

## Perspectives on the combination of radiotherapy and targeted therapy with DNA repair inhibitors in the treatment of pancreatic cancer

Shih-Hung Yang, Ting-Chun Kuo, Hsu Wu, Jhe-Cyuan Guo, Chiun Hsu, Chih-Hung Hsu, Yu-Wen Tien, Kun-Huei Yeh, Ann-Lii Cheng, Sung-Hsin Kuo

Shih-Hung Yang, Jhe-Cyuan Guo, Chiun Hsu, Chih-Hung Hsu, Kun-Huei Yeh, Ann-Lii Cheng, Sung-Hsin Kuo, Department of Oncology, National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei 100, Taiwan

Shih-Hung Yang, Ann-Lii Cheng, Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei 100, Taiwan

Shih-Hung Yang, Jhe-Cyuan Guo, Graduate Institute of Clinical Medicine National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei 100, Taiwan

Ting-Chun Kuo, Department of Traumatology, National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei 100, Taiwan

Hsu Wu, Department of Oncology, National Taiwan University Hospital, Yun-Lin Branch, Yunlin 655, Taiwan

Chiun Hsu, Chih-Hung Hsu, Kun-Huei Yeh, Ann-Lii Cheng, Sung-Hsin Kuo, Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei 100, Taiwan

Yu-Wen Tien, Department of Surgery, National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei 100, Taiwan

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**Correspondence to:** Sung-Hsin Kuo, MD, PhD, Department of Oncology, National Taiwan University Hospital and National Taiwan University Cancer Center, No. 7, Chung-Shan South Road, Taipei 100, Taiwan. [shkuo101@ntu.edu.tw](mailto:shkuo101@ntu.edu.tw)  
Telephone: +886-2-23123456- 67144  
Fax: +886-2-23711174

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### Abstract

Pancreatic cancer is highly lethal. Current research that combines radiation with targeted therapy may dramatically improve prognosis. Cancerous cells are characterized by unstable genomes and activation of DNA repair pathways, which are indicated by increased phosphorylation of numerous factors, including H2AX, ATM, ATR, Chk1, Chk2, DNA-PKcs, Rad51, and Ku70/Ku80 heterodimers. Radiotherapy causes DNA damage. Cancer cells can be made more sensitive to the effects of radiation (radiosensitization) through inhibition of DNA repair pathways. The synergistic effects, of two or more combined non-lethal treatments, led to co-administration of chemotherapy and radiosensitization in *BRCA*-defective cells and patients, with promising

results. ATM/Chk2 and ATR/Chk1 pathways are principal regulators of cell cycle arrest, following DNA double-strand or single-strand breaks. DNA double-stranded breaks activate DNA-dependent protein kinase, catalytic subunit (DNA-PKcs). It forms a holoenzyme with Ku70/Ku80 heterodimers, called DNA-PK, which catalyzes the joining of nonhomologous ends. This is the primary repair pathway utilized in human cells after exposure to ionizing radiation. Radiosensitization, induced by inhibitors of ATM, ATR, Chk1, Chk2, Wee1, PP2A, or DNA-PK, has been demonstrated in preclinical pancreatic cancer studies. Clinical trials are underway. Development of agents that inhibit DNA repair pathways to be clinically used in combination with radiotherapy is warranted for the treatment of pancreatic cancer.

**Key words:** Radiotherapy; Pancreatic cancer; DNA damage; DNA repair; Molecular targets

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**Core tip:** Radiotherapy causes DNA damage, including double-strand breaks, which is more readily repaired in normal cells than in cancerous cells. Radiosensitization, using DNA repair pathway inhibitors, has been well documented in various cancer types, including pancreatic cancer. Further development of optimal protocols, for the combined use of these inhibitors with radiotherapy, with/without chemotherapy, is warranted for the clinical treatment of pancreatic cancer.

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## INTRODUCTION

Pancreatic cancer is not a common disease; there are approximately 330000 cases a year worldwide. However, it is highly lethal, with nearly equal numbers of new cases and deaths. The majority (> 80%) of pancreatic cancers are ductal adenocarcinoma, for which the prognosis remains poor, even with recent advances in detection, supportive care, and therapeutics<sup>[1]</sup>. It remains challenging to make an early diagnosis for sporadic pancreatic cancer, because of the low lifetime risk of developing pancreatic cancer and the lack of adequate screening methods<sup>[2]</sup>. Endoscopic ultrasonography and MRI screening tools may play a limited detection role in patients with high risks, such as family history or known germline mutations<sup>[3,4]</sup>.

Only 20% of pancreatic cancer patients are good

candidates for curative resection at diagnosis. The 5-year survival rate doubled from 10.4% to 20.7%, after 6-mo of treatment with adjuvant gemcitabine, in the CONKO-001 study<sup>[5]</sup>. This randomized trial revealed that application of adjuvant gemcitabine significantly improved median disease-free survival (13.4 mo vs 6.9 mo), compared with that by surgery alone<sup>[6]</sup>. However, at least 50% of the patients eventually developed distant metastases<sup>[6]</sup>. Systemic dissemination occurs early in the disease process, in a mouse model of pancreatic cancer<sup>[7]</sup>. Clinical trials, in the past decade, have attempted to administer modern adjuvant radiotherapy, alone or combined with chemotherapy, to decrease the local recurrence and eventual metastasis that remain significant issues for operable pancreatic cancer<sup>[6]</sup>. However, the local recurrence rate is still more than 30%<sup>[8]</sup>. In addition, the survival benefit with adjuvant radiotherapy is controversial and may be outweighed by the toxicity of the treatments<sup>[9]</sup>.

