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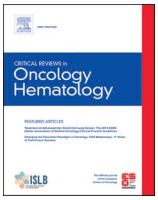

Targeting the DNA damage response to enhance radiotherapy in soft tissue sarcomas

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ABSTRACT

Radiotherapy plays an important role in treating non-metastatic soft tissue sarcomas by inducing DNA damage and subsequent cell death. However, all cells possess defence mechanisms to repair DNA damage via DNA damage response (DDR) pathways. Inhibition of these DDR pathways may enhance tumour sensitivity to radiation, potentially improving treatment outcomes. This review assesses the potential of DDR inhibition to enhance radiosensitivity in soft tissue sarcomas, by evaluating both preclinical and clinical studies that combined DDR inhibitors and radiotherapy. Studies were identified by searching literature databases, clinical trial registries and conference abstracts, and focused on the relevance for combining DDR inhibitors and radiotherapy in soft tissue sarcoma treatment. Targeting DDR pathways through key proteins like PARP, ATM and ATR appears to be a promising approach to increase the radiosensitivity of soft tissue sarcomas in preclinical studies with minimal increased toxicity. Although phase I and II clinical trials observed that DDR inhibitors are mostly well tolerated, phase II trials observed limited to no improvement in disease control or overall survival. Moreover, some trials observed increased severe toxicities, especially at higher radiation doses or accelerated schedules. Nevertheless, DDR inhibitors have a great potential to sensitize soft tissue sarcomas to radiotherapy. Unfortunately, the currently developed DDR inhibitors have shown limited effect on overall survival and recurrence rates. Therefore, efforts should be made to either improve their efficacy or to reduce radiation doses through DDR inhibitor-mediated radiosensitization while maintaining efficacy.

1. Introduction

Soft tissue sarcomas (STS) are rare malignant tumours of mesenchymal origin that make up roughly one percent of all newly diagnosed malignancies worldwide (WHO Classification of Tumours Editorial Board, 2020). They can be divided into approximately 70 different histological subtypes, many of which have an incidence as low as 1 in 1.000.000 (Gamboa et al., 2020). This makes STS a heterogeneous group of cancers for which it is difficult to develop subtype specific treatment schedules.

Surgery is the cornerstone for the treatment of non-metastatic STS. In case of deep-seated intermediate and high-grade STS of ≥ 5 cm length or width, surgery is normally combined with preoperative radiotherapy to improve local control (Haas et al., 2012). This combined surgery-radiotherapy approach is applicable to STS of the extremities, chest wall, and retroperitoneum, but is not uniformly applied to all sarcoma types. For instance, in Ewing sarcoma, osteosarcoma and paediatric rhabdomyosarcoma systemic chemotherapy plays a central role in treatment. Even with the combined treatment of radiotherapy and surgery, 5–15 % of patients relapse locally and about 30–50 % distantly, emphasizing the need for further reduction of local relapses. One of the potential strategies to realize such reduction is enhancing the therapeutic effectiveness of radiotherapy.

Radiotherapy causes damage to DNA molecules leading to damaged

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bases, single strand DNA breaks (SSBs) and double strand DNA breaks (DSBs). It induces around 10,000 damaged bases, 1000 SSBs and 40 DSBs per Gray (Gy) per cell (Biau et al., 2019). Accumulated unrepaired DNA damage may result in cell death, senescence, apoptosis or the induction of malignant transformation.

All cells possess defence mechanisms to repair DNA damage through the DNA damage response (DDR) pathway. Unlike normal cells, tumour cells have shown to partially develop dysfunctional DDR pathways, making them more dependent upon the remaining intact DDR pathways to repair DNA damage, and thus more susceptible to DDR inhibition (Carrassa and Damia, 2017). This narrative review therefore aims to assess the potential treatment opportunities of adding DDR inhibitors to radiotherapy in STS.

2. Irradiation induced DNA damage response pathways

The DDR is a complex network of several interacting proteins and systems that maintain genetic integrity by identifying and repairing DNA damage. The various DDR pathways and mechanism part of these systems are already well described in other literature (Jackson and Bartek, 2009; Pearl et al., 2015; Giglia-Mari et al., 2011). A simplified overview of the most important DDR pathways and their key proteins is shown in Fig. 1. The activation of these pathways is dependent on the type of DNA damage as well as the cell cycle phase.

Radiation causes DNA damage in the form of single base damage, single strand breaks (SSBs) and double strand breaks (DSBs) (Giglia-Mari et al., 2011; Desouky et al., 2015). Accumulated unrepaired DNA damage ultimately results in cell death or senescence. Consequently, the effect of radiotherapy is determined by the ability of cells to adequately repair the induced DNA damage. In general, damaged bases and SSBs can easily be repaired through reference of the non-damaged complementary DNA strand. DSBs, on the other hand, are more toxic and far more difficult to repair due to the absence of a non-damaged complementary DNA strand for reference. Notably, even a single unrepaired DSB can result in cell death (Jeggo and Löbrich, 2007). As a result, DSBs account for the majority of the therapeutic effect of radiotherapy. In the case of radiation DSBs repair is particularly dependent on repair via the immediate and error-prone non-homologous end joining (NHEJ) pathway, rather than the precise and slower homologous recombination (HR) pathway. A schematic overview of the most important DDR pathways for radiotherapy and their key proteins is shown in Fig. 2, a more detailed description is provided in Supplementary Material 1.

