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Review

Molecular targets that sensitize cancer to radiation killing: From the bench to the bedside

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ABSTRACT

Radiotherapy is a standard cytotoxic therapy against solid cancers. It uses ionizing radiation to kill tumor cells through damage to DNA, either directly or indirectly. Radioresistance is often associated with dysregulated DNA damage repair processes. Most radiosensitizers enhance radiation-mediated DNA damage and reduce the rate of DNA repair ultimately leading to accumulation of DNA damages, cell-cycle arrest, and cell death. Recently, agents targeting key signals in DNA damage response such as DNA repair pathways and cell-cycle have been developed. This new class of molecularly targeted radiosensitizing agents is being evaluated in preclinical and clinical studies to monitor their activity in potentiating radiation cytotoxicity of tumors and reducing normal tissue toxicity. The molecular pathways of DNA damage response are reviewed with a focus on the repair mechanisms, therapeutic targets under current clinical evaluation including ATM, ATR, CDK1, CDK4/6, CHK1, DNA-PKcs, PARP-1, Wee1, & MPS1/TTK and potential new targets (BUB1, and DNA LIG4) for radiation sensitization.

1. Introduction

Preservation of genomic sequence information in biological systems is crucial for the survival of life. On one hand, mutagenesis is critical for genetic variation necessary for natural selection, on the other hand it could predispose for the development of cancer and other diseases. DNA is an innately reactive molecule that is sensitive to chemical alterations from both endogenous and exogenous sources [1]. Endogenous DNA damage may be caused by cellular factors such as hydrolysis, oxidation, alkylation or reactive chemical species (e.g., reactive oxygen species, ROS, and reactive nitrogen species, RNS) that are generated during physiochemical reactions. Exogenous DNA damage are caused by environmental (ionizing radiation, UV radiation), physical or chemical agents [2]. DNA lesions, such as single- and double-strand breaks, mismatches, chemical modifications of the bases, and inter- or intra-strand cross-links can be caused by ionizing radiation, UV, and chemotherapeutic agents. Fig. 1 shows the most common sources of DNA damage. A variety of clinical abnormalities, including dementia, infertility, immunodeficiencies, and cancer susceptibility, are, at least in part, caused by cells' inability to properly repair DNA damage [3]. Additionally, the chance of developing cancer is increased by the development of DNA damage in cells upon exposure to carcinogens. Genomic instability and mutation, one of the hallmarks of cancer will result if DNA damage is not repaired [4].

1.1. DNA damage response mechanism

The DNA damage response (DDR) is an evolutionarily-conserved defensive mechanism against various DNA lesions that may recognize, signal, and repair the damage through a series of enzymatic activities controlled by multiple proteins [3,5]. Proteins that are involved in the DDR identify and process different forms of DNA damage [5]. A majority of cancer cells have DDR pathway defects that promote malignant growth and increase the chance of tumor cell survival through natural selection [3]. Cancer cells become more reliant on alternative DDR pathways to preserve the integrity of their chromosomes when one or more DDR pathways are disrupted [6]. As a result, there is interest in the therapeutic development of inhibitors that target a specific subset of DDR network components; several are approved while many are undergoing clinical trials [7].

Nucleus and mitochondria are the two primary organelles that contain DNA in mammalian cells. Major pathways for nuclear DNA

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repair (Fig. 2) include:

a) Direct reversal which rectifies damage caused by alkylating chemicals,

b) Base excision repair (BER) which targets non-bulky defective DNA bases and DNA single strand breaks (SSBs),

c) Nucleotide excision repair (NER) which reconstitutes large DNA damages that deform the DNA helix,

d) Base-base mismatch repair, insertion or deletion loop repair, and mismatch repair (MMR),

e) Recombination repair which is categorized into homologous recombination repair (HR) and non-homologous end joining (NHEJ),

f) Repair of DSBs is achieved via alternative non-homologous end joining (alt-NHEJ),

g) Translesion synthesis (TLS) which is a DNA damage tolerance process.

In contrast, the mitochondrial DNA (mtDNA) repair pathways that repair damaged DNA retain mitochondrial integrity, safeguard mtDNA from oxidative damage, and enhance survival are typically those that result in direct reversal: MMR, BER, TLS, and DSB repair [8], although mutations to the mitochondrial DNA still occur.

SSBs and minor alterations in DNA are repaired via the BER [9] components XRCC1, PARP-1, apurinic apyrimidinic endonuclease (APE1), and DNA ligase IIIa. The excision repair cross-complementing protein 1 (ERCC1)-dependent NER mechanism [10] handles bulky DNA lesions including pyrimidine dimers induced by UV-irradiation. MMR pathway can fix base mismatches that occur as a consequence of replication errors [11].

The MRE11–RAD50–NBS1 (MRN) complex identifies and binds to DSB sites. It subsequently autophosphorylates and triggers ataxia telangiectasia mutated (ATM) kinase [12,13]. When ATM is activated, it phosphorylates many downstream proteins [14]. Phosphorylation of CHK2 causes CDC25A, a protein phosphatase, to phosphorylate, causing cell cycle arrest. BRCA1 phosphorylation results in DSB repair and S phase cell cycle arrest, whereas p53 activation results in G1 phase cell cycle arrest or apoptosis. The ataxia telangiectasia and Rad3-related (ATR) kinase is triggered and recruited to the DNA damage sites during the primary response to SSBs/DNA replication fork collapse [15]. CHK1 [16], which controls the activation of CDC25 phosphatases and consequently plays a role in the S and G2/M cell checkpoints, is phosphorylated and activated by ATR. To repair several forms of DNA damage, the DNA repair processes can function alone or in tandem.

Radiation mediated base damages and SSBs are quickly and efficiently repaired by cells. Most cytotoxic effects occur due to cells inability to repair DSBs. The two most prominent strategies to repair DSBs are NHEJ and HR [17]. NHEJ is an error-prone repair process that involves directly re-joining two broken ends and it is the most efficient DSB repair process. NHEJ is mediated by a group of proteins that includes the Ku70/Ku80 complex, DNA-PK catalytic subunit (DNA-PKcs), Artemis nuclease, XRCC4-like factor (XLF), DNA ligase IV, and X-ray repair cross complementing 4 (XRCC4). Binding of heterodimer Ku70/Ku80 at DSB ends [18] is the initial stage of NHEJ, and it facilitates the recruitment of catalytic component DNAPKcs to create an active holoenzyme complex [19]. H2AX [20], Artemis [21], XRCC4, ligase IV complex [22], and XLF [23] are attracted to the DSB site and partake in its repair. NHEJ is probably much more precise than previously thought due to the flexibility of the NHEJ components, but if the DSB ends are incompatible, NHEJ-mediated repair can cause minor deletions, insertions, or indels. Given these factors, NHEJ seems to be a reliable repair mechanism that might help a cell increase its chances of surviving [24]. It is also the main pathway through which radiation damage is repaired and impairing this pathway may lead to radiosensitization.