Patients with advanced pancreatic cancer frequently suffer from local symptoms. Local control of the main tumor is paramount to palliate these complaints, in addition to surgical bypass, and biliary/intestinal stenting or drainage<sup>[10]</sup>. The local control rate with chemotherapy alone varies over a wide range, which is probably due to the use of a single agent versus combined chemotherapy<sup>[10,11]</sup>. It is questionable if local control can translate into a survival benefit. Bolus 5-FU-based chemoradiotherapy (CCRT) concurrent with maintenance chemotherapy was shown, in the 1980s, to double overall survival from 22.9 wk to more than 40 wk compared to that by radiotherapy alone<sup>[12]</sup>. However, a comparison of CCRT to chemotherapy alone did not show a consistent survival benefit<sup>[13,14]</sup>. Moreover, the use of modern radiotherapy techniques, to obtain a survival benefit in locally advanced pancreatic cancer, is of great debate<sup>[10,15,16]</sup>.

The underlying reasons for inconsistent benefits in adding radiotherapy to chemotherapy, in the adjuvant or palliative setting, are multifactorial. Potential explanations are poor quality control of the delivery of radiotherapy, the use of old techniques with high radiation-induced toxicity, breaks with divided radiotherapy courses, and the use of agents with poor radiosensitization and high toxicity. However, pancreatic cancer metastasizes early<sup>[7]</sup>. The choice of the most appropriate medicine added to the radiotherapy, rather than radiotherapy itself, may be the most important answer. The most common current daily practice combines radiosensitizing agents, 5-FU and gemcitabine, with radiotherapy in the adjuvant or advanced setting. However, the single-agent activity of gemcitabine or 5-FU in advanced disease is poor<sup>[17]</sup>. In addition, significant toxicities of CCRT are always of concern<sup>[9]</sup>. The aim of this review is to present an overview of the types of DNA damage in pancreatic cancer, summarize new evidence in non-chemotherapy agents, with the focus on DNA repair-related targeted therapy (Table

1). Additionally, we will provide direction for further development of use of these agents combined with radiotherapy in pancreatic cancer.

## TYPES OF DNA DAMAGE IN PANCREATIC CANCER

Radiotherapy has a local therapeutic role for pancreatic cancer, however, it is much less frequently used than systemic therapy<sup>[18,19]</sup>. The theoretical mechanism of cytotoxicity, induced directly or indirectly by radiotherapy, is DNA damage, regardless of whether it is caused by photons, charged particles with protons or carbon ions, or any emerging technique. The types of DNA damage induced by ionizing radiation (IR) include single-strand break (SSB), double-strand break (DSB), base modifications, and DNA-protein cross-linking. The damage can be repaired, in normal mammalian cells, through several mechanisms. The repair mechanism can be homologous recombination (HR), nonhomologous end joining (NHEJ), nucleotide excision repair (NER), base excision repair (BER), and mismatch repair (MMR), regardless of whether the damage was induced by IR or occurred spontaneously (Figure 1).

The pancreatic cancer genome is unstable. Telomere shortening was obvious in pancreatic intraepithelial neoplasia (PanIN) lesions, even in the earliest PanIN-1A lesions. However, this phenomenon was not found in atrophic or inflammatory pancreatic lesions<sup>[20]</sup>. The telomeres were much shorter in cancer cells than in PanIN-1 or PanIN-2 lesions<sup>[21]</sup>. The activation of telomeres expression seen in the majority of pancreatic cancers may be resulted from the protective mechanism of telomeres against catastrophic DNA damage<sup>[22]</sup>. Previous studies also demonstrated that telomere shortening was closely associated with the DNA repair impairment<sup>[23,24]</sup>. In addition, widespread DNA damage was found in PanIN lesions. Increased  $\gamma$ H2AX<sup>Ser139</sup>, phospho-ataxia-telangiectasia mutated (ATM)<sup>Ser1981</sup>, and phospho-cell cycle checkpoint kinase 2 (Chk2)<sup>Thr68</sup> signals were noted in PanIN lesions, compared to that in the normal pancreatic epithelium<sup>[25]</sup>. Intraductal papillary mucinous neoplasm, another type of pancreatic cancer precursor, was also shown to have an increased phospho-Chk2<sup>Thr68</sup> nuclear signal, compared to that in the normal pancreatic epithelium<sup>[26]</sup>.  $\gamma$ H2AX<sup>Ser139</sup>, phospho-ATM<sup>Ser1981</sup>, phospho-Chk1<sup>Ser345</sup>, phospho-Chk2<sup>Thr68</sup>, phospho-DNA-PKcs<sup>Ser2056</sup>, Rad51, and Ku70 expression levels are increased in invasive pancreatic cancer tissues compared to that in normal pancreatic tissues<sup>[27]</sup>. Therefore, DNA damage lesions, induced by exogenous or endogenous reagents, must accumulate early in the carcinogenic process. These lesions induce universal activation of DNA damage responses; however, the repair machinery does not work perfectly and may itself be the victim of mutation. This hypothesis is supported by the observation that some familial pancreatic cancers

are associated with genetic defects in DNA damage responses and repair machinery, such as *TP53*, *BRCA2*, *ATM*, *PALB2*, and MMR-related genes (e.g., *hMLH1*, *hMSH2*, and *hMSH6*)<sup>[28]</sup>.

Notably, a recent study, which applied whole-genome sequencing and copy number variation analysis, demonstrated that four subtypes of structural variation could be identified in pancreatic cancer<sup>[29]</sup>. Among them, the “unstable” subtype was characteristic of defects in genomic stability with considerable structural variations. Ten of 14 patients in this subgroup were in the top quintile of the *BRCA* signature, with deleterious mutations in *BRCA1*, *BRCA2*, or *PALB2* genes. Most importantly, five patients in this subtype responded very well to platinum-based therapy<sup>[29]</sup>. In fact, the DNA repair mechanisms implicated in platinum or IR treatment are overlapping, including DSB repair, SSB repair, NER, BER, and MMR. This study provides a strong rationale for radiosensitization, using agents to inhibit the DNA repair machinery in pancreatic cancer cells treated with IR, so that lethal DNA lesions will go unrepaired. We present a comprehensive review of the mechanism and clinical histories of these agents.

