, M.Y.V., van Hooft, J.E., Kerver, E.D., Luelmo, S.A.C., Neelis, K.J., Nuyttens, J., Paardekooper, G.M.R.M., Patijn, G.A., van der Sangen, M.J.C., de Vos-Geelen, J., Wilmink, J.W., Zwinderman, A.H., Punt, C.J., van Eijck, C.H., van Tienhoven, G., Dutch Pancreatic Cancer Group, 2020. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 38, 1763–1773. <https://doi.org/10.1200/JCO.19.02274>
- Vyas, S., Chesarone-Cataldo, M., Todorova, T., Huang, Y.-H., Chang, P., 2013. A systematic analysis of the PARP protein family identifies new functions critical for cell physiology. *Nat. Commun.* 4. <https://doi.org/10.1038/ncomms3240>
- Waddell, Nicola, Pajic, M., Patch, A.-M., Chang, D.K., Kassahn, K.S., Bailey, P., Johns, A.L., Miller, D., Nones, K., Quek, K., Quinn, M.C.J., Robertson, A.J., Fadlullah, M.Z.H., Bruxner, T.J.C., Christ, A.N., Harliwong, I., Idrisoglu, S., Manning, S., Nourse, C., Nourbakhsh, E., Wani, S., Wilson, P.J., Markham, E., Cloonan, N., Anderson, M.J., Fink, J.L., Holmes, O., Kazakoff, S.H., Leonard, C., Newell, F., Poudel, B., Song, S., Taylor, D., Waddell, Nick, Wood, S., Xu, Q., Wu, J., Pinese, M., Cowley, M.J., Lee, H.C., Jones, M.D., Nagrial, A.M., Humphris, J., Chantrill, L.A.,

Chin, V., Steinmann, A.M., Mawson, A., Humphrey, E.S., Colvin, E.K., Chou, A., Scarlett, C.J., Pinho, A.V., Giry-Laterriere, M., Rooman, I., Samra, J.S., Kench, J.G., Pettitt, J.A., Merrett, N.D., Toon, C., Epari, K., Nguyen, Nam Q., Barbour, A., Zeps, N., Jamieson, N.B., Graham, J.S., Niclou, S.P., Bjerkvig, R., Grützmann, R., Aust, D., Hruban, R.H., Maitra, A., Iacobuzio-Donahue, C.A., Wolfgang, C.L., Morgan, R.A., Lawlor, R.T., Corbo, V., Bassi, C., Falconi, M., Zamboni, G., Tortora, G., Tempero, M.A., Biankin, A.V., Johns, A.L., Mawson, A., Chang, D.K., Scarlett, C.J., Brancato, M.-A.L., Rowe, S.J., Simpson, S.H., Martyn-Smith, M., Thomas, M.T., Chantrill, L.A., Chin, V.T., Chou, A., Cowley, M.J., Humphris, J.L., Jones, M.D., Scott Mead, R., Nagrial, A.M., Pajic, M., Pettit, J., Pinese, M., Rooman, I., Wu, J., Tao, J., DiPietro, R., Watson, C., Steinmann, A., Ching Lee, H., Wong, R., Pinho, A.V., Giry-Laterriere, M., Daly, R.J., Musgrove, E.A., Sutherland, R.L., Grimmond, S.M., Waddell, Nicola, Kassahn, K.S., Miller, D.K., Wilson, P.J., Patch, A.-M., Song, S., Harliwong, I., Idrisoglu, S., Nourse, C., Nourbakhsh, E., Manning, S., Wani, S., Gongora, M., Anderson, M., Holmes, O., Leonard, C., Taylor, D., Wood, S., Xu, C., Nones, K., Lynn Fink, J., Christ, A., Bruxner, T., Cloonan, N., Newell, F., Pearson, J.V., Bailey, P., Quinn, M., Nagaraj, S., Kazakoff, S., Waddell, Nick, Krisnan, K., Quek, K., Wood, D., Fadlullah, M.Z.H., Samra, J.S., Gill, A.J., Pavlakis, N., Guminski, A., Toon, C., Asghari, R., Merrett, N.D., Pavey, D., Das, A., Cosman, P.H., Ismail, K., O'Connor, C., Lam Duncan McLeod, V.W., Pleass, H.C., Richardson, A., James, V., Kench, J.G., Cooper, C.L., Joseph, D., Sandroussi, C., Crawford, M., Gallagher, J., Texler, M., Forest, C., Laycock, A., Epari, K.P., Ballal, M., Fletcher, D.R., Mukhedkar, S., Spry, N.A., DeBoer, B., Chai, M., Zeps, N., Beilin, M., Feeney, K., Nguyen, Nan Q., Ruzkiewicz, A.R., Worthley, C., Tan, C.P., Debreceni, T., Chen, J., Brooke-Smith, M.E., Papangelis, V., Tang, H., Barbour, A.P., Clouston, A.D., Martin, P., O'Rourke, T.J., Chiang, A., Fawcett, J.W., Slater, K., Yeung, S., Hatzifotis, M., Hodgkinson, P., Christophi, C., Nikfarjam, M., Mountain, A., Eshleman, J.R., Hruban, R.H., Maitra, A., Iacobuzio-Donahue, C.A., Schulick, R.D., Wolfgang, C.L., Morgan, R.A., Hodgkin, M., Scarpa, A., Lawlor, R.T., Beghelli, S., Corbo, V., Scardoni, M., Bassi, C., Tempero, M.A., Biankin, A.V., Grimmond, S.M., Chang, D.K., Musgrove, E.A., Jones, M.D., Nourse, C., Jamieson, N.B., Graham, J.S., Biankin, A.V., Chang, D.K., Jamieson, N.B., Graham, J.S., Oien, K., Hair, J., Gill, A.J., Eshleman, J.R., Pilarsky, C., Scarpa, A., Musgrove, E.A., Pearson, J.V., Biankin,