HR, on the other hand, is an error-free repair strategy that uses a non-damaged complementary chromatid as a template [17]. HR is mediated by BRCA1 and 2, replication protein A (RPA), MRN complex, CtBP-interacting protein (CtIP), RAD51, and PALB2. The DSB site binds the MRN complex, DNA2-BLM (Bloom syndrome), CtIP, BRCA1, and exonuclease 1 (EXO1), which play a role in DNA reprocessing and the production of 3′ single-strand DNA, which is consequently encapsulated by RPA protein [25]. The missing sections can be synthesized by DNA polymerases. Holliday junctions, branched nucleic acid structure that impair function, are eventually resolved by cleaving and ligating neighboring ends [26]. Although HR is considered “error-free” repair, the process can be error prone when templates are swapped, as in repeat sequences [27]. Cell cycle stage, chromatin context, and availability of critical players such as Ku complex, RAD51, and 53BP1 may impact the selection between NHEJ and HR [28].

1.2. Human cancers with aberrations in DDR

Enhanced autophosphorylation of ATM as well as ATM-dependent phosphorylation of CHK2 have been seen in early-stage malignancies, implying that the DDR may prevent progression to malignancy [29,30]. In radiation-resistant malignancies, DNA-PKcs have been found to be increased [31,32]. Upregulation of PARP1, BRCA1, APE1, RAD51, and ERCC1 have been observed in a variety of malignancies and have been linked to chemotherapy resistance [33]. In human sporadic malignancies, p53 is one of the most commonly altered genes. The reported frequency of p53 mutations vary by cancer type with more than half of all malignancies having inactivated p53 as a result of mutations, deletions, loss of heterozygosity, or reduced expression [34,35]. While BRCA1 and 2, as well as ATM inactivating mutations are less prevalent than p53 inactivating mutations [36–40], reduced expression of the MRN complex, ATM, BRCA1 and 2, CHK2, RAD51, and ERCC1 is widespread in sporadic malignancies, suggesting that DNA damage response aberration is common [41–49]. Interestingly, functional inactivation BRCA2 was observed in cancer cells that abnormally expressed SYCP3 [3] a cancer/testis antigen that is known to regulate strand

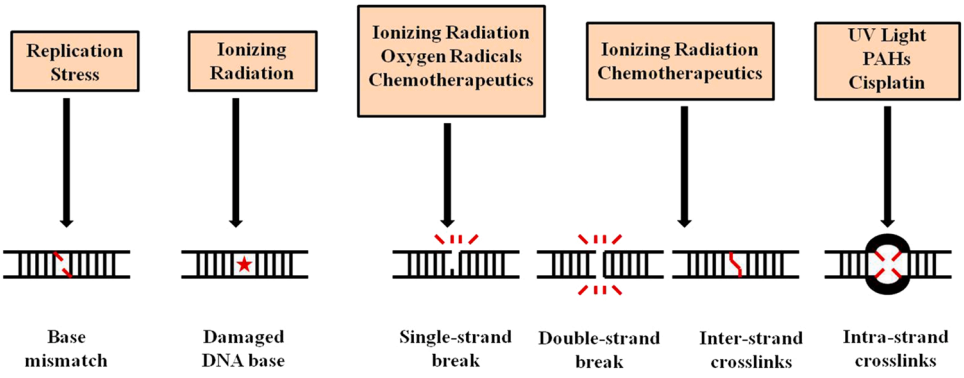

Fig. 1. Most common sources of DNA damage. There are possibly other mechanisms for causing DNA damage but they are omitted here for simplicity.

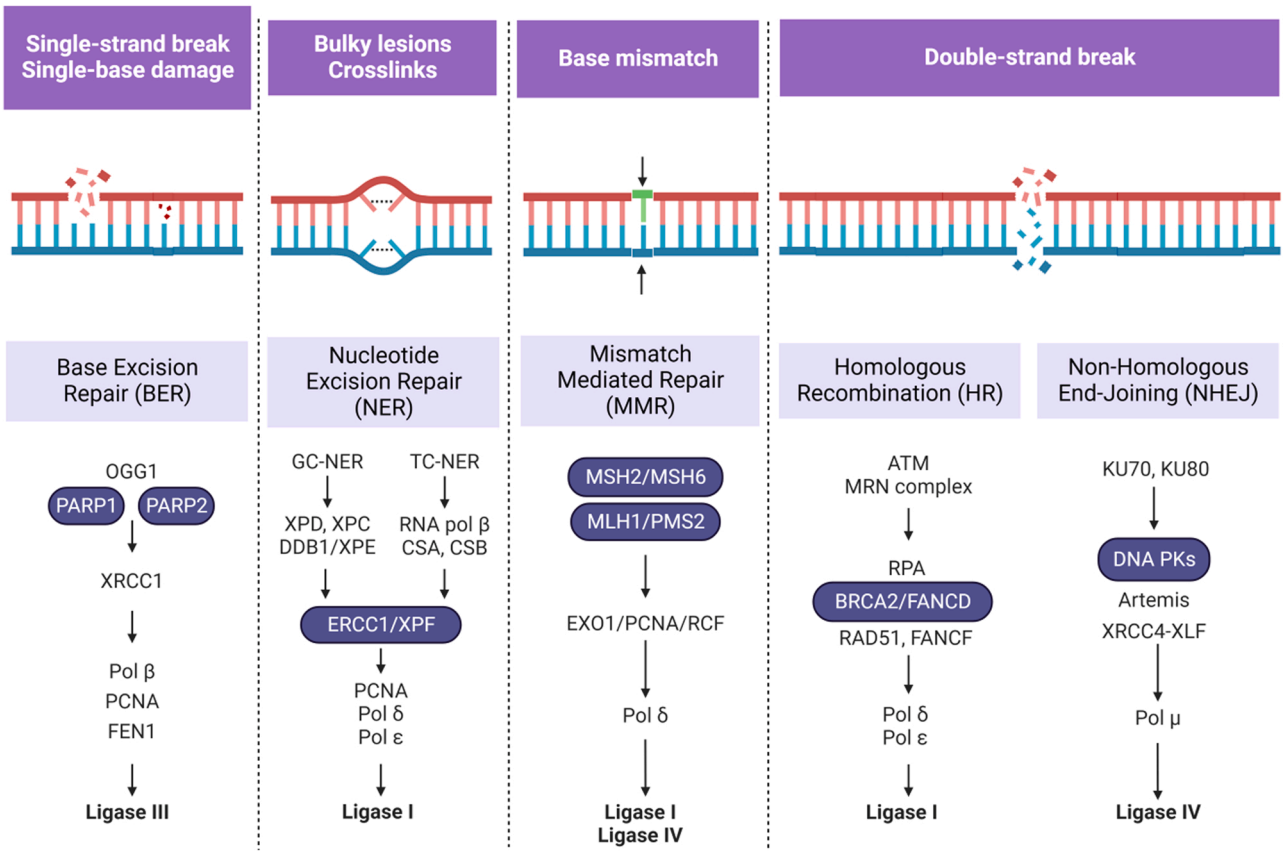

Fig. 2. Major pathways for DNA repair (Adapted from "DNA Repair Mechanisms", by BioRender.com (2022).

invasion activities of Rad51.