## POLY (ADP-RIBOSE) POLYMERASE INHIBITORS

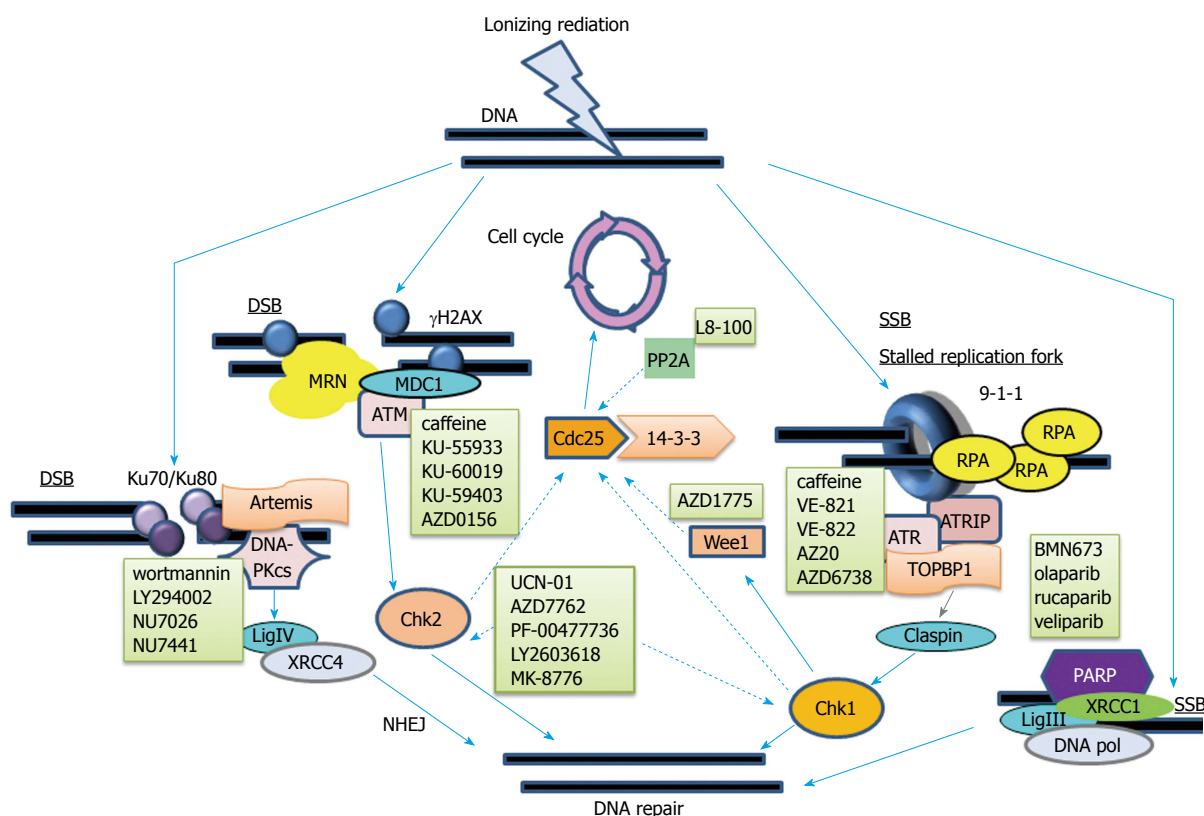
Poly (ADP-ribose) polymerases (PARPs) are nuclear proteins that play important roles in SSB repair. DNA breaks induce PARP to bind to the lesions, through its N-terminal zinc finger motifs, which causes massive ADP-ribose polymerization. PARP hydrolyzes nicotinamide adenine dinucleotide to generate ADP-ribose units. It covalently adds the units to the side chains of aspartate, arginine, lysine, and glutamate amino acids on the surfaces of nearby protein substrates and PARP itself. Then, DNA repair machinery, which has a high affinity for ADP-ribose polymers, is recruited to the DNA nicks and performs DNA repair<sup>[30]</sup>. Preclinical and clinical studies demonstrated that cancers, with mutated *BRCA1* and/or *BRCA2*, were highly sensitive to PARP inhibitors<sup>[31-37]</sup>; this confirms the “synthetic lethal” hypothesis<sup>[38]</sup>. *BRCA1* binds to CtBP-interacting protein and the MRE11-RAD50-NBS1 (MRN) complex, when double strand DNA breaks occur. This forms a functional unit that senses and resects the damaged DNA. Then, *BRCA1*, *BRCA2*, and *PALB2* mediate RAD51 recombinase-dependent HR<sup>[39]</sup>. However, cancer cells with defective *BRCA1*, *BRCA2*, or *PALB2* have high genomic instability<sup>[29]</sup>. Therefore, these HR-defective cancer cells are vulnerable to PARP inhibitors that interfere with SSB repair. They suffer from error-prone DNA repair, cell cycle arrest, and ultimately cell death.

Pancreatic cancer, with defective HR, is highly sensitive to PARP inhibitors<sup>[34,37,40-42]</sup>. Capan-1, a prototypical pancreatic cancer cell line with defective *BRCA2* (6174delT), has *in vitro* sensitivity to molecular