- A.V., Grimmond, S.M., 2015. Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature* 518, 495–501. <https://doi.org/10.1038/nature14169>
- Wei, D., Parsels, L.A., Karnak, D., Davis, M.A., Parsels, J.D., Marsh, A.C., Zhao, L., Maybaum, J., Lawrence, T.S., Sun, Y., Morgan, M.A., 2013. Inhibition of Protein Phosphatase 2A Radiosensitizes Pancreatic Cancers by Modulating CDC25C/CDK1 and Homologous Recombination Repair. *Clin. Cancer Res.* 19, 4422–4432. <https://doi.org/10.1158/1078-0432.CCR-13-0788>
- Wéra, A.-C., Lobbens, A., Stoyanov, M., Lucas, S., Michiels, C., 2019. Radiation-induced synthetic lethality: combination of poly(ADP-ribose) polymerase and RAD51 inhibitors to sensitize cells to proton irradiation. *Cell Cycle* 18, 1770–1783. <https://doi.org/10.1080/15384101.2019.1632640>
- Witkiewicz, A.K., McMillan, E.A., Balaji, U., Baek, G., Lin, W.-C., Mansour, J., Mollae, M., Wagner, K.-U., Koduru, P., Yopp, A., Choti, M.A., Yeo, C.J., McCue, P., White, M.A., Knudsen, E.S., 2015. Whole-exome sequencing of pancreatic cancer defines genetic diversity and therapeutic targets. *Nat. Commun.* 6, 6744. <https://doi.org/10.1038/ncomms7744>
- Zhu, C.-P., Shi, J., Chen, Y.-X., Xie, W.-F., Lin, Y., 2011. Gemcitabine in the chemoradiotherapy for locally advanced pancreatic cancer: A meta-analysis. *Radiother. Oncol.* 99, 108–113. <https://doi.org/10.1016/j.radonc.2011.04.001>