1.3. Radiation-induced DDR

DDR is a complex protein network that coordinates cell cycle regulation and DNA repair. It disrupts the cell cycle, stopping DNA damage from propagating to daughter cells by allowing time for repair. DDR signaling is crucial for the initiation of apoptosis [50]. It is estimated that 1 Gray (Gy) of radiation results in approximately 10,000 damaged bases, 1000 SSBs, and 40 DSBs per cell [51,52]. Most base damages and SSBs are promptly repaired [53]. DSBs are the most damaging to cells despite their low frequency since even a single unrepaired DSB could result in cell death. Radiation therapy causes DSBs directly by ionizing molecules on DNA and indirectly by hydrolyzing molecules it encounters, i.e. predominantly water, to produce free radicals such as a hydroxyl free radical that interacts with and inactivates DNA indirectly. If the resultant DNA damage is not repaired (particularly DSBs), it leads to cell death during replication [54,55].

1.4. Repair of radiation-induced DNA damage

As described, following exposure to ionizing radiation, multiple types of damages can occur to DNA resulting in activation of repair processes. The BER repairs damaged bases caused by oxidative stress [56–61]. DNA glycosylases excise damaged bases during BER, resulting in apurinic (AP) sites. Following that, apurinic endonuclease 1 (APE1) cleaves these AP sites, resulting in SSBs. SSB repair is a component of the BER pathway that repairs SSBs [62]. Depending on the lesion type and cell cycle phase, either short- or long-patch SSB repair is utilized. PARP binds to SSB, which stimulates auto-PARylation and causes BER/SSBR proteins to be recruited. PARP-1 has been implicated as a DNA repair gene regulator in the E2F1 pathway [63]. While most of the radiation-mediated oxidative damage is repaired by BER, damage that occurs under hypoxic conditions is repaired through NER [64]. ERCC2, a DNA helicase and part of the NER system, reconstitutes intrastrand crosslinks induced by genotoxins like UV irradiation and cisplatin. Mutation of ERCC2 has been linked to the risk of breast cancer caused by ionizing radiation [65]. The activation of three important PIKK family enzymes, ATM, ATR, and DNA-PK is triggered by the creation of DSBs [66] which initiates downstream signaling cascades to access DNA damage and trigger DNA repair [67]. Phosphorylation of γ-H2AX indicates the existence of DSB and directs proteins to repair irradiation-induced foci (IRIF) in initial stages [68].

1.5. Radiotherapy sensitization targets in cancer

Cancer cells' natural ability to repair DNA damage may cause cellular resistance and restrict the effectiveness of treatment, despite the fact that radiation-induced DNA DSBs are the most efficient molecular events for eliminating cancer cells [69]. It is expected that target-based radiosensitization approaches would increase the effectiveness of radiotherapy by selectively sensitizing tumor tissue to ionizing radiation [70]. Recently, a variety of approaches have been used to develop radiosensitizers that are highly effective and have low toxicity [71].

Targeting DDR signaling pathways has emerged as a promising approach to overcome tumor radioresistance, and significant advancements and discoveries have already been made in this area in recent years. Utilizing DDR to sensitize the cancer cells to ionizing radiation is considered as a viable therapeutic alternative for treating cancer patients effectively. Table 1 summarizes the types of DNA damage-inducing therapies (cytotoxic chemotherapies, targeted therapies and combination approaches for radiation sensitization) employed in cancer treatment with few examples.

Table 1
Types of DNA damage-inducing therapies employed in cancer treatment.

DNA Damage-Inducing Therapies	Types
Cytotoxic Chemotherapy	A. Alkylating Agents Monofunctional alkylating agents (Temozolomide and Dacarbazine) Bifunctional agents (Aziridines and Epoxides) B. Platinum-Based Compounds Cisplatin, Carboplatin, and Oxaliplatin C. Antimetabolites 5-fluorouacil (5-FU), Gemcitabine, 6-mercaptopurine, Fludarabine, Cytarabine, Methotrexate, and Pemetrexed D. Topoisomerase Inhibitors Type I topoisomerases (TOPI) poisons (Topotecan and Irinotecan) Type II topoisomerase (TOPII) (Etoposide) E. Antitumor Antibiotics Anthracyclines, Dactinomycin, Mitomycin C, and Bleomycin
Targeted Therapies	PARP inhibitors (Olaparib, Niraparib, Rucaparib and Talazoparib) HER2 inhibitors (Trastuzumab [72,73] and Pertuzumab [74,75]) EGFR inhibitors (Erlotinib [76,77], Osimertinib [78, 79], Cetuximab [80,81], Panitumumab [82,83], and gefitinib [84,85]) VEGF and mTOR inhibitors (Sorafenib [86,87], Sunitinib [88,89] and Pazopanib [90,91], Bevacizumab [92,93], Temsirolimus [94,95] and Everolimus [96, 97])
Combination Approaches	Radiotherapy and Chemotherapy Combinations such as • Oxaliplatin, Irinotecan and the antimetabolite 5-FU (FOLFIRINOX) • Combination of Cisplatin with Radiotherapy • 5FU-Cisplatin with Radiotherapy • 5FU/Capecitabine with Radiotherapy • Temozolomide with Radiotherapy • Gemcitabine with Radiotherapy • Carboplatin with Radiotherapy, and so on.