**Table 1 Summary of compounds entering clinical trials of pancreatic cancer or radiotherapy**

Compound	Target	RT	Clinical trial
Rucaparib	PARP	-	A Study of Rucaparib in Patients With Pancreatic Cancer and a Known Deleterious BRCA Mutation (NCT02042378)
Olaparib (AZD2281)	PARP	-	Ph II Olaparib for BRCAness Phenotype in Pancreatic Cancer (NCT02677038) Olaparib in gBRCA Mutated Pancreatic Cancer Whose Disease Has Not Progressed on First Line Platinum-Based Chemotherapy (POLO)(NCT02184195) Trial of ICM With or Without AZD2281 (Olaparib) in Patients With Advanced Pancreatic Cancer (NCT01296763) Efficacy and Safety of PARPi to Treat Pancreatic Cancer (NCT02511223) Study to Assess the Safety and Tolerability of a PARP Inhibitor in Combination With Gemcitabine in Pancreatic Cancer (NCT00515866)
		+	Olaparib Dose Escalating Trial + Concurrent RT With or Without Cisplatin in Locally Advanced NSCLC (olaparib) (NCT01562210) Olaparib and Radiotherapy in Inoperable Breast Cancer (NCT02227082) Olaparib and Radiotherapy in Head and Neck Cancer (NCT02229656) Phase I Study of Olaparib Combined With Cisplatin-based Chemoradiotherapy to Treat Locally Advanced Head and Neck Cancer (ORCA-2) (NCT02308072)
BMN673 (Tazaloparib)	PARP	-	Study of Talazoparib, a PARP Inhibitor, in Patients With Advanced or Recurrent Solid Tumors (NCT01286987)
Veliparib (ABT-888)	PARP	-	Gemcitabine Hydrochloride and Cisplatin With or Without Veliparib or Veliparib Alone in Treating Patients With Locally Advanced or Metastatic Pancreatic Cancer (NCT01585805) Veliparib, Oxaliplatin, and Capecitabine in Treating Patients With Advanced Solid Tumors (NCT01233505) Veliparib, Cisplatin, and Gemcitabine Hydrochloride in Treating Patients With Advanced Biliary, Pancreatic, Urothelial, or Non-Small Cell Lung Cancer (NCT01282333) Veliparib in Treating Patients With Malignant Solid Tumors That Did Not Respond to Previous Therapy (NCT00892736) Veliparib and Irinotecan Hydrochloride in Treating Patients With Cancer That Is Metastatic or Cannot Be Removed by Surgery (NCT00576654) ABT-888 With Modified FOLFOX6 in Patients With Metastatic Pancreatic Cancer (NCT01489865)
		+	A Phase I Study of Veliparib (ABT-888) in Combination With Gemcitabine and Intensity Modulated Radiation Therapy in Patients With Locally Advanced, Unresectable Pancreatic Cancer (VelGemRad) (NCT01908478) A Study Evaluating the Efficacy and Tolerability of Veliparib in Combination With Paclitaxel/Carboplatin-Based Chemoradiotherapy Followed by Veliparib and Paclitaxel/Carboplatin Consolidation in Subjects With Stage III Non-Small Cell Lung Cancer (NCT02412371) Veliparib With or Without Radiation Therapy, Carboplatin, and Paclitaxel in Patients With Stage III Non-small Cell Lung Cancer That Cannot Be Removed by Surgery (NCT01386385) A Clinical Study Conducted in Multiple Centers Comparing Veliparib and Whole Brain Radiation Therapy (WBRT) Versus Placebo and WBRT in Subjects With Brain Metastases From Non Small Cell Lung Cancer (NSCLC) (NCT01657799) A Phase I Study of ABT-888 in Combination With Conventional Whole Brain Radiation Therapy (WBRT) in Cancer Patients With Brain Metastases (NCT00649207) ABT-888, Radiation Therapy, and Temozolomide in Treating Patients With Newly Diagnosed Glioblastoma Multiforme (NCT00770471) Pre-Operative Radiation and Veliparib for Breast Cancer (NCT01618357)
Iniparib (BSI-201)	PARP	+	A Trial Evaluating Concurrent Whole Brain Radiotherapy and Iniparib in Multiple Non Operable Brain Metastases (RAPIBE) (NCT01551680)
VX-970 (VE-822)	ATR	+	VX-970, Cisplatin, and Radiation Therapy in Treating Patients With Locally Advanced HPV-Negative Head and Neck Squamous Cell Carcinoma (NCT02567422) VX-970 and Whole Brain Radiation Therapy in Treating Patients With Brain Metastases From Non-Small Cell Lung Cancer (NCT02589522)
AZD6738	ATR	+/-	Phase I Study to Assess Safety of AZD6738 Alone and in Combination With Radiotherapy in Patients With Solid Tumours (Patriot) (NCT02223923)
UCN-01	Chk1	-	UCN-01 and Gemcitabine in Treating Patients With Unresectable or Metastatic Pancreatic Cancer (NCT00039403) UCN-01 and Fluorouracil in Treating Patients With Metastatic Pancreatic Cancer (NCT00045747) 7-Hydroxystaurosporine and Irinotecan Hydrochloride in Treating Patients With Metastatic or Unresectable Solid Tumors or Triple Negative Breast Cancer (NCT00031681)
LY2603618	Chk1	-	A Study for Patients With Pancreatic Cancer (NCT00839332)
MK-1775 (AZD1775)	Wee1	-	Paclitaxel Albumin-Stabilized Nanoparticle Formulation and Gemcitabine Hydrochloride With or Without WEE1 Inhibitor MK-1775 in Treating Patients With Previously Untreated Pancreatic Cancer That Is Metastatic or Cannot Be Removed by Surgery (NCT02194829)
		+	Dose Escalation Trial of MK1775 and Gemcitabine (+Radiation) for Unresectable Adenocarcinoma of the Pancreas (NCT02037230)
LB-100	PP2A	-	Phase I Study of LB-100 With Docetaxel in Solid Tumors (NCT01837667)
MSC2490484A	DNA-PK	+	Phase 1 Trial of MSC2490484A, an Inhibitor of a DNA-dependent Protein Kinase, in Combination With Radiotherapy (NCT02516813)