3. Sarcomas and DNA damage response defects

Sarcomas can be classified according to their histological characteristics. In addition, sarcomas can be divided into two groups based on their genomic alterations: simple genome and complex genome sarcomas (Taylor et al., 2011; Vibert and Watson, 2022). Simple genome sarcomas have specific driver alterations like oncogenic gene fusions, activating or inactivating driver mutations, or gene amplifications, and typically have minimal genomic alterations aside the driver alteration. In contrast, complex genome sarcomas have large numbers of chromosomal aberrations, copy number alterations or point mutations resulting in unbalanced karyotypes and thereby often possessing genomic instability (Taylor et al., 2011; Vibert and Watson, 2022). Complex genome sarcomas can have DNA repair defects with severe chromosomal instability (Quesada and Amato, 2012). These DNA repair defects make cells more dependent on the remaining non-defective DDR pathways, and thus more susceptible to radiation when the remaining functional DDR pathways are inhibited (Spring et al., 2001; Moding et al., 2014, 2015; Hammond and Muschel, 2014). Likewise, inhibition of already defective DDR pathways is not effective.

According previously published literature, approximately 10–15 % of all sarcomas, primarily complex genome sarcomas, have mutations within DDR genes such as *BRCA2*, *RAD51*, *CHK2* or *ATM*, with certain histological subtypes have higher reported frequencies, e.g. leiomyosarcoma (10–24 %), pleomorphic sarcoma (23 %), sarcoma not otherwise specified (17 %) and angiosarcoma (13–25 %) (Nacev et al., 2022; Gounder et al., 2022; Lopes-Brás et al., 2022; Chelsky et al., 2022; Lucchesi et al., 2018; Kanojia et al., 2015; Bialick et al., 2022). Of note,

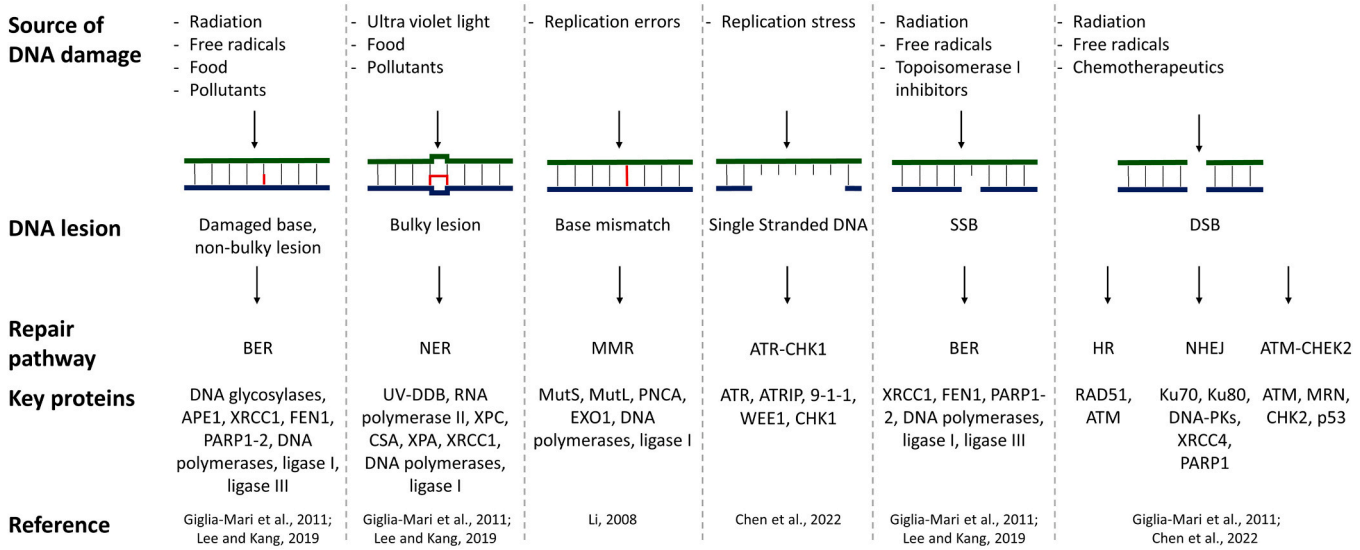

Fig. 1. Sources of DNA damage and their corresponding repair pathways. The common causes of DNA damage are illustrated at the top, the repair pathway and key proteins are illustrated at the bottom of the corresponding columns. 9–1–1, RAD9/RAD1/Hus1; APE1, apurinic/apyrimidinic endonuclease 1; ATM, ataxia-telangiectasia mutated; ATR, ataxia-telangiectasia and Rad3-related; ATRIP, ATR-interacting protein; BER, base excision repair; CHK1, checkpoint kinase 1; CHK2, checkpoint kinase 2; CHK1/2, checkpoint kinase 1 and 2; CSA, Cockayne syndrome group A; DDR, DNA damage response; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; DSB, double strand break; EXP1, exonuclease 1; FEN1, Flap structure-specific endonuclease 1; HR, homologous recombination; MMR, mismatch repair; MRN, MRE11/RAD50/NBS1, MutL, Mutator L; MutS, Mutator S; NER, nuclear excision repair; NHEJ, nonhomologous end-joining; PARP, poly (ADP-ribose) polymerase; PNCA, pyrazinamidase/nicotinamidase; SSB, single strand break; UV-DDB, ultraviolet DNA damage-binding protein; XPA, Xeroderma pigmentosum, complementation group A; XPC, Xeroderma pigmentosum, complementation group C; XRCC, X-ray repair cross-complementing protein (Lee and Kang, 2019; Li, 2008).