1.5.1. ATM/ATR

ATM was found during a clinical case observation when Gotoff et al. [98] identified immunodeficiency in a patient with a rare inherited autosomal-recessive genetic A–T syndrome in 1967 [99]. Bentley et al. [100] discovered in 1996 that ATR could improve esr1–1 radiosensitivity in *S. cerevisiae*. ATM is triggered and attracted to DSB sites by the MRN complex, which functions as a DNA damage sensor, whilst ATR is triggered and attracted to DSB sites by its binding partner ATR-interacting protein [12]. AZD1390, a brain penetrant ATM kinase inhibitor is highly potent and exhibits powerful activity in combination with radiation. This orally accessible drug is under Phase 1 clinical trial in patients with glioblastoma multiforme, brain metastases or leptomeningeal metastases. By preventing ATM from repairing tumor DNA, AZD1390 increases the likelihood that radiation will be able to kill cancer cells (NCT03423628) [101]. XRD-0394, an oral dual kinase inhibitor of ATM and DNA-PK is also under Phase 1 trial to evaluate in combination with palliative radiotherapy for the treatment of solid cancers that have spread or that are recurrent or locally progressed. This drug may enhance the effectiveness of radiotherapy by increasing the sensitivity and responsiveness of cancer tumors by inhibiting proteins that allow cells to respond to DNA damage caused by radiation (NCT05002140) [102]. AZD6738 (Ceralasertib), Berzosertib, BAY1895344, Schisandrin B, NU6027, and NVP-BEZ235 are all reported ATR inhibitors. A Phase I trial of AZD6738 was done to assess the biological effects, tolerance, and safety of palliative radiotherapy in cancer patients. To examine the impact of a fractionation schedule appropriate for radical therapy, the radiation dosage in this experiment was increased from 20 to 30 Gy over the course of 2 Gy fractions. If the combination treatment is well tolerated, the study is intended to move on with a randomised trial that compares the addition of AZD6738 to standard-of-care radiotherapy or chemoradiotherapy in a patient group receiving treatment with radical intent (status of this trial is still unknown) [103]. Berzosertib, formerly named as (M6620, VX-970), a highly potent and selective inhibitor which has an IC_{50} of 19 nM is used in Phase 1 clinical trial to test the combination of M6620 with palliative radiotherapy in oesophageal cancer. Since this combination is well-tolerated, the combination of M6620 with chemoradiotherapy was evaluated to improve the current standard of care and provide a targeted, efficient method of treating oesophageal cancer and squamous cell carcinoma (NCT03641547) [104]. An oral inhibitor BAY1895344 in combination with stereotactic body radiation and pembrolizumab is also under Phase 1 clinical trial to study the possible benefits in recurrent and unresectable head and neck cancer (NCT04576091) [105]. As of Aug 30, 2022, there are 12 active clinical studies (clinicaltrials.gov) with ATM/ATR inhibitors alone or in combination with RT in malignancies such as ovarian and SCLC.

1.5.2. CDK1

CDK1 regulates cell cycle progression and the G1/S transition by controlling the centrosome cycle and mitotic initiation, regulating G1 advancement, and boosting the G2/M transition [106]. When ionizing radiation causes DNA damage, CDK1 is blocked, which causes the cell cycle to stop at G2 checkpoint, allowing DSB repair [107]. A non-specific CDK1 inhibitor MEK162, inhibits and dephosphorylates CDK1, CDK2, and Wee1 [108], and is shown to delay DDR in glioblastoma cells after ionizing radiation. Raghavan et al., [109] investigated AZD5438, a new-generation CDK1 inhibitor in lung cancer cell lines in conjunction with radiation. Radiation sensitivity of lung cancer cells was significantly boosted by AZD5438. In lymphoma, JNJ-7706621, a CDK1 and AURKA/B dual inhibitor has been demonstrated to reverse radioimmunotherapy resistance [110]. Dinaciclib, a CDK1/2/5/9 inhibitor, decreased tumor growth in ten out of ten subcutaneous pancreatic ductal adenocarcinoma mice models studied, with considerable growth reduction (>40%) in eight of ten [111]. Rohitukine, from which P276–00 is generated, is found to be a selective CDK4-D1 and CDK1-B inhibitor in preclinical studies. Cell cycle events are prevented at initial stage of development when these CDKs are inhibited, which results in cell cycle arrest between the G1-S transition. As a result, it may be effective while having fewer negative effects (NCT00408018) [112]. EM-1421, (also terameprocol) is used under Phase 1/2 clinical trials for patients with refractory solid cancers [113]. This inhibitor is also used in combination with survivin (inhibitor of apoptosis protein) in patients with hematological malignancies under Phase 1 trials [114]. With IC_{50} values ranging from 30 to 200 nM, AG-024322, a potent, multi-targeted inhibitor showed strong antiproliferative effect in various human cancer cell lines [115]. There are currently 16 clinical trials utilizing CDK1 inhibitors, with three active and the rest terminated. Although based on strong preclinical data, the results from several clinical trials showed only weak to moderate benefits. Moreover, no radiotherapy studies using this inhibitor are currently in clinical trials [116–118].

1.5.3. CDK4/6

CDK4 and CDK6, directly regulate cell-cycle transitions and cell division [119]. Cyclin-CDK complexes, which are largely formed by the association of CDK4 and CDK6, with D-type cyclins (Cyclin D1, D2, and D3), control the course of the cell cycle by phosphorylating the tumor suppressor protein retinoblastoma [120]. The G1-S checkpoint, which controls genome replication in the cell cycle, is crucial for CDK4/6 [121]. Fig. 3 depicts where various DDR targeting drugs act in cell cycle. Radiosensitivity of multiple cell lines is increased by CDK4/6 inhibitors [122]. Three CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) were approved as combination treatments for HR+ , HER2-, and metastatic breast cancers in recent years [123]. Palbociclib, the first

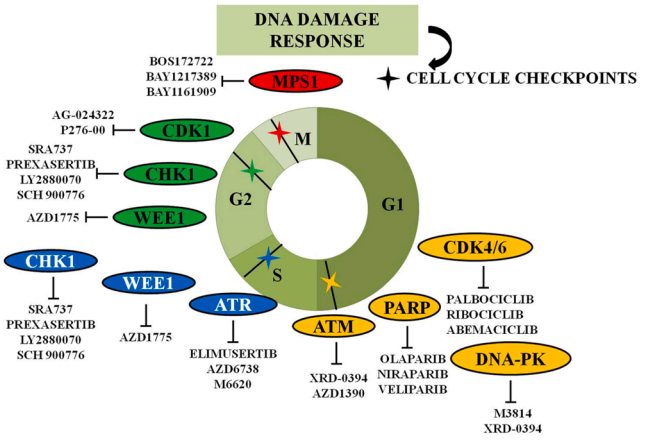

Fig. 3. Cell cycle phases and DDR targeting in cancer (G1 = Gap/growth Phase 1, S = DNA replication phase, G2 = Gap/growth phase 2, M = Cell division phase; ATM - Ataxia-Telangiesctasia Mutated, ATR - ataxia telangiectasia and Rad3-related, CDK1 - Cyclin-dependent kinase 1, CDK4/6 - Cyclin-dependent kinase 4/6, CHK1 - Checkpoint kinase 1, DNA-PK - DNA-dependent protein kinase, MPS1 - Monopolar spindle1, PARP - Poly (ADP-ribose) polymerases).