**Figure 1 Major DNA repair pathways and molecular agents that inhibit DNA repair.** Here we demonstrate the main DNA repair pathways that are activated by IR-induced DNA damage. DNA repair machinery, with high affinity for ADP-ribose polymers, is recruited to DNA nicks after PARP binds SSB lesions; this executes DNA repair. RPA binds to ssDNA and recruits ATR and ATRIP. This is followed by recruitment of the 9-1-1 complex, TOPBP1, and claspin. Finally, Chk1 activates downstream repair machinery and phosphorylates Cdc25 proteins, which are inhibited by 14-3-3 proteins; this arrests the cell cycle. Wee1 and PP2A are also able to modulate the activity of Cdc25. DSB repair requires H2AX phosphorylation and recruitment of the MRN complex, MDC1, and ATM. Then Chk2 is phosphorylated, activated, and mediates repair and cell cycle arrest. NHEJ is the main IR-induced DSB repair method. It starts with Ku70/Ku80 heterodimer recruitment, which is followed by DNA-PKs to form the active DNA-PK. Then DNA ligase IV and XRCC4 mediate DNA ligation. The respective molecular inhibitors for PARP, ATR, Chk1/Chk2, ATM, and DNA-PK are indicated. IR: Ionizing radiation; PARP: Poly ADP ribose polymerase; SSB: Single-strand break; DSB: Double-strand break; RPA: replication protein A; ATR: Ataxia-telangiectasia and Rad3 related; ATRIP: ATR-interacting protein; TOPBP1: Topoisomerase-binding protein-1; MRN: MRE11-RAD50-NBS1; NHEJ: Non-homologous end joining; ATM: Ataxia-telangiectasia mutated.

targeted agents, including rucaparib, olaparib, and BMN 673<sup>[37,40,41]</sup>. Increased formation of nuclear  $\gamma$ H2AX foci was found<sup>[37,41]</sup> after treatment of Capan-1 with rucaparib or BMN 673, which indicated an increased number of DNA breaks. In contrast, nuclear RAD51 foci did not increase<sup>[37,41]</sup>. A study, in the xenograft model of Capan-1, combined rucaparib with carboplatin, a DNA-damaging agent. The results showed better efficacy than that observed with either agent alone<sup>[37]</sup>. A patient-derived xenograft model, with mutated *BRCA2*, received BMN 673 treatment, which decreased cancer cell mitosis and increased cell apoptosis<sup>[41]</sup>. A phase II clinical trial of olaparib enrolling 23 pancreatic cancer patients with germline *BRCA1/2* mutations, who were heavily pretreated; the response rate and stable disease were 21.7% and 35%, respectively<sup>[34]</sup>. Hematological toxicities became a matter of concern, in a phase II study that had enrolled patients without enrichment of *BRCA* mutations, despite clinical responses to the combination of gemcitabine and olaparib that seemed to be promising<sup>[43]</sup>.

IR can induce SSB and DSB and may be synergistic

with PARP inhibitors, especially in cancer cells with defective DNA repair abilities<sup>[44]</sup>. In fact, preclinical studies demonstrated that PARP inhibitors had radiosensitizing effects in various cancer types<sup>[37,45-52]</sup>, including pancreatic cancer<sup>[53-57]</sup>, regardless of the DNA repair machinery integrity. Increased apoptosis and DNA breaks, accompanied by decreased proliferation of cancer cells, were observed in a lung cancer model using veliparib<sup>[45]</sup>. Importantly, veliparib caused comparable radiosensitization in oxic and hypoxic conditions<sup>[46]</sup>. Diminished angiogenesis was also observed in the lung cancer model that used veliparib<sup>[45]</sup>; however, increased vascular perfusion was noted in another lung cancer model using olaparib<sup>[52]</sup>. The discrepancy, in the effects of different PARP inhibitors on blood vessels, may be an epiphenomenon that is not truly associated with radiosensitization.

A synergistic effect was also shown when MiaPaCa-2, a *BRCA*-intact pancreatic cancer cell line, was treated with IR, veliparib, or both. The combination increased apoptosis *in vitro* and inhibited tumor growth in an animal model compared to that by either treatment

alone<sup>[56]</sup>. S phase arrest and then G2/M arrest were induced in MiaPaCa-2, by combining olaparib with either  $\gamma$ -irradiation or carbon-ion irradiation<sup>[54]</sup>. Rad51 foci were increased after rucaparib, IR, or combined treatment, which indicated the presence of functional HR<sup>[55]</sup>. Rucaparib induced more  $\gamma$ H2AX foci in Capan-1 than in MiaPaCa-2; however, the magnitude of  $\gamma$ H2AX foci induction after IR, or IR combined with rucaparib, was similar in the two cell lines<sup>[55]</sup>. Differences in DNA repair machinery, other than PARP-related SSB repair and BER, between Capan-1 and MiaPaCa-2 may partially explain the finding.

Gemcitabine, oxaliplatin, irinotecan, and 5-FU are all radiosensitizing agents and are current standards for advanced pancreatic cancer<sup>[11,17]</sup>. Platinum drugs, such as cisplatin, oxaliplatin, and carboplatin, have the potential to enhance the radiosensitizing effects of PARP inhibitors in patients with defective HR<sup>[29]</sup>. Synergistic effects between PARP inhibitors and oxaliplatin have been observed already in colon cancer models<sup>[58,59]</sup>. In addition, IR combined with oxaliplatin and veliparib showed further enhanced synergistic effects *in vitro* and *in vivo*<sup>[59]</sup>. Chemoradiosensitization with PARP inhibitors was also noted with irinotecan<sup>[48,59]</sup>, 5-FU<sup>[59]</sup>, and gemcitabine<sup>[55]</sup>, in different cancer models. However, the underlying mechanisms for these agents are not clear.

## ATM/ATR INHIBITORS

Increased ATM activation was observed in premalignant and invasive lesions of pancreatic cancer<sup>[25,27]</sup>. In addition, oncogenic Ras can lead to increased oxidative DNA damage<sup>[60]</sup> and DNA replication stress-induced DNA damage. It eventually activates ataxia-telangiectasia and Rad3-related (ATR)/Chk1-related DDR<sup>[61,62]</sup>. ATM and ATR belong to the phosphatidylinositol 3-kinase-related kinase (PIKK) family of serine/threonine protein kinases; they share a number of substrates. The MRN complex is recruited upon DNA DSB, induced by IR, chemicals, or endogenous processes. It processes damaged DNA ends and initiates NHEJ through all cell cycle phases or HR in late S/G2 phase only<sup>[63]</sup>. The MRN complex aids the conversion of inactive ATM homodimers to active monomers, after autophosphorylation at serine<sup>1981</sup><sup>[64,65]</sup>. Then, ATM and DNA-PK phosphorylate H2AX at serine<sup>139</sup>, which forms  $\gamma$ H2AX at sites close to the DNA DSB<sup>[66,67]</sup>. The association of the MRN complex, MDC1, and  $\gamma$ H2AX enhances the accumulation of phosphorylated ATM and further phosphorylation of H2AX at DNA DSB sites<sup>[68]</sup>. Next, the DSB repair machinery is recruited and p53 and Chk2 are phosphorylated<sup>[69-71]</sup>. The replication protein A (RPA) coated ssDNA structure recruits ATR and ATR-interacting protein (ATRIP) to bind with RPA, at sites of damaged DNA or stalled replication forks<sup>[72,73]</sup>. The RAD9-HUS1-RAD1 (9-1-1) clamp complex<sup>[74]</sup> localizes to the damaged DNA sites, with the aid of RAD17 clamp loader. This event brings the ATR/ATRIP complex activator topoisomerase-binding protein-1 (TOPBP1)