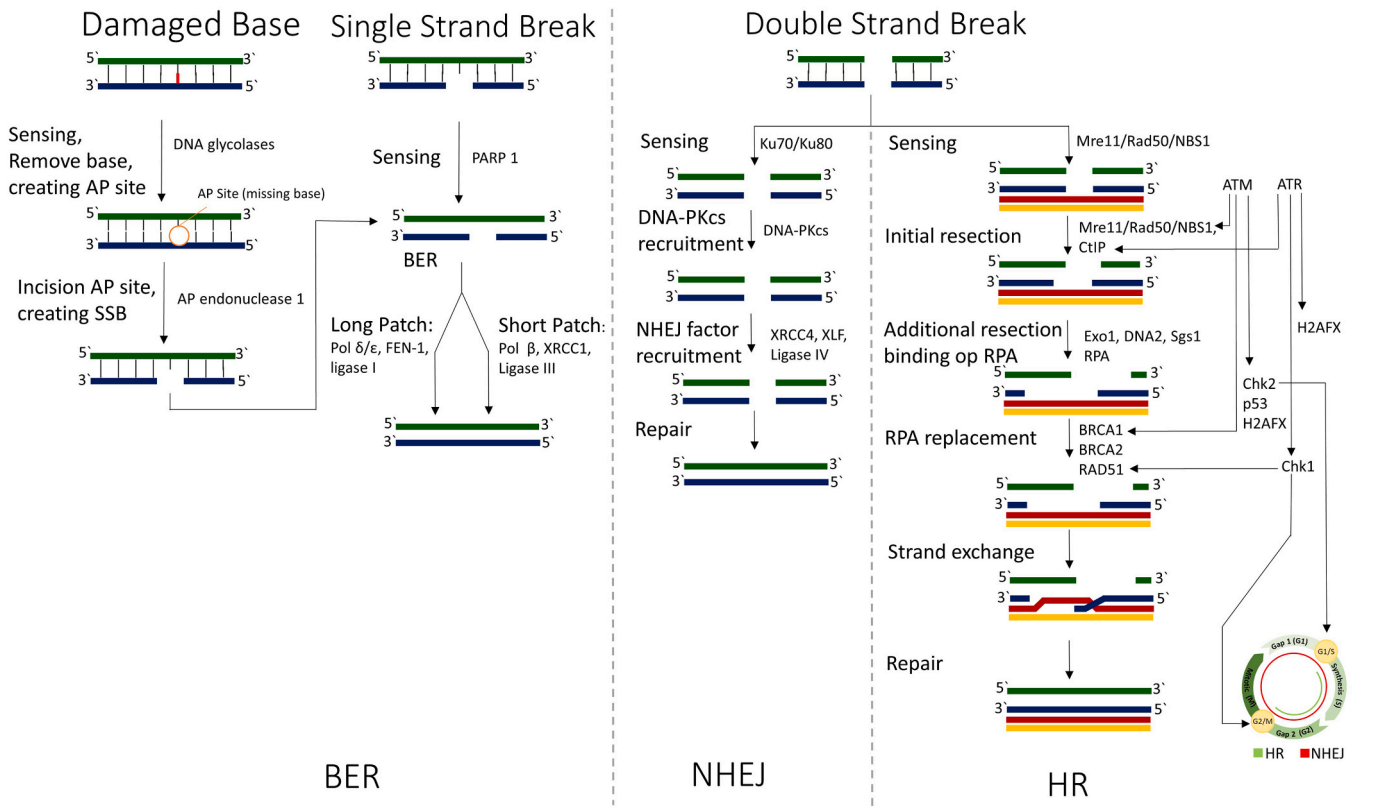

Fig. 2. Schematic overview BER, HR and NHEJ. The figure summarizes the main components and mechanism of the BER, NHEJ and HR repair pathways. ATM, ataxia-telangiectasia mutated; ATR, ataxia-telangiectasia and Rad3-related; BER, base excision repair; BRCA, breast cancer gene; CHK1, checkpoint kinase 1; CHK2, checkpoint kinase 2; CtIP, carboxy-terminal binding protein-interacting protein; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; EXP1, exonuclease 1; FEN1, flap structure-specific endonuclease 1; H2AFX, H2A histone family member X; HR, homologous recombination; NHEJ, nonhomologous end-joining; PARP, poly (ADP-ribose) polymerase; Pol, polymerase; RPA, replication protein A; sgs1, slow growth suppressor 1; XPA, Xeroderma pigmentosum, complementation group A; XPC, Xeroderma pigmentosum, complementation group C; XLF, XRCC4-like factor; XRCC, X-ray repair cross-complementing protein.

less than 1 % of all sarcomas are MisMatch Repair (MMR) deficient (Lam et al., 2021). However, comparing and interpreting the reported prevalence across these studies is challenging due to the difference in sequencing techniques, selection of DDR genes and substantial variation in sample size. Moreover, the identified studies report an overall percentage of DDR mutations or focus on HR and MMR, without breaking down the prevalence across the various DDR pathways.

For instance, Lam et al. reported that less than 1 % of all sarcomas are MMR deficient based on immunohistochemical expression and gene mutations of *MLH1*, *MSH2, MSH6* and *PMS2* in STS (Lam et al., 2021). In contrast, Gounder et al. reported a 2.1 % prevalence of MMR deficiency in bone and soft tissue sarcomas after assessing the same four genes with the addition of *MSH3* (Gounder et al., 2022). On the other hand, data from the publicly available American Association for Cancer Research project GENIE registry version 17.0 indicate a higher frequency of 3.5 % *MLH1, MSH2, MSH6* and *PMS2* gene mutations in STS (AACR Project, 2017). However, when mutations in other core MMR genes, like *EXO1*, *MLH3*, *MSH3*, and *PMS1* are included, the prevalence further increases to 5.0 %, highlighting the influence of gene selection and difference between study populations on the prevalence of DDR mutations (Supplementary Table 1).