CDK4/6 inhibitor, received approval for women with untreated metastatic HR+ , HER2- breast cancer in 2015 on the basis of the outcomes of a randomized Phase 2 research carried out in a front-line setting (PALOMA-1 trial) [124]. According to Huang et al., [125] combination of radiation and palbociclib significantly suppressed radiation-induced cell proliferation and decreased radiation resistance in hepatocellular carcinoma. As shown by Naz et al., [126] palbociclib and ribociclib did not increase radiation sensitivity in non-small cell lung cancer cell lines when administered either pre- or post-IR. On the other hand, abemaciclib, when administered post-IR, it increased radiosensitivity in the non-small cell lung cancer cell lines [122]. *In vivo* studies showed that palbociclib with IR improved median survival time in brain cancer xenografts [127]. DeWire et al., [128] reported the ribociclib administration following radiation therapy in diffuse intrinsic pontine gliomas and diffuse midline glioma. Increased tumor necrosis was observed as a side effect of this therapy (NCT02607124). In children with diffuse intrinsic pontine gliomas and high-grade glioma, a combination of ribociclib and everolimus following radiation therapy was well-tolerated in Phase 1 trials (NCT03355794) [129]. There are now six active clinical trials, the majority of which are directed at patients with HR+ /HER2- metastatic breast cancer. Beyond those included here, a number of ongoing trials continue to investigate these inhibitors in various patient populations and with various treatment regimens.

1.5.4. CHK1

CHK1 is essential for DNA repair activation and checkpoint-mediated cell-cycle arrest in response to DNA damage [130]. As cellular proliferation and survival are greatly controlled by CHK1, increasing evidence suggests that targeting them as prospective techniques for sensitizing cancer cells to radiation is a viable option [131]. The first selective CHK1 inhibitor identified was LY2606368 (Prexasertib). This inhibitor is used in Phase 1 clinical trials in combination with anti-cancer drugs (Cetuximab and Cisplatin) and radiation therapy for patients with head and neck cancer (NCT02555644) [132]. PF-00477736, a selective CHK1 inhibitor, significantly increased the radiosensitivity of multiple cancer cell lines. [133]. This inhibitor entered in Phase 1 clinical trials in combination with gemcitabine for advanced solid tumors, but the study was terminated due to business reasons (NCT00437203) [134]. CCT244747, the first orally accessible CHK1 inhibitor, sensitized head and neck cancer and bladder cancer cells to radiation through modulating G2/M checkpoint, implying that CCT244747 could be acceptable for oral administration [135,136]. Another inhibitor, SRA737, was discovered to have the ability to restrict cell proliferation when combined with Niraparib [137]. Several CHK1 inhibitors have entered into clinical trials which include AZD7762, GDC-0575, MK-8776, Prexasertib, PF-00477736, Rabusertib, and SRA737 [138].

1.5.5. DNA-PKcs

DNA-PKcs was initially linked to repairing DSBs via the NHEJ pathway; however, later studies demonstrated that DNAPKcs has additional activities including the choice of NHEJ and HR repair pathways [139–142], cell cycle checkpoint regulation [143,144], and telomere maintenance [145–147]. DNA end processing is made possible by autophosphorylation, which occurs when DNAPKcs autophosphorylates at Thr2609, Thr2647, and Ser2056 [148–150]. DNA-PKcs depletion is known to increase cancer cells sensitivity to ionizing radiation and genotoxic chemotherapy [151,152]. Several DNA-PKCs inhibitors with varying selectivity and radiosensitization potential have been described including LY294002 [153,154], NU7026 [155], Vanillin, [156], IC87102, IC87361, & IC86621 [157], VX-984 [158] and AZD7648 [159] among others. Doxycycline was the first FDA approved DNA-PK inhibitor and is a good radiosensitizer of breast cancer cells [160]. Zenke et al., [161] demonstrated the radiosensitizing efficacy of orally bioavailable M3814 (Peposertib), a DNAPK inhibitor in preclinical models. Currently, M3814 and XRD-0394 (ATM and DNA-PK dual inhibitor) are under Phase 1 trials in combination with radiotherapy to examine the tolerability and safety.

1.5.6. PARP-1

PARP-1 is a widely studied DNA DSB repair protein [162]. PARP-1 can catalyze the heterodimer produced by XPC-RAD23B and free PAR, suggesting that PARP-1 is involved in the radiation-induced DNA damage [163]. Inhibiting PARP-1 could make cancer cells more sensitive to radiation [164]. Several PARP inhibitors with varying degree of specificity and radiosensitization potential have been developed including KJ-28d [165], ABT-888 [166], Mk-4827 [167], AZD2281 (Olaparib) [168], Niraparib [169,170], Veliparib, Rucaparib, Talazoparib, etc. Olaparib was the first PARP inhibitor to receive approval from the FDA and the European Union for treating advanced ovarian cancer patients with BRCA mutations. Olaparib received Breakthrough Therapy Designation from the FDA in 2016 for patients with metastatic castration-resistant prostate cancer who have mutations in BRCA1/2 or ATM. There are > 600 clinical trials at clinicaltrial.gov with search term "PARP" and > 60 when co-searched with "radiation" (as of Nov 30, 2022). These results indicate the importance of targeting PARP for anti-cancer therapies. There are 19 clinical trials on PARP-1 inhibitors in combination with radiation out of which 5 completed, 7 enrolling and rest not yet enrolled/withdrawn. Several of these trials will be game changer for patient management. For example, Olaparib is currently under Phase 1/2a trial combined with intensity modulated radiotherapy (IMRT) and temozolomide in first-line treatment of glioblastoma (NCT03212742) [171]. Similarly, Niraparib is being evaluated with Dostarlimab and radiation in either PD-L1 negative TNBC or in patients who failed to respond to prior immunotherapy (NCT04837209) [172]. Likewise, Veliparib is undergoing Phase 2 trial in combination with temozolomide and radiotherapy to assess its efficacy in treating individuals with malignant glioma (NCT03581292) [173].