to the complex<sup>[75]</sup>. This step is essential for ATR/ATRIP activation and further signaling. Claspin functions as the adaptor that brings Chk1 to the ATR/ATRIP complex<sup>[76]</sup>. Phosphorylation of the ATRIP, 9-1-1 complex, TOPBP1, the minichromosome maintenance protein (MCM) complex, and RPA also follow ATR activation.

Inhibitors of ATM or ATR are under active development for the treatment of various cancer types. Caffeine, a methylxanthine alkaloid, inhibited the kinase activities of ATM and ATR with an IC<sub>50</sub> in millimolar ranges. It subsequently induced Ser<sup>15</sup> phosphorylation of p53, 2 effects that can contribute to radiosensitization<sup>[77]</sup>. Notably, caffeine also induced radiosensitization in p53-deficient cells, through the activation of Cdk1<sup>[78]</sup>. However, the clinical use of caffeine as a radiosensitizer is limited, due to its low serum level and high systemic toxicity. KU-55933, the first potent and selective ATM inhibitor, was shown to induce radiosensitization and inhibit IR-induced ATM-mediated phosphorylation of p53, H2AX, and Chk1. However, the radiosensitizing dose of KU-55933 was much higher than the dose required to inhibit ATM<sup>[79]</sup>. KU-60019, an analog of KU-55933 with better pharmacokinetics, bioavailability, and selective potency for ATM, had a higher radiation dose to enhancement ratio in glioma cells than KU-55933 did. The radiosensitizing effect of KU-55933 was attributed to the indirect inhibition of AKT phosphorylation<sup>[80]</sup>; the aforementioned effect was more pronounced in xenograft tumors with mutant p53<sup>[81]</sup>. However, the oral bioavailability of KU-60019 was still poor<sup>[81]</sup>. KU59403, another analog of KU-55933 with higher potency and oral bioavailability had plasma and intra-tumor concentrations in therapeutic ranges in the xenograft model compared with those of KU-55933. However, its radiosensitizing effects were not addressed<sup>[82]</sup>. A few ATM inhibitors are entering clinical trials; an example is a phase I trial for AZD0156 (ClinicalTrials.gov: NCT02588105), which was developed by AstraZeneca.

Unlike ATM, the loss of ATR results in early embryonic lethality. ATR is essential for proliferating cells to ensure proper DNA replication and genomic integrity. Schisandrin B, a herbal ingredient isolated from *Fructus schisandrae*, is the first selective ATR inhibitor with an IC<sub>50</sub> in the micromolar range. Schisandrin B inhibited phosphorylation of p53 and Chk1 following UV irradiation; thereby, providing radiosensitization in A549 lung adenocarcinoma cells<sup>[83]</sup>. VE-821, developed by Vertex Pharmaceuticals, was the first selective and potent ATR inhibitor<sup>[84]</sup>. It conferred radiosensitization among all 12 cell lines that were tested. Notably, it could induce radiosensitization and reduce Chk1 phosphorylation in hypoxic conditions<sup>[85]</sup>. Radiosensitization was observed, in pancreatic cancer cell lines with defective p53, when VE-821 was used concurrently with IR or 24 h after IR; it occurred under normoxic and hypoxic conditions. G2/M phase was delayed and reduced in this study, which indicated that IR-induced checkpoint activation was inhibited by VE-821<sup>[86]</sup>. Foci of 53BP1 and  $\gamma$ H2AX increased

following IR and VE-821 treatment. Interestingly, Rad51 foci were reduced, which suggested inhibition of HR repair<sup>[86]</sup>. VE-822, also known as VX-970, is an analog of VE-821. It is the first selective ATR inhibitor to enter clinical trials. In a pancreatic cancer cell line model, VE-822 induced radiosensitization, by downregulating Chk1 phosphorylation and Rad51 foci and upregulating 53BP1 and  $\gamma$ H2AX foci<sup>[87]</sup>. VE-822 did not have an antitumor effect *in vivo*; however, it enhanced the efficacy of IR, without significant weight loss in animals<sup>[87]</sup>. Moreover, tumor growth delay was more significant with gemcitabine-VE-822 plus IR, compared with that by either agent used singly with IR<sup>[87]</sup>. AZD6738, derived from ATR and mTOR inhibitor AZ20<sup>[88]</sup>, is an orally available, selective, and potent ATR inhibitor; it is under phase I clinical trial development in combination with radiotherapy (ClinicalTrials.gov: NCT02223923). AZD6738 was shown to inhibit Chk1 phosphorylation and *in vitro* and *in vivo* radiosensitization<sup>[89]</sup>.

## CHECKPOINT KINASE INHIBITORS

Chk1 and Chk2 are functionally overlapping serine/threonine protein kinases. Chk1 or Chk2, activated by phosphorylation (Ser<sup>317</sup> and Ser<sup>345</sup> on Chk1, Thr<sup>68</sup> on Chk2), binds to, and phosphorylates Cdc25 phosphatases. Then, 14-3-3 proteins bind to, sequester, and inhibit Cdc25 phosphatases<sup>[90,91]</sup>. In addition, Chk1 activates (never in mitosis gene A)-related kinase-11 (Nek11), which phosphorylates Cdc25A and mediates its polyubiquitination and degradation<sup>[92]</sup>. Human cells have 3 isoforms of Cdc25, all of which can dephosphorylate and activate Cdks. Cdc25s are rapidly degraded when DNA is damaged and the activities of Cdk1 and Cdk2 are inhibited; this results in cell cycle arrest<sup>[93]</sup>.