Nevertheless, the ACCR GENIE registry may provide the most reliable estimate of the prevalence of DDR gene mutations due to its large sample size and ability to select specific DDR genes. Based on the GENIE registry and selection of core DDR pathway genes as described by Knijnenburg et al., the prevalence of mutations in BER is less than 1 %, NER is 5 %, HR is 10 %, NHEJ is 2 % and MMR is 5 % on average for STS (Supplementary Table 1–4) (Knijnenburg et al., 2018). Importantly, no specific subtypes have a high rate of mutations in targetable DDR protein genes or DDR pathways. However, it is important to note that these DDR mutations do not necessarily indicate non-functional DDR pathways, as functional assays were not included. Furthermore, the reported prevalence of DDR mutations in STS above were solely based on DDR gene mutations, whereas DDR defects can also occur as a result of promoter methylation or loss of heterozygosity. Consequently, the prevalence of DDR defects may be both underestimated and overestimated. Therefore, there appears to be no clear rationale to target one specific DDR pathway or protein based on these findings.

4. Methods

4.1. General methodology

The primary aim of this narrative literature review was to assess the potential treatment opportunities of adding DDR inhibitors to radiotherapy in STS. A structured literature review was conducted to identify records of clinical trials, as well as preclinical, observational and retrospective studies that assessed the efficacy and/or tolerability of combining DDR inhibitors and radiotherapy. To ensure transparent and a systematic approach, the search strategy and study selection were developed and executed in collaboration with an experienced research librarian.

4.2. Search strategy

The literature search encompassed literature databases and trial registries and was conducted in three phases. In the first phase, we searched MEDLINE via Pubmed, Embase.com and Scopus using a

strategy based on key terms related to sarcoma, DNA damage, DNA repair, radiation and DDR inhibitors, including ATM, ATR, APE1, CHK1, CHK2, DNA-PK, PARP, and WEE1. This phase aimed to identify relevant articles as well as compile a list of DDR inhibitors.

In the second phase, targeted searches were performed in PubMed and trial registries for each identified DDR inhibitor, including their synonyms and former names. This phase aimed to identify clinical trials investigating the combination of a DDR inhibitor and radiotherapy. Clinical trial information was obtained from the European Union Clinical Trials Register (EUCTR) and the U.S. National Library of Medicine ClinicalTrials.gov database.

In the third phase, Pubmed and Embase.com were searched for conference abstracts reporting results of the identified clinical trials by searching trial registration numbers (NCT) and the identified DDR inhibitors. Results were pooled, and duplicates were manually removed. Reference lists of all included studies were also manually reviewed to identify additional relevant studies. The final search was conducted on December 1, 2024. The full search protocol and search queries are provided in Supplementary Materials 2 and 3.

4.3. Study selection

Eligible studies included preclinical studies, phase I, II and III clinical trials, observational and retrospective studies that assed the efficacy and/or tolerability of combining DDR inhibitors and radiotherapy. Reviews, case reports, case series that include non-consecutive patients and/or have less than 5 patients, expert opinions, additional adjuvant treatment and non-English studies were excluded. Preclinical studies were required to report at least one efficacy outcome such as cell survival for a combination of the relevant DDR inhibitor and radiotherapy, without the addition of additional treatments. All records were screened by a single reviewer using Rayyan. In case of the slightest doubt regarding the inclusion or exclusion of an article, one of the senior co-authors was asked for advice, and a discussion was completed until consensus was reached.

4.4. Data extraction and outcomes

Predetermined study characteristics and outcomes were extracted from all included records. For preclinical studies, extracted characteristics included the type of cell lines used, details of radiation delivery, and the treatment modality and regimen. For primary outcomes, data on efficacy and safety were extracted. Efficacy was assessed based on cell survival and the degree of radiosensitization. Safety was assessed by comparing the degree of DNA damage and radiosensitization between normal healthy cell lines and tumour cell lines exposed to the same treatment. For clinical studies, extracted characteristics included the number of patients, tumour characteristics, details on radiotherapy, and treatment modality and regimen. For the primary outcome efficacy and tolerability data was extracted, including response rates, local recurrence and survival data. Tolerability was evaluated based on all reported treatment related adverse events and serious adverse events.

4.5. Data synthesis, and study quality assessment

Results were described narratively, no statistical analysis was performed given the heterogeneous patient populations and treatment regimens. All outcomes are presented in tables, with preclinical studies and clinical trials reported separately. Preclinical outcomes are reported per DDR inhibitor category. The potential impact of heterogeneity between studies was discussed narratively when of relevance. No formal missing data analysis or risk of bias assessment was conducted.

5. Results

5.1. Search results

In the first phase, 2472 records were identified through searches in PubMed, Embase.com and Scopus. After removing duplicates, 1592 unique records remained. Title and abstract screening, followed by full-text review, resulted in the inclusion of 12 studies. In addition, 57 distinct DDR inhibitors were identified to serve as a basis for targeted searches in subsequent phases (Supplementary Table 5).

The second phase yielded 2096 records through targeted searches in PubMed and clinical trial registries for each identified DDR inhibitor, including their synonyms and former names. Following, title and abstract screening and full-text review, 214 studies were included. Across phases one and two, 132 preclinical studies and 94 clinical trials were identified.

In the third phase, PubMed and Embase searches for follow-up publications and conference abstracts reporting results from the 94 previously identified clinical trials yielded 1672 records. After removal of duplicates, 1544 records remained. Title and abstract screening, followed by full-text review, resulted in the inclusion of 44 additional reports presenting results from the previously identified clinical trials. No new clinical trials were identified. Reference lists of all included studies were also reviewed, but no additional studies were identified.