1.5.7. Wee1

Wee1 acts as a negative regulator of cell cycle during the G2 to M transition [174] and Wee1 inhibition enhances cell death in response to chemotherapy and ionizing radiation by affecting both cell cycle progression and DNA damage repair [175]. Several Wee1 inhibitors have shown radiosensitization in preclinical models including Wee 1 inhibitor

II (681641) [176], R1–1 [176], PD0166285 [177], AZD1775 (also MK-1775, Adavosertib) [178–180]. Four Wee 1 inhibitors IMP7068, AZD1775, Zn-c3, and SY-4835 have moved into the clinical trials. There are more than 50 clinical trials for AZD1775 listed on the clinical trial website (as of Nov 30, 2022). Majority of these clinical studies have used a combination of chemotherapy and radiation to treat different cancers and identified that p53 mutation may be a cancer- or chemotherapy-specific prognostic biomarker for responsiveness to Wee1 inhibition. Early results from Wee1 clinical studies have been encouraging. For example, AZD1775 improved 1-year survival to 90% in head and neck cancer when combined with radiation therapy and cisplatin [180]. AZD1775 also improved overall survival in locally advanced pancreatic adenocarcinoma (Phase 2 trial) when combined with radiotherapy and gemcitabine (NCT02037230) [181].

1.5.8. MPS1/TTK

Monopolar spindle 1 (MPS1) is an important spindle assembly checkpoint kinase. It is overexpressed in several cancers including breast, bronchogenic, lung, and thyroid papillary carcinomas [182]. Increased MPS1 levels correlate with a higher histological grade [183]. It is implicated in the genotoxic stress response, such as stress produced by DNA damage. Inhibition of MPS1 causes cell death by polyploidization and mitotic collapse [184] and prevents DNA repair after RT, allowing DNA damage to accumulate leading to mitotic catastrophe. Genetic and pharmacological MPS1/TTK inhibition is shown to radiosensitize basal-like breast [185] and glioblastoma [186] cell lines. Inhibitors of MPS1 (Mps-BAY2b and MPS-IN-3) have been demonstrated in human colon cancer and glioblastoma cells to improve sensitivity to microtubule poisons (Paclitaxel and Vincristine) [187]. Currently, there are three MPS1 inhibitors (BAY1217389, BAY1161909, and BOS172722) in clinical trials. BAY1217389, an oral selective inhibitor led to increased toxicity (nausea, fatigue and diarrhea) when given in combination with paclitaxel in patients with solid tumors (NCT02366949) [188]. BAY1161909 has demonstrated enhanced efficacy in xenograft models when combined with paclitaxel and found to be well-tolerated with manageable adverse events (Phase 1) in patients with advanced malignancies (NCT02138812) [189]. BOS172722, another orally bioavailable inhibitor is currently under clinical trials in combination with paclitaxel for patients with advanced non-hematologic malignancies (NCT03328494) [190]. MPS1 inhibitors have not been evaluated in combination with radiation in human patients. The Table 2 below lists molecular targets evaluated in clinical trials for radiosensitizing different cancers.

1.6. Other novel targets

1.6.1. DNA LIG4

In radiation-induced NHEJ pathway, the DNA LIG4 is an important DNA repair factor [191]. XRCC4, LIG4, and Cernunos-XLF are commonly recruited to the break site and form temporary connections with the DNA ends to guarantee that the break is ligated [192]. Patients with LIG4 syndrome have higher radiation sensitivity, higher chance of neurological problems, bone marrow dysfunction, and cancer predisposition [193]. LIG4 mutations have been linked to clinical radiosensitization in a number of investigations. According to Riballo et al., [194] LIG4 mutation impairs synthesis of adenylate complex while also lowering rejoining activity. Furthermore, healthy patients with LIG4 rs1805388 polymorphism were more vulnerable to radiation than healthy individuals by H2AX foci analysis [195]. DNA-binding protein-1 suppresses the production of LIG4 and hence negatively influences DNA repair mechanisms. In a screen of 5280 compounds, Tseng et al., [196] showed that rabeprazole and U73122 could selectively disrupt adenylate transfer phase and DNA rejoining to impede radiation-induced DNA repair by targeting LIG4. NU7026 affects the radiosensitivity of LIG4 wild-type mouse embryonic fibroblasts [197]. A specific DNA LIG4 inhibitor SCR7 blocks NHEJ [198] and enhances HR-mediated gene editing in mammalian cells [199]. It is found to effectively inhibit the cell proliferation of various breast, lung and cervical cancer cell lines with IC_{50} values ranging from 5 to 50 μM [200]. Treatment with SCR7 in vivo prolongs lifespan by four times and lowers breast adenocarcinoma-induced tumor. It greatly increases the cytotoxic effects of radiation, etoposide, and 3-Aminobenzamide on tumors generated from Dalton's lymphoma cells [200]. Further research into LIG4 activities in the radiation-induced DDR will be useful in characterizing it as a molecular target for radiosensitization.

1.6.2. BUB1

The spindle assembly checkpoint ensures faithful chromosome segregation during cell division [201]. Budding Uninhibited by Benzimidazole 1 (BUB1) is a key component of spindle assembly checkpoint and it also facilitates chromosome alignment and mitotic duration [202]. Upregulation of mitotic factors is a significantly more common event in human tumors, and increased BUB1 levels have been reported in various cancers including breast, gastric, lung, brain and lymphoma [203]. Furthermore, BUB1 upregulation is linked to a poor clinical outcome in different tumor types [204]. In transgenic mice, BUB1 overexpression was observed to promote spontaneous carcinogenesis and promote the development of Myc-induced lymphoma [205]. Reduced BUB1 mRNA levels in colon carcinomas were associated with shorter relapse-free survival after surgery [206]. BUB1 has been identified as a possible radio-enhancing target and the lack of mitotic spindle checkpoints may actually elicit fatal mitotic events during RT, as BUB1 suppression was correlated with an increased production of micronuclei [207]. A focused human kinome screen identified BUB1 as one of the potential radiosensitizing target in breast cancer [208]. BUB1 is known to localize near DSB sites where Rad53 and H2AX are also recruited [209] and it also co-localizes with 53BP1 suggesting a role in NHEJ pathway. Knockdown of BUB1 results in prolonged H2AX foci and comet tail formation as well as hypersensitivity in response to ionizing radiation [210]. BUB1 expression is known to associate with poor outcome in a study analyzing DNA repair gene expression patterns as prognostic and predictive factors in breast cancer subtypes [211]. To enhance the efficacy of cancer therapies, further research into the underlying mechanisms of BUB1 mediated DDR is needed. Our lab is actively seeking to decipher the mechanism of BUB1 mediated radioresistance by combining genomic (siRNA, CRISPR) and biochemical (BAY1816032) ablation of BUB1 with biochemical, molecular, and radio-biological techniques.