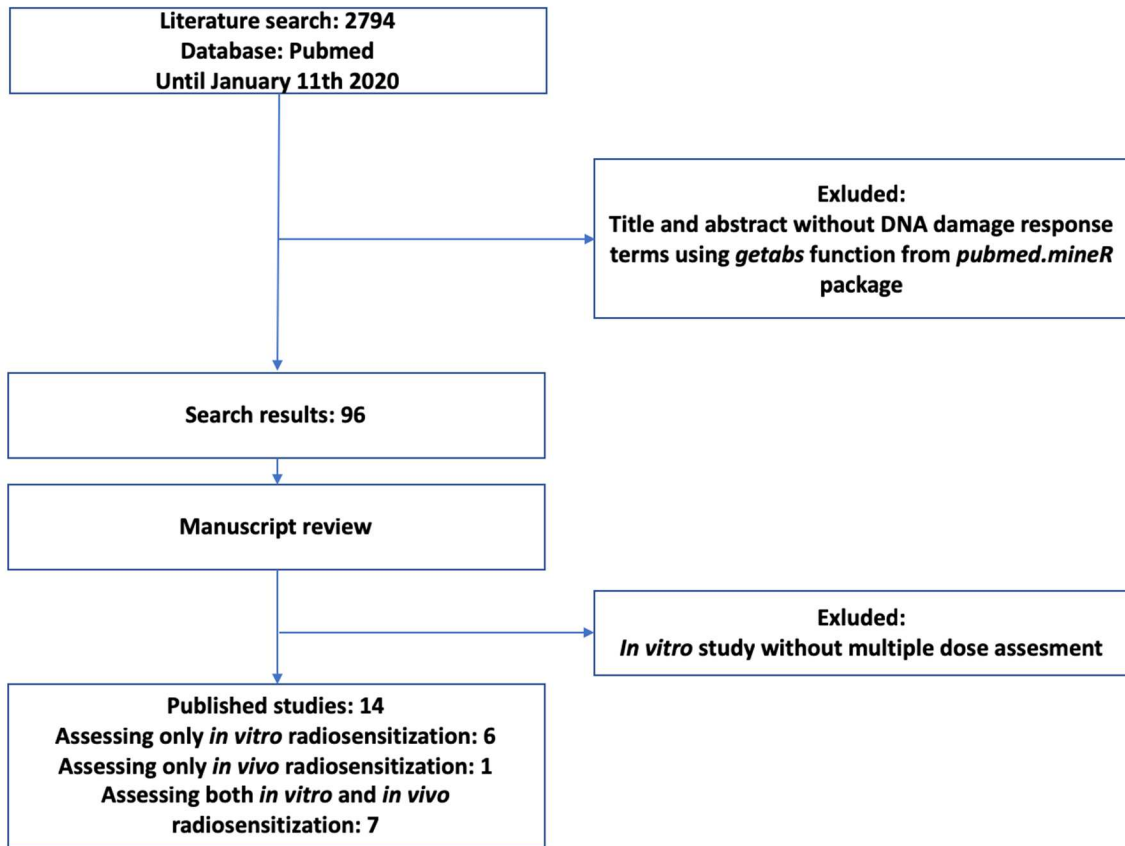


Figure 1: Flow chart of the systematic review for Pubmed database search and analysis.