In total, 226 unique studies were included across all three phases, comprising 132 preclinical studies and 94 clinical trials, alongside 178 associated reports. The full search process and study selection are illustrated in Supplementary Figure 1.

5.2. Preclinical studies with DNA damage response inhibitors and radiosensitivity

Multiple studies have attempted to exploit DDR pathways by inhibiting DDR specific proteins to enhance the efficacy of radiation or systemic treatments. This review focuses on DDR pathways that can be targeted by investigational medical products or registered medicines (Fig. 3). Registered DDR inhibitors include the PARP inhibitors: niraparib, olaparib, rucaparib, talazoparib, fluzoparib and pamiparib. Investigational DDR inhibitors include new PARP inhibitors, as well as APE1, ATM, ATR, CHK1/2, WEE1 and DNA-PK inhibitors (Table 1).

Following our search, 132 preclinical studies combining DDR inhibitors and radiation were identified. Only four of these included an STS cell line, with three investigating PARP inhibitors and one DNA-PK inhibitor (Supplementary Table 6). Below, we summarize the findings of these preclinical studies for each DDR target and discuss their potential for radiosensitization in STS.

5.3. PARP

Poly ADP ribose polymerase (PARP) consist of a large family of enzymes that are involved in several cellular processes. In case of DNA damage, PARP plays an important role in DNA repair in the BER of SSBs by detecting DNA damage and subsequent recruitment of other DDR repair proteins (Morales et al., 2014; Amé et al., 2004; Herceg and Wang, 2001).

The BER is the primary pathway for SSB repair. Unrepaired SSBs ultimately result in DSB through replication fork stalling, which then offers cells an alternative method to repair the DNA damage through HR and NHEJ (Cannan and Pederson, 2016). This makes tumours with compromised DSB repair mechanisms and pathways such as HR-deficiency by *BRCA1/2* mutations especially vulnerable for PARP inhibitors through synthetic lethality. This mechanism has been proven to be effective in multiple clinical trials, most notably with olaparib in HR-deficient ovarian cancer.

Multiple preclinical studies have shown that PARP inhibition enhances the radiosensitivity of various tumour cells including sarcomas

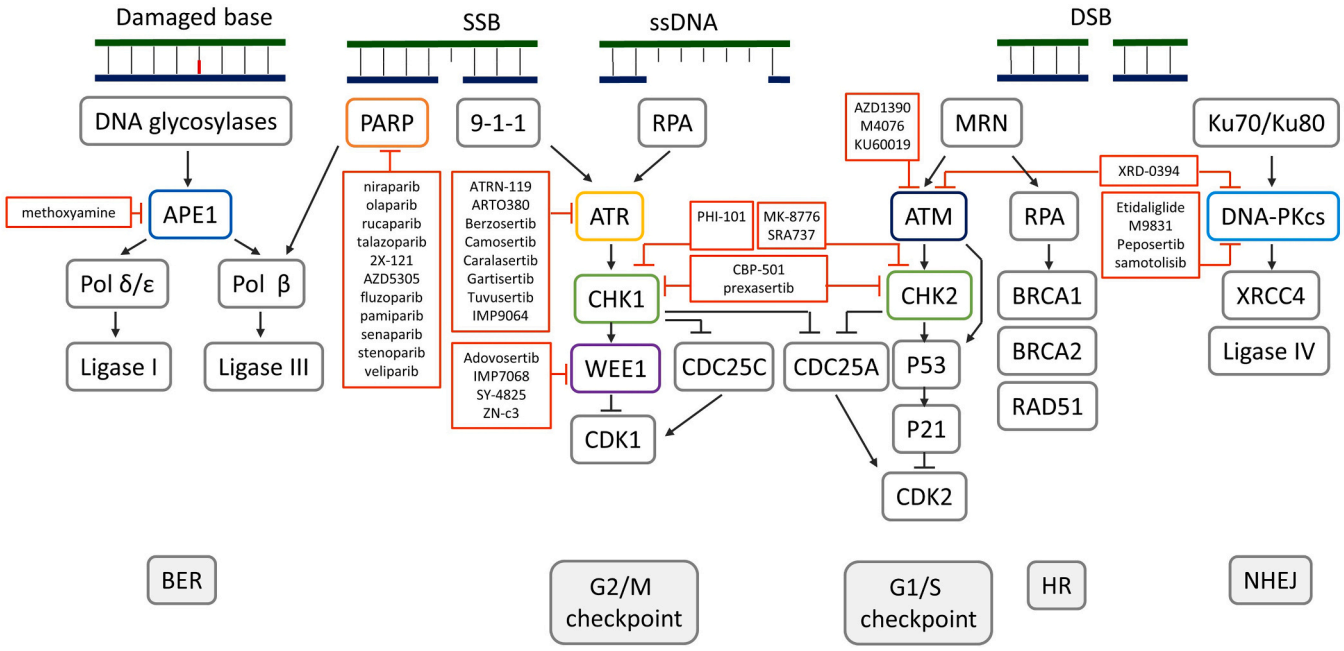

Fig. 3. Targetable DDR proteins and pathways. The targetable proteins of DDR pathways are illustrated. Inhibition of these proteins may inhibit the corresponding pathway, thereby potentially increasing the therapeutic effect of radiation. 9–1–1, RAD9/RAD1/Hus1; APE1, apurinic/apyrimidinic endonuclease 1; ATM, ataxia-telangiectasia mutated; ATR, ataxia-telangiectasia and Rad3-related; BRCA, breast cancer gene; BER, base excision repair; CHK1, checkpoint kinase 1; CHK2, checkpoint kinase 2; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; DSB, double strand break; HR, homologous recombination; MRN, MRE11/RAD50/NBS1, NHEJ, nonhomologous end-joining; PARP, poly (ADP-ribose) polymerase; SSB, single strand break; RPA, replication protein A; XRCC, X-ray repair cross-complementing protein.