UCN-01 (7-hydroxystaurosporine) is the first Chk1 inhibitor that has a non-specific inhibitory spectrum, low volumes of distribution, and systemic clearance. Unexpectedly, UCN-01 strongly binds to  $\alpha$ 1-acid glycoprotein<sup>[94]</sup>. The long half-life, decreased bioavailability, and pharmacokinetics that are highly variable among patients, may be attributed to  $\alpha$ 1-acid glycoprotein; this precluded UCN-01 from more advanced clinical development<sup>[95]</sup>. In addition, the activity of UCN-01 in pancreatic cancer was poor<sup>[96]</sup>. AZD7762, an ATP competitive and non-selective inhibitor of Chk1 and Chk2, was shown to have *in vitro* and *in vivo* chemosensitization, through stabilization of Cdc25A, following gemcitabine treatment<sup>[97]</sup>. IR plus AZD7762, in the HT-29 colon cancer cell model, delayed tumor growth more than IR alone, due to impairment of DNA repair by AZD7762<sup>[98]</sup>. AZD7762 showed better radiosensitization, with or without concurrent treatment with olaparib, in pancreatic cell lines with defective P53, including MiaPaCa-2<sup>[53]</sup>. A combination of IR and AZD7762, in the same model, resulted in Ser<sup>345</sup> phosphorylation of Chk1, Cdc25A

stabilization, decreased Rad51 foci, and delayed *in vivo* tumor growth<sup>[99]</sup>. However, cardiac toxicities, including increased troponin I, myocardial ischemia, abnormal electrocardiogram, and decreased ejection fraction, precluded AZD7762 from further clinical development<sup>[100,101]</sup>.

PF-00477736, a selective and potent ATP competitive Chk1 inhibitor, was shown to inhibit Chk2. It abrogated gemcitabine-induced S-phase arrest, increased  $\gamma$ H2AX expression, and induced apoptosis in a HT-29 cell line<sup>[102]</sup>. In addition, the sequential administration of gemcitabine and PF-00477736, in an *in vivo* model, resulted in more inhibition of tumor growth than gemcitabine alone<sup>[103]</sup>. Remarkably, three-component chemoradiation, with PF-00477736, gemcitabine, and Lutetium-177 Lu-labeled anti-EGFR antibody, completely eradicated pancreatic cancer xenografts<sup>[102]</sup>. However, the phase I clinical trial was prematurely terminated, because of business-related reasons (ClinicalTrials.gov: NCT00437203).

LY2603618 and MK-8776 (SCH 900776) are other Chk1 and/or Chk2 inhibitors entering clinical trials. Studies showed that both agents cause chemosensitization with gemcitabine<sup>[104-106]</sup>. Expanded studies showed that a combination of MK-8776, gemcitabine, and radiotherapy was the most promising treatment for inhibition of tumor growth, in animal models of pancreatic cancer<sup>[105]</sup>. The most common grade 3 or more toxicity, encountered with the use of gemcitabine or LY2603618, was hematological<sup>[107]</sup>. Grade 3 or higher hematological toxicities and fatigue were the most common negative effects in response to gemcitabine and MK-8776 treatment; however, such occurrences were rare with MK-8776 alone<sup>[108]</sup>. A variety of Chk1 and/or Chk2 inhibitors are under active preclinical development, including EXEL-9844 (also called XL-844), CEP-3891, PD-321852, Chir-124, CCT241533, LY2606368, CCT245737, SAR-020106, and GNE-900<sup>[109-118]</sup>.

## WEE1 AND PP2A INHIBITORS

Chk1 activates Wee1 kinase1 at the G2-M checkpoint, upon DNA damage. Activated Wee1 phosphorylates CDC2 (Cdk1)<sup>Tyr15</sup>, which enables CDC2/Cdk1 inactivation; this process contributes to G2-M arrest<sup>[119]</sup>. At the same time, activated Chk1 phosphorylates and inactivates Cdc25 to prevent the dephosphorylation and inactivation of CDC2/Cdk1. In contrast, protein phosphatase 2A (PP2A) is able to dephosphorylate and inhibit Cdc25, through 14-3-3 protein<sup>[120]</sup>. Therefore, inhibitors of Wee1 or PP2A can be used to maintain the activity of Cdc25; thus, they theoretically allow cell cycle progression, without adequate time for DNA repair.

*In vitro* studies, in p53-defective MCF-7 cancer cells derived from breast cancer cell lines, showed that compared to p53-intact cells, these cells were much more sensitive to Wee1 inhibition by MK-1775

(AZD1775)<sup>[121]</sup>. In addition, radiosensitization was observed in the p53-defective MCF-7 cells in a clonogenic assay. Cells pretreated with MK-1775 (AZD1775) had a reduction in Cdk1<sup>Tyr15</sup> phosphorylation and 53BP1 foci; however, they had an increase in  $\gamma$ -H2AX after IR<sup>[121]</sup>. The defective DNA repair was through inhibition of HR, but not NHEJ<sup>[121]</sup>. MK-1775 (AZD1775) monotherapy, in patient-derived pancreatic cancer xenografts, was ineffective<sup>[122]</sup>. However, a combination of gemcitabine and MK-1775 (AZD1775) abrogated G2-M checkpoint arrest, which was accompanied by pancreatic tumor regression, increased mitotic entry and apoptosis in pancreatic cancer cells<sup>[122]</sup>. MK-1775 (AZD1775) increased gemcitabine-induced radiosensitization, in MiaPaCa-2 pancreatic cancer cell lines, through inhibition of Cdk1<sup>Tyr15</sup> phosphorylation and upregulation of  $\gamma$ -H2AX expression<sup>[123]</sup>. However, the radiosensitization phenomenon was not observed in HR and *BRCA2*-defective Capan-1 cells. A combination of AZD1775, gemcitabine, and radiotherapy enhanced a delay in tumor growth and impaired RAD51 focus formation, in xenografts derived from patients with pancreatic cancer<sup>[124]</sup>. In fact, MK-1775 (AZD1775) is the first-in-class Wee1 inhibitor, with high specificity and potency, to enter clinical trial development. A phase I study, which used single agent MK-1775 (AZD1775) to treat refractory solid tumors, had activities in patients with a *BRCA* mutation; however, myelosuppression and supraventricular tachycardia were dose-limiting toxicities<sup>[124]</sup>. Clinical trials combining MK-1775 (AZD1775) and radiotherapy in various cancer types are underway.