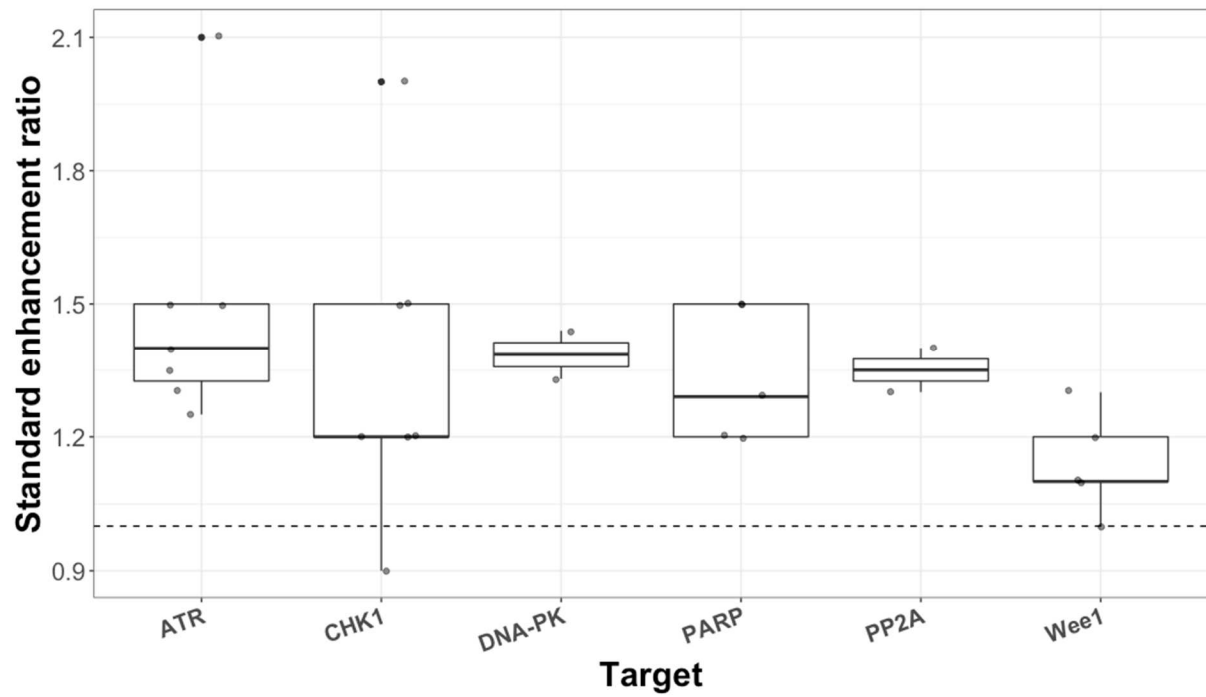


Figure 2: Boxplot representing the radiosensitization standard enhancement ratio as a function of six DNA damage response inhibitors (ATR, CHK1, DNA-PK, PARP, PP2A and Wee1) in pancreatic cancer cell lines.

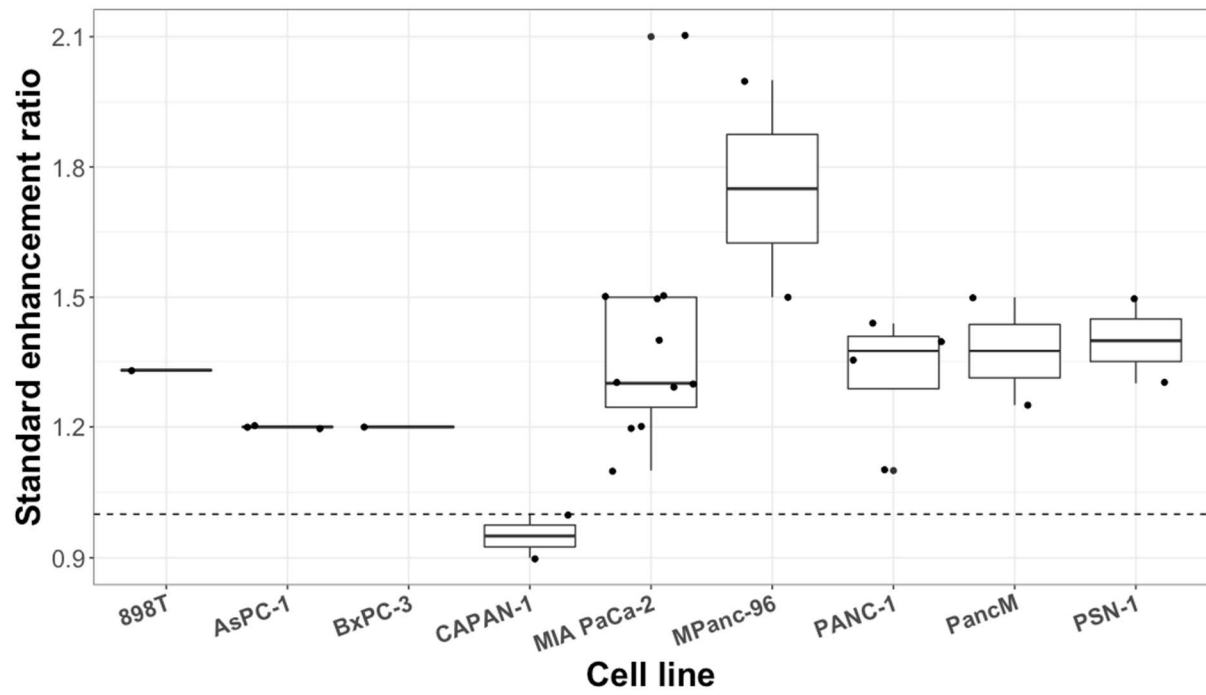


Figure 3: Boxplot representing the radiosensitization standard enhancement ratio as a function of nine pancreatic cell lines (898T, AsPC-1, BxPC-3, CAPAN-1, MIA PaCa-2, MPanc-96, PANC-1, PancM and PSN-1).