(Supplementary Table 6). In STS, olaparib, veliparib and iniparib were able to induce significant radiosensitization in irradiated rhabdomyosarcoma, fibrosarcoma, leiomyosarcoma and liposarcoma cells (Mangoni et al., 2018). Radiosensitization was most substantial in rhabdomyosarcoma, where the combination increased DNA damage compared to either treatment alone indicating synergism. More importantly, the addition of PARP inhibitors sensitized all tested subtypes, indicating that this non-specific treatment strategy may also be effective in untested subtypes. Additionally, olaparib and the discontinued PARP inhibitor AZD2461 significantly increased DNA damage and G2 cell cycle arrest in irradiated alveolar and embryonal rhabdomyosarcoma cell lines compared to either treatment alone (Camero et al., 2019).

Surprisingly, while Mangoni et al. reported that olaparib pre-treatment sensitized fibrosarcoma and leiomyosarcoma cells to radiation, Lee et al. observed no radiosensitization in their colony-forming assay (Mangoni et al., 2018; Lee et al., 2013). However, Lee et al.'s colony forming assay method is unclear, making it difficult to determine the cause of these contradictory findings, besides suggesting that adequate inhibition and timing are essential for effective radiosensitization (Lee et al., 2013). Similar findings were observed for other tumour types, with radiosensitization being especially notable in DDR impaired, primarily HR-deficient, cell lines (Supplementary Table 6). Thus, these preclinical findings highlight the potential of PARP inhibition to enhance the radiosensitivity of STS.

5.4. APE1

Apurinic/apyrimidinic endonuclease 1 (APE1) inhibitors are one of the least studied DDR proteins and have not been studied in the context of STS. APE1 is an endonuclease that nicks the DNA backbone at abasic (AP) sites, which are produced by DNA glycosylases following the removal of damaged bases, and it is a critical component of the BER pathway (Fig. 2) (Chen et al., 2022). APE1 inhibition has been demonstrated to increase the accumulation of radiation-induced DNA damage, eventually leading to cell death, which may enhance the radiosensitivity of cancer cells (Supplementary Table 6). However, it is uncertain whether APE1 inhibition will increase STS radiosensitivity, as it has not been investigated and there is limited preclinical evidence in other tumour types.

5.5. ATM

Ataxia-telangiectasia mutated (ATM) is a key DDR signal transducers and is rapidly activated in response to DNA damage. ATM plays a role in activating HR components and the ATM-CHK2 pathway (Fig. 2). It induces DNA repair through the activation of various DDR proteins and affects cell cycle checkpoints through p53, CHK1, CHCK2, BRCA1 and yH2AX. Moreover, ATM is involved in sensing DSBs caused by irradiation as well as oxidative stress (Guo et al., 2010; Kastan and Lim, 2000; Falck et al., 2005).

Multiple preclinical studies have demonstrated that inhibiting ATM enhances the radiosensitivity of various cancer cell lines and improves the survival of xenograft mice (Supplementary Table 6). For example, the ATM inhibitor KU59403 sensitized colon, breast and osteosarcoma cell lines to radiation, increasing DSBs and G2 cell cycle arrest, while having limited toxicity (Dohmen et al., 2017). Moreover, the ATM inhibitor AZD1390 sensitized Small Cell Lung cancer cells and two patient derived xenografts to radiation, and caused up to double the amount of DNA damage compared to radiation alone. Importantly, ATM inhibition sensitized all cell lines, despite differences in their radiosensitivity and mutation status (Ran et al., 2024). However, it is unclear whether ATM inhibitors will enhance radiosensitivity in STS, as no STS specific studies were identified. Given their role in DSB repair and promising preclinical results in other tumour types, ATM inhibition may represent a promising strategy for radiosensitization in STS.

5.6. ATR

Ataxia telangiectasia and Rad3 related (ATR) is a signalling kinase that plays an important role in maintaining genomic stability by

Table 1
DDR inhibitors in ongoing clinical trial development.

DDR target	Drug	Trial phase
PARP	AZD5305	II
	AZD9574	I
	senaparib *(IMP4297)*	III
	stenoparib *(E7449, 2X−121, MGI25036)*	II
	veliparib *(ABT−888)*	III
APE1	methoxyamine *(TRC102)*	I
ATM	AZD1390	I
	M4076	I
	KU 60019	II
ATM + DNA-PK	XRD−0394	I
ATR	ATRN−119	I
	ART0380	I/II
	berzosertib *(VE−822, VX−970, M6620)*	II
	camonsertib *(RP3500)*	I/II
	ceralasertib *(AZD6738)*	III
	elimusertib *(BAY1895344)*	I/II
	gartisertib *(VX803, M4344)*	I
	tuvusertib *(M1774)*	I
	IMP9064	I
CHK1/2	CBP−501	II
	prexasertib *(LY2606368)*	II
CHK1	MK8776 *(SCH900776)*	II
	SRA737 *(CCT245737)*	II
CHK2	PHI−101	I
WEE1	adavosertib *(AZD1775, MK1775)*	II
	IMP7068	I
	SY−4825	I
	ZN-c3	I
DNA-PK	etidaligide *(AsiDNA)*	II
	M9831 *(VX−984)*	I
	peposertib *(M3814, nedisertib)*	II
	samotolisib *(LY3023414)*	II

APE1, apurinic/apyrimidinic endonuclease 1; ATM, ataxia-telangiectasia mutated; ATR, ataxia-telangiectasia and Rad3-related; CHK1, checkpoint kinase 1; CHK2, checkpoint kinase 2; CHK1/2, checkpoint kinase 1 and 2; DDR, DNA damage response; DNA-PK, DNA-dependent protein kinase; PARP, poly (ADP-ribose) polymerase.

stabilizing replication forks, resulting in cell cycle arrest and DNA repair. ATR is activated in response to ssDNA, which is a common intermediate of other DDR pathways and occurs in stalled replication forks.