2. Conclusion and future perspectives

Deficits in the DNA damage repair pathway may sensitize cancer cells to cytotoxic agents. Drugs that target the DDR have been clinically validated in small groups of patients, and various combination approaches to block multiple pathways that cancer cells rely on for survival are now being investigated. Indeed, better understanding the fundamental mechanisms of radiation-induced DDR and specific functions of major genes and proteins in DDR pathways, as well as their interaction partners, are critical for clinical identification of novel intervention targets and the development of efficacious cancer treatments. A variety of tumors are being targeted by the therapeutic landscape of anti-tumor drugs that target the DDR, which has rapidly extended to encompass inhibitors of other crucial mediators of DNA repair [212]. While increasing the effectiveness of killing tumor cells is the main goal of radiation-drug combinations, it is also critical to reduce the toxicities to normal tissue because the therapeutic benefit depends on the difference between efficacy and toxicity. Recently, MPS1/TTK has entered clinical trials but only with Taxols (chemotherapy). It will be interesting to see if a combination of TTK inhibitor with radiation provides any clinical benefit. Additionally, novel molecular targets such as (BUB1, LIG4 etc.) warrant further clinical exploration for evaluating

Table 2
Molecular targets evaluated in clinical trials in combination with DNA-damaging agents or radiation.

Target	Interventions	Conditions	Clinical status & Identifier	Status
ATM	• Drug: AZD1390 • Radiation: Radiation Therapy • Intensity-modulated radiation therapy (IMRT) and whole brain radiation therapy (WBRT)	Brain Cancer	Phase 1 NCT03423628	Recruiting
	Drug: XRD-0394 Radiation: Palliative radiotherapy	Metastasis Locally Advanced Solid Tumor Recurrent Cancer	Phase 1 NCT05002140	Recruiting
ATR	Drug: M6620 Drug: Cisplatin Drug: Capecitabine Radiation: Radiotherapy	Oesophageal Adenocarcinoma Squamous Cell Carcinoma Solid Tumor	Phase 1 NCT03641547	Completed
	Drug: AZD6738 Radiation: Palliative radiotherapy	Solid Tumour Refractory to Conventional Treatment	Phase 1 NCT02223923	Unknown
	Drug: Elimusertib Biological: Pembrolizumab Other: Quality-of-Life Assessment Radiation: Stereotactic Body Radiation Therapy	Head and Neck Cancer	Phase 1 NCT04576091	Recruiting
CDK1*	Drug: P276–00	Neoplasm	Phase 1 NCT00408018	Terminated
	Drug: P276–00	Neoplasm	Phase 1 NCT00407498	Completed
	Drug: P276–00	Melanoma	Phase 2 NCT00835419	Completed
	Drug: Terameprocol (EM-1421)	Leukemias Acute Myeloid Leukemia (AML) Acute Lymphocytic Leukemia (ALL) Adult T Cell Leukemia (ATL) Chronic Myeloid Leukemia (CML-BP) Chronic Lymphocytic Leukemia (CLL) Myelodysplastic Syndrome (MDS)Chronic Myelomonocytic Leukemia (CMML)	Phase 1 NCT00664677	Terminated
	Drug: Terameprocol (EM-1421)	Refractory Solid Tumors Lymphoma	Phase 1 NCT00664586	Terminated
	Drug: Terameprocol (EM-1421)	Cervical Intraepithelial Neoplasia	Phase 1 Phase 2 NCT00154089	Completed
	Drug: Terameprocol (EM-1421) Other: Pharmacological Study	High Grade Glioma (III or IV)	Phase 1 NCT02575794	Active, not recruiting
	Drug: Terameprocol (EM-1421)	Cancer	Phase 1 NCT00259818	Completed
	Drug: Terameprocol (EM-1421) Other: Pharmacological Study	Brain and Central Nervous System Tumors	Phase 1 Phase 2 NCT00404248	Completed
	Drug: AG-024322	Neoplasms Lymphoma, Non-Hodgkin	Phase 1 NCT00147485	Terminated
CDK4/6	Drug: Ribociclib (following Radiation therapy)	High Grade Glioma Diffuse Intrinsic Pontine Glioma Bithalamic High Grade Glioma	Phase 1 Phase 2 NCT02607124	Terminated
	Drug: Ribociclib Drug: Everolimus (following Radiation therapy)	Diffuse Intrinsic Pontine Glioma Malignant Glioma of Brain High Grade Glioma Bithalamic High Grade Glioma Brainstem Glioma Glioblastoma Anaplastic Astrocytoma	Phase 1 NCT03355794	Active, not recruiting
	Drug: Palbociclib Drug: Cetuximab Radiation: Intensity Modulated Radiation Therapy	Head and Neck Cancer Locally Advanced	Phase 1 Phase 2 NCT03024489	Active, not recruiting
	Drug: Palbociclib Drug: Cetuximab Drug: Cisplatin Radiation: Intensity-Modulated Radiation Therapy Procedure: Tumor biopsy Procedure: Peripheral blood draw	Head and Neck Squamous Cell Carcinoma	Phase 2 NCT03389477	Active, not recruiting
	Drug: Anastrozole Drug: Exemestane Drug: Fulvestrant Drug: Letrozole Drug: Palbociclib Radiation: Radiation Therapy Drug: Tamoxifen	Anatomic Stage IV Breast Cancer AJCC v8 Estrogen Receptor Positive HER2/Neu Negative Metastatic Breast Carcinoma Metastatic Malignant Neoplasm in the Bone Progesterone Receptor Positive Prognostic Stage IV Breast Cancer AJCC v8	Phase 2 NCT03691493	Active, not recruiting
	Radiation: Stereotactic Body Radiation Therapy (SBRT) (50GY in 5 fractions)	Breast Cancer	Phase 2 NCT04220476	Withdrawn (Initiating a new study with revised statistics)

(*continued on next page*)

Table 2 (*continued*)