Author	Target	DDR inhibitor	Cell line	Radiosensitization	SER±SE	Mean SER±SE		
(Fokas et al., 2012)	ATR	VE-822	MIA PaCa-2	Yes	2.1* (N=3)	1.48 ± 0.11		
			PSN1	Yes	1.5* (N=3)			
			PancM	Yes	1.5* (N=3)			
(Prevo et al., 2012)		VE-821	MIA PaCa-2	Yes	1.4* (N=3)			
			PSN1	Yes	1.3* (N=3)			
			PANC-1	Yes	1.35* (N=3)			
			PancM	Yes	1.25* (N=3)			
(Morgan et al., 2010)		CHK1	AZD7762	MIA PaCa-2	Yes		1.5±0.08 (N=4)	1.35 ± 0.13
(Vance et al., 2011)				MIA PaCa-2	Yes		1.5±0.0 (N=3)	
Mpanc-96	Yes			2±0.01 (N=3)				
(Engelke et al., 2013)	MK8776		AsPc-1	Yes	1.2±0.1 (N=3)			
			MIA PaCa-2	Yes	1.2±0.1 (N=3)			
			BxPC-3	Yes	1.2±0.1 (N=3)			
			CAPAN-1	No	0.9±0.1 (N=3)			
(Tuli et al., 2014)	PARP	Veliparib	MIA PaCa-2	Yes	1.29# (N=NC)	1.33 ± 0.06		
(Vance et al., 2011)		Olaparib	MIA PaCa-2	Yes	1.5±0.1 (N=3)			
			Mpanc-96	Yes	1.5±0.1 (N=3)			
			AsPC-1	Yes	1.2±0.2 (N=3)			
			MIA PaCa-2	Yes	1.2±0.1 (N=3)			
(Karnak et al., 2014)								
(Kausar et al., 2015)	Wee1	AZD1775	MIA PaCa-2	No	1.1±0.1 (N=4)	1.14 ± 0.05		
			PANC-1	No	1.1±0.1 (N=4)			
			CAPAN-1	No	1±0.3 (N=4)			
(Karnak et al., 2014)			AsPC-1	Yes	1.2±0.1 (N=3)			
			MIA PaCa-2	Yes	1.3±0.1 (N=3)			
(Li et al., 2012)	DNA-PK	NU7026	PANC-1	Yes	1.44* (N=3)	1.38 ± 0.06		
			898T	Yes	1.33* (N=3)			
(Wei et al., 2013)	PP2A	LB100	MIA PaCa-2	Yes	1.3±0.04 (N=3)	1.35 ± 0.05		
			PANC-1	Yes	1.4±0.04 (N=3)			

Table 1: *In vitro* radiosensitizing effects of DNA damage response inhibitors on pancreatic cancer cell lines. *: Data extracted from cell survival curves. #: Standard error was not described in the manuscript.

DDR=DNA damage response; SER=Standard enhancement ratio; SE=standard error.