Multiple preclinical studies have shown that inhibition of ATR enhances the radiosensitivity of various tumour cells, including bone sarcomas (Supplementary Table 6). For example, VE-821 sensitized chondrosarcoma and osteosarcoma to radiation, increasing permanent DNA damage and significantly suppressing DNA repair mechanisms (Lohberger et al., 2023; Fujisawa et al., 2015). Additionally, ceralasertib sensitized Non-Small Cell Lung Carcinoma (NSCLC) cells to radiation and increased DSBs, with little effect on normal healthy bronchial epithelial cells. Moreover, the combination of ceralasertib and radiation in NSCLC xenograft mice significantly delayed tumour growth compared to either treatment alone. Although no studies investigating STS were identified, ATR inhibition sensitized various tumour types to radiation, suggesting they could potentially also sensitize STS to radiation.

5.7. CHK1 and CHK2

Checkpoint Kinase 1 (CHK1) and Checkpoint Kinase 2 (CHK2) are kinases playing an important role in the coordination of the DNA damage response and cell cycle checkpoint response by inhibition of cyclin-dependent kinase activity through different mechanisms, thereby halting the cell cycle allowing time for DNA repair (Alhmoud et al., 2020).

Although several preclinical studies demonstrated that inhibiting CHK1 or CHK2 increases the radiosensitivity of various tumours with limited toxicity effect on normal healthy tissue derived cells, no STS studies have been identified (Supplementary Table 6). Therefore, while these preclinical findings are promising, it remains unclear whether CHK1 and/or CHK2 inhibition will result in similarly increased radiosensitivity in STS.

5.8. WEE1

WEE1 plays an important role in regulating the G2/M cell cycle transition by serving as a negative regulator. Upon activation, WEE1 blocks entry into mitosis at the G2 to M transition cell cycle phase via CDK1, enabling DNA repair (Huang and Zhou, 2020). Thus, WEE1 inhibition can serve as a target for G2/M checkpoint inhibition to enhance radiotherapy. Although multiple preclinical studies have shown that inhibiting WEE1, specifically with adavosertib, enhances the radiosensitivity of various tumours, no studies in STS have been performed (Supplementary Table 6). Therefore, it remains unclear whether WEE1 inhibition will increase radiosensitivity of STS.

5.9. DNA-PK

DNA-dependent protein kinase (DNA-PK) plays an essential role in the repair of DSB by phosphorylating several of the NHEJ pathway components. In addition, DNA-PK overlaps with various ATM targets and plays a key role in the selection of the NHEJ and HR pathways in response to DSBs (Huang and Zhou, 2020). As a result, DNA-PK inhibition will be especially effective in *ATM*-mutant cells, as both HR and NHEJ will be inhibited. Thus, DNA-PK inhibition can serve as a target to impair DSB repair and thereby potentiate radiotherapy.

Multiple preclinical studies have shown that inhibiting DNA-PK enhances the radiosensitivity of cancer cells, (Supplementary Table 6). In STS, the addition of the DNA-PK inhibitor AZD7648 to radiation sensitized leiomyosarcoma, liposarcoma to radiation, increasing DNA damage and apoptosis. Importantly, although the sensitising effect varied between the three subtypes, all were sensitized to radiation in synergistic manner. Moreover, combining AZD7648 and radiation in undifferentiated pleomorphic sarcomas xenograft mice increased DNA damage and reduced tumour volume more than either treatment alone (Laroche-Clary et al., 2024). Thus, these findings suggest that targeting DNA-PK is a promising strategy to enhance the radiosensitivity of STS.

5.10. Clinical trials with DNA damage response inhibitors and radiotherapy

Multiple preclinical studies have observed a potential role for DDR inhibitors to enhance radiosensitivity. Nevertheless, clinical implementation of DDR inhibitors is still in its early stages. A search of clinical trial registries (EU-CTR, ClinicalTrials.gov) identified 94 trials investigating the combination of radiotherapy and DDR inhibitors. These include 11 trials with preliminary results, 34 completed trials, 4 completed trials without published results, 4 terminated trials (Table 2) and 41 ongoing trials (Table 3). For STS, there are no completed clinical trials, but four ongoing clinical trials, all in phase 1, namely RADIOSARP (NCT02787642), NCC-4016 (NCT05938374), PRIMA (NCT06074692) and SADDRIN-I (NCT05116254).

The RADIOSARP investigates the PARP inhibitor olaparib with concomitant radiotherapy in locally advanced or unresectable trunk or extremity STS (Sargos et al., 2022). Forty-one patients have been included so far. Patients were treated with radiotherapy 60 Gy delivered in 33 fractions plus olaparib at from one week before the start until the end of radiotherapy. Preliminary results show that the combination is well tolerated (Sargos et al., 2022). The RADIOSARP is currently awaiting follow-up to assess survival.