Knockdown of the PP2A and PPP2R1A subunit, in MiaPaCa-2 and Panc-1 cell lines, resulted in significant radiosensitization and persistent  $\gamma$ -H2AX expression. The main mechanisms, of radiosensitization by PP2A inhibition, are through the activation of CDC25C/Cdk1<sup>Tyr15</sup> and inhibition of HR<sup>[125]</sup>. The aforementioned phenomenon was reproduced using the PP2A inhibitor, LB-100, which increased CDC25C<sup>Thr130</sup>, but decreased Cdk1<sup>Tyr15</sup> phosphorylation<sup>[126]</sup>. The synergistic effects of LB-100 and radiotherapy on delayed tumor growth were also observed in the MiaPaCa-2 xenograft model<sup>[126]</sup>. At present, a phase I clinical trial, in which LB-100 is administered alone or in combination with docetaxel, is ongoing. Initial outcomes show that one patient, with stage IV disease, had a long, stable disease<sup>[125]</sup>.

## DNA DEPENDENT PROTEIN KINASE INHIBITORS

A member of the PIKK family of serine/threonine protein kinases, along with ATM and ATR, DNA-PK, is essential for NHEJ, the major repair mechanism for IR-induced DSB in human cells. A catalytic subunit, DNA-PKcs, and a regulatory heterodimer (Ku70 and Ku80 subunits) combine to form active DNA-PK, which is an ATM and ATR target. It can phosphorylate Ku70/Ku80, RPA,  $\gamma$ -H2AX, Chk2, Artemis, DNA ligase IV, XRCC4,

p53, and itself. The Ku heterodimer binds to the ends of dsDNA, which become available because of DNA DSB, and recruits DNA-PKcs<sup>[127]</sup>. DNA ligase IV and XRCC4 are recruited to join the DNA ends, after the blunt DNA ends are processed and in place<sup>[120]</sup>.

Wortmannin is the first identified DNA-PK inhibitor; it is equipotent to PI3K, therefore, it is non-selective. Radiosensitization has been observed with Wortmannin<sup>[128]</sup>; however, its lack of specificity and *in vivo* toxicity precluded its clinical use. Another radiosensitizer<sup>[129]</sup>, LY294002 (structurally unrelated to Wortmannin), is a reversible kinase domain inhibitor with non-selective *in vivo* toxicity. Repair of IR-induced DNA DSB, in pancreatic cancer cell lines, was delayed by Wortmannin. Its effect was comparable between cell lines, with or without defective *BRCA2*, which indicated that NHEJ, but not HR, was successfully inhibited<sup>[130]</sup>. Wortmannin and LY294002 have demonstrated activities, as single agents, in a pancreatic cancer cell line. In addition, chemosensitization of gemcitabine by LY294002 was shown in xenograft models of pancreatic cancer. However, the involvement of DNA-PK inhibition was not addressed<sup>[131]</sup>. NU7026, which is structurally related to LY294002, was shown to have better potency and selectivity for the PIKK family kinases. It chemosensitized cells for gemcitabine<sup>[132]</sup> and impaired NHEJ repair of DNA DSB, following IR in pancreatic cancer cell lines; however, HR repair was inefficiently increased and cells showed prolonged  $\gamma$ -H2AX expression. These data indicated that radiosensitization occurred through inhibition of DNA-PK<sup>[133]</sup>. NU7441, developed from the LY294002 backbone, sensitized cells to gemcitabine in PANC-1 cells<sup>[132]</sup>. In addition, radiosensitization was only demonstrated in V3-YAC cells, with proficient DNA-PKcs, but not in V3 cells without it; this confirmed the mechanism of NU7441<sup>[134]</sup>. However, the poor pharmacokinetics of NU7026 and NU7441 precluded them from further clinical development<sup>[135]</sup>. Other DNA-PK inhibitors, including IC86621, IC87102, IC87361, OK-1035, SU11752, and KU-00600648, are currently in preclinical development<sup>[135,136]</sup>.

## CONCLUSION

In general, the clinical development of PARP, ATM, ATR, Chk1, Chk2, Wee1, PP2A, and DNA-PK inhibitors is being pursued actively (Table 1). DNA damage is a universal characteristic of pancreatic cancer cells from the premalignant to invasive stages; therefore, the use of DNA repair inhibitors, either singly or in combinations, is of great potential. The concept of synthetic lethality has been supported by the impressive clinical success of PARP inhibitors in *BRCA*-defective cancers. The optimal combination of each of these agents with radiotherapy has yet to be determined for pancreatic cancer, because of limited clinical data. Reliable biomarkers for these agents, with or without radiotherapy, are largely unknown. Chemosensitization, between these agents and genotoxic chemotherapy



drugs, has been well defined in pancreatic cancer preclinical studies. However, the best regimen and administration sequence, of a combination of chemotherapy, radiotherapy, and these agents, remain to be elucidated. Finally, immune checkpoint inhibitors have the potential for creating neoantigens, through the combined action of radiation, inhibitors of DNA repair enzymes, and genotoxic chemotherapeutic agents. This approach may open a new field of therapeutics in cancers without high mutation loads, such as pancreatic cancer<sup>[137]</sup>.

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