Author	Target	DDR inhibitor	Cell line	Type of graft	Fractionation	Endpoint	Endpoint for RT (days)	Endpoint for RT + inhibitor (days)	P	Radiosensitization
(Morgan et al., 2010)	CHK1	AZD7762	MIA PaCa-2	xeno	1.8 Gy/fraction, 5 days a week for 2 weeks (18Gy)	Tumor DT	89 (68-nd)	>114 (83-nd)	NS	No
			PDX	xeno		Tumor DT	15(9-18)	44 (39-53)	<0.001	Yes
			PDX	xeno		Tumor DT	32,5(16-42)	44,5(43-47)	<0.001	Yes
(Engelke et al., 2013)		MKK8776	MIA PaCa-2	xeno	1 Gy/fraction, 5 days a week for 2 weeks (10Gy)	Tumor DT	NR	NR	NR	No
(Fokas et al., 2012)	ATR	VE-822	PSN-1	xeno	6 Gy once	Tumor GD	NR	NR	<0.001	Yes
			PSN-1	xeno	2 Gy/fraction, 5 days a week for 1 week (10Gy)	Tumor GD	NR	NR	<0.001	Yes
			MIA PaCa-2	xeno	6 Gy once	Tumor GD	NR	NR	<0.001	Yes
(Karnak et al., 2014)	PARP	Olaparib	MIA PaCa-2	xeno	1.8 Gy/fraction, 5 days a week for 1 week (9Gy)	Tumor DT	13 (10-16)	10 (4-15)	NS	No
(Lohse et al., 2016)			PDX	xeno	12 Gy once	Tumor GD	53.5	53.167	NS	No
			PDX	xeno	12 Gy once	Tumor GD	61.5	58	NS	No
(Tuli et al., 2014)		Veliparib	MIA PaCa-2	ortho	5 Gy once	Tumor GD	28	36	<0.05	Yes
(Kausar et al., 2015)	Wee1	AZD1175 AZD1175	PDX	xeno	1.8 Gy/fraction, 5 days a week for 2 weeks (18Gy)	Tumor DT	17 (8-25)	21(16-26)	NS	No
(Karnak et al., 2014)			MIA PaCa-2	xeno	1.8 Gy/fraction, 5 days a week for 1 week (9Gy)	Tumor DT	13 (10-16)	17 (10-18)	<0.05	Yes
(Karnak et al., 2014)	PARP/Wee1	Olaparib/ AZD1175	MIA PaCa-2	xeno	1.8 Gy/fraction, 5 days a week for 1 week (9Gy)	Tumor DT	13 (10-16)	26(18-36)	<0.05	Yes
(Wei et al., 2013)	PP2A	LB100	MIA PaCa-2	xeno	1.2 Gy/fraction, 5 days a week for 2 weeks (12Gy)	Tumor GD	24	33.5	<0.05	Yes

Table 2: *In vivo* radiosensitizing effects of DNA damage response inhibitors in pancreatic xenografts mouse model.

DDR=DNA damage response; DT=Doubling time; GD=Growth delay compared to control; PDX=Patient-derived xenografts: xeno=Xenotopic;

NR=Not reported and NS=Not significant.

Author	Treatment	Target	Cell line	Gemcitabine SER	DDRi and Gemcitabine combination SER	Enhancement of Gemcitabine-based CRT
(Engelke et al., 2013)	MK8776	CHK1	AsPC-1	1.1±0.1	1.6±0.1	Yes
			MIA PaCa-2	1.2±0.1	1.6±0.1	Yes
			BxPC-3	1.1±0.2	1.7±0.3	Yes
			CAPAN-1	1.3±0.1	1.3±0.1	No
(Kausar et al., 2015)	AZD1775	Wee1	MIA PaCa-2	1.3±0.2	2.1±0.2	Yes
			PANC-1	1.1±0.4	1.5±0.2	Yes
			CAPAN-1	1.8±0.4	1.9±0.2	No

Table 3: *In vitro* radiosensitizing effects of DNA damage response inhibitors association with gemcitabine compared to gemcitabine alone in pancreatic cancer cell lines.

DDRi=DNA damage response inhibitor and DT=Doubling time.

Author	Cell line	Type of graft	Treatment	Target	Fractionation	Tumor DT after RT + Gem	Tumor DT after RT + Gem + DDRi	P	Radiosensitization compared to Gemcitabine-based CRT
(Kausar et al., 2015)	PDX	Xenograft	AZD1775	Wee1	1.8 Gy/fraction, 5 days a week for 2 weeks (18 Gy)	21.5	34	0.07	Trend
(Engelke et al., 2013)	MIA PaCa-2	Xenograft	MK8776	CHK1	1 Gy/fraction, 5 days a week for 2 weeks (10 Gy)	NR	NR	0.0087	Yes
(Fokas et al., 2012)	PSN-1	Xenograft	VE-822	ATR	6 Gy once	NR	NR	P<0.001	Yes

Table 4: *In vivo* radiosensitizing effects of DNA damage response inhibitors association with gemcitabine compared to gemcitabine alone in pancreatic xenografts mouse model.

DDRi =DNA damage response inhibitor; DT=Doubling time and NR=Not reported.