Target	Interventions	Conditions	Clinical status & Identifier	Status
	Drug: Letrozole 2.5Mg Tab Drug: Palbociclib 125 mg			
CHK1	Drug: Prexasertib Drug: Cisplatin Drug: Cetuximab Radiation: Intensity Modulated Radiation Therapy	Head and Neck Neoplasms	Phase 1 NCT02555644	Completed
	Drug: LY3300054 Drug: Prexasertib (LY2606368)	Cancer	Phase 1 NCT03495323	Completed
	• Drug: Cytarabine • Drug: SCH 900776 Other: Laboratory Biomarker Analysis	Acute Myeloid Leukemia	Phase 2 NCT01870596	Completed
	Drug: SRA737	Advanced Solid Tumors or Non-Hodgkin's Lymphoma	Phase 1 Phase 2 NCT02797964	Completed
	Drug: SRA737, Gemcitabine, Cisplatin Drug: SRA737, Gemcitabine	Advanced Solid Tumors	Phase 1 Phase 2 NCT02797977	Completed
	Drug: Prexasertib Drug: Olaparib	Solid Tumor	Phase 1 NCT03057145	Completed
	Drug: LY2880070 Drug: Gemcitabine	Ewing Sarcoma Ewing-Like Sarcoma	Phase 2 NCT05275426	Recruiting
	Drug: Prexasertib	Advanced Cancers	Phase 2 NCT02873975	Completed
	Drug: Prexasertib	Neoplasm	Phase 1 NCT02514603	Completed
	Drug: Prexasertib	Ovarian Cancer Breast Cancer Prostate Cancer	Phase 2 NCT02203513	Terminated
	Drug: Prexasertib Drug: Cyclophosphamide Drug: Gemcitabine Biological: Filgrastim Biological: Peg-filgrastim	Brain Tumor	Phase 1 NCT04023669	Active, not recruiting
DNA-PKcs	Drug: MSC2490484A (M3814) Radiation: Fractionated RT Drug: Cisplatin	Advanced Solid Tumors	Phase 1 NCT02516813	Completed
	Drug: XRD-0394 Radiation: Palliative radiotherapy	Metastasis Locally Advanced Solid Tumor Recurrent Cancer	Phase 1 NCT05002140	Recruiting
PARP-1	Drug: Niraparib Drug: Dostarlimab Radiation: Radiation therapy	Breast Cancer Triple Negative Breast Cancer	Phase 2 NCT04837209	Recruiting
	Drug: Olaparib Drug: Temozolomide (TMZ) Radiation: IMRT (Intensity Modulated Radiation Therapy)	Malignant Gliomas	Phase 1 Phase 2 NCT03212742	Recruiting
	Biological: Pembrolizumab Drug: Olaparib Drug: Cisplatin Radiation: IMRT (intensity modulated radiation therapy)	Squamous Cell Carcinoma of Head and Neck	Phase 2 NCT05366166	Not yet recruiting
	Drug: Niraparib Radiation: Radiation Therapy	Triple Negative Breast Cancer Residual Disease	Phase 1 NCT03945721	Recruiting
	Radiation: Radiotherapy Drug: Olaparib	Laryngeal Cancer Stage II Laryngeal Cancer Stage III Carcinoma, Squamous Cell Head and Neck Neoplasms	Phase 1 NCT02229656	Active, not recruiting
	Radiation: Radiotherapy Drug: Olaparib	Locally Advanced Malignant Neoplasm Inflammatory Breast Carcinoma Triple-Negative Invasive Breast Carcinoma	Phase 1 NCT02227082	Completed
	Radiation: Radiation Therapy Drug: Temozolomide Drug: Veliparib	Anaplastic Astrocytoma Glioblastoma Malignant Glioma	Phase 2 NCT03581292	Active, not recruiting
	Radiation: Radiation combined with Iniparib (BSI-201)	Brain Metastases	Phase 1 NCT01551680	Terminated
	Biological: Durvalumab Drug: Olaparib Radiation: Radiation Therapy	Pancreatic Cancer	Phase 1 NCT05411094	Not yet recruiting
	Drug: Veliparib Drug: Capecitabine Radiation: Radiation Therapy	Locally Advanced Rectal Cancer	Phase 1 NCT01589419	Completed
	Drug: Olaparib Radiation: Radiation Therapy	Breast Inflammatory Carcinoma	Phase 2 NCT03598257	Recruiting

(*continued on next page*)

Table 2 (*continued*)

Target	Interventions	Conditions	Clinical status & Identifier	Status
Wee1	Drug: AZD1775/MK-1775/Adavosertib Drug: Gemcitabine Radiation: Radiation Therapy	Adenocarcinoma of the Pancreas	Phase 1 Phase 2 NCT02037230	Completed
	Drug: AZD1775/MK-1775/Adavosertib Drug: Cisplatin Radiation: Radiotherapy	Hypopharynx Squamous Cell Carcinoma Oral Cavity Squamous Cell Carcinoma Larynx Cancer	Phase 1 NCT03028766	Completed
	Drug: AZD1775/MK-1775/Adavosertib Radiation: Radiation Therapy	Esophageal Adenocarcinoma Gastroesophageal Junction Adenocarcinoma	Phase 1 NCT04460937	Suspended
	Drug: AZD1775/MK-1775/Adavosertib Drug: Cisplatin Radiation: Intensity Modulated Radiotherapy Treatments	Carcinoma, Squamous Cell of Head and Neck	Phase 1 NCT02585973	Completed
	Drug: AZD1775/MK-1775/Adavosertib Drug: Cisplatin Radiation: External Beam Radiation Therapy	Cervical Carcinoma Endometrioid Adenocarcinoma	Phase 1 NCT03345784	Active, not recruiting
MPS1/ TTK*	Drug: BAY1217389 Drug: Paclitaxel	Medical Oncology	Phase 1 NCT02366949	Completed
	Drug: BAY1161909 Drug: Paclitaxel	Medical Oncology	Phase 1 NCT02138812	Terminated
	Drug: BOS172722 Drug: Paclitaxel	Advanced Nonhaematologic Malignancies	Phase 1 NCT03328494	Completed

* Targets that exclude combination with radiation therapy as there are no radiation therapy studies in clinical trials (as on Nov 30, 2022)

their usability in enhancing radiation-induced cell killing and improving clinical outcomes. A greater knowledge is needed into how these new targets and their inhibitors contribute to radiation-induced DNA damage leading to radiation sensitization. We believe that a better knowledge of the molecular processes behind the DDR, as well as the genetic interactions between distinct DDR pathways and other cellular pathways such as epithelial to mesenchymal transition (EMT), cell-cycle regulation, cancer stem cells (CSCs) resilience, tumor-immune microenvironment will lead to new treatment options for a variety of human diseases including cancer.

CRediT authorship contribution statement

Shyam Nyati, Sushmitha Sriramulu: Conceptualization. **Shyam Nyati:** Supervision. **Sushmitha Sriramulu:** Writing – original draft. **Shyam Nyati, Stephen L. Brown, Farzan Siddiqui, Benjamin Movsas, Shivani Thoidingjam, Sushmitha Sriramulu:** Writing – review & editing. All authors read and approved the final manuscript.

Conflict of interest statement

Benjamin Movsas receives research support from Varian Medical Systems, ViewRay, and Philips. Farzan Siddiqui has received honoraria from Varian Medical Systems for lectures and presentations, reimbursement for travel, food and lodging expenses; Honoraria from American College of Radiology for services provided as Radiation Oncology Practice Accreditation site surveyor, reimbursement for travel, food and lodging expenses; Honoraria from Varian Noona Medical Advisory Board for services as a board member. All other authors have no conflicts of interest related to this publication.

Data availability

No data was used for the research described in the article.

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Ethics approval and consent to participate

Not Applicable.

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