The NCC-4016 combines the PARP inhibitor fluzoparib with preoperative radiotherapy in patients with unresectable or borderline resectable extremity or trunk STS. Of the 49 patients enrolled, 46 completed radiotherapy. Treatment consisted of 43.5 Gy delivered in 15 fractions combined with 10 weeks of fluzoparib starting concurrently

Table 2
Ongoing clinical trials with preliminary results and completed clinical trials investigating radiotherapy with DDR inhibitors.

DDR target	Drug	Phase, status	Trial identifier, name, ref	Treatment	Tumour type	Outcome measures	No of patients	Notable outcomes	Absolute no Grade 3–4 AE (% of patients affected)
PARP	veliparib *(ABT−888)*	Ib, completed	NCT01589419, (Czito et al., 2017)	veliparib + nRT (28×1.8 Gy) + capecitabine	rectal cancer	MTD, RP2D	*32*	pCR 29 %	*4* (12)
		I, completed	NCT01908478, (Tuli et al., 2019)	veliparib + RT (15×2.4 Gy) + gemcitabine	pancreatic cancer	MTD	*30*	Median OS 15 months	*26* (87)
		I, completed	NCT01264432, (Reiss et al., 2016)	veliparib + LDFWAR (36×0.6 Gy)	peritoneal carcinomatosis, epithelial ovarian, fallopian or primary peritoneal cancer	MTD, RP2D	*32*	Decrease in QoL higher at higher dose levels.	*NA* (59)
		I, completed	NCT01477489, TBCRC 024, (Jagsi et al., 2018)	veliparib + RT (25×2 Gy + 10 Gy boost)	breast cancer	MTD	*30*	Increase in grade 3 AE over time, mostly fibrosis	During: *5/30* (17) FU year 1: *2/20* (10) FU year 2: *3/18* (17) FU year 3: *7/15* (47)
		I, completed	NCT00649207, (Mehta et al., 2015)	veliparib + WBRT (10×3 or 15×2.5 Gy)	brain metastases	DLT, MTD, RP2D	*81*	Increased median survival time, limited increase in toxicity	*NA* (30)
		I, completed	NCT02412371, (Kozono et al., 2021)	veliparib + RT (30×2 Gy) + carboplatin, followed by veliparib + carboplatin + paclitaxel	NSCLC	R2PD	*48*	Acceptable safety profile	*38* (79)
		I, completed, no results reported	NCT01618357	veliparib + RT	breast cancer	NA	*NA*	NA	*NA* (NA)
		I/II, completed	NCT01386385, SWOGS1206, (Argiris et al., 2021)	veliparib + RT (30×2 Gy) + carboplatin + paclitaxel, followed by veliparib + carboplatin + paclitaxel	NSCLC	I: MTD II: PFS	I:*21* II:*31*	No difference in response or disease control compared to placebo	I: *16* (76) II: *17* (55)
		I/II, completed	NCT01514201, PBTC−033, (Baxter et al., 2020)	veliparib + RT (30×1.8 Gy) followed by veliparib + temozolomide	diffuse pontine glioma	I: RP2D II: OS	I:*12* II:*53*	Well tolerated, no survival benefit	*40* (33)
		I/II, completed	NCT00770471, ABTC−0801, (Kleinberg et al., 2013)	veliparib + aRT (30×1.8 Gy) + temozolomide, followed by veliparib + temozolomide	glioblastoma	I: MTD, DLT	*18*	No survival benefit, severe haematological toxicity	*8* (44)
		II, completed	ACTRN12615000407594, VERTU, (Sim et al., 2021)	veliparib + aRT (30×2 Gy), followed by followed by veliparib + temozolomide	glioblastoma	6 month PFS	*125* (control *41*, veliparib *84*)	Well tolerated, no increased clinical benefit	Control: *40* (55) Veliparib: *83* (55)
		II, completed	NCT01657799, (Chabot et al., 2017)	WBRT (10×3 Gy)	lung cancer brain metastases	OS	*307* control: *102*, 50 mg: *103*, 200 mg: *102*	No difference in median OS 6 months	Control: *43* (43) 50 mg: *29* (28) 200 mg: *26* (25)
		II, completed	NCT02921256, NRG-GI002, (George et al., 2023)	nRT (25×1.8 Gy + 3×1.8 Gy boost) + capecetabine + FOLFOX	rectal cancer	NAR	*178* *90* veliparib	Safe, no difference in NAR, pCR, cCR,	*NA* (NA)
		II, completed	NCT03581292, ACNS1721, (Karajannis et al., 2022)	veliparib + aRT (30×2 Gy), followed by veliparib + temozolomide	glioma	PFS	IDH WT: *23* IDH mutant: *14*	Well tolerated, IDH WT: 1 year PFS 29 %, 1 year OS 67 %, IDH mutant: 1 year PFS 57 %, 1 year OS 90 %	*NA* (NA)
	niraparib *(Zejula, MK4827, ZL2306)*	I, completed	NCT03945721, (Keenan et al., 2022)	niraparib + aRT (dose not stated)	TNBC	MTD	*21*	Well tolerated, the occurrence of AE was similar to radiation alone.	10 (NA)
		I, terminated, results reported	NCT05666349	niraparib + RT (dose not stated)	recurrent glioblastoma	NA	*NA*	NA	NA

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Table 2 (*continued*)

DDR target	Drug	Phase, status	Trial identifier, name, ref	Treatment	Tumour type	Outcome measures	No of patients	Notable outcomes	Absolute no Grade 3–4 AE (% of patients affected)
		II, completed	NCT04409002, (Parikh et al., 2022)	niraparib + RT (3×8 Gy) + dostarlimab, followed by dostarlimab	pancreatic cancer	DCR	*15*	No increase in disease control	*15* (56)
		II, follow-up	NCT04715620, (Jiang and Wang, 2022)	niraparib + RT or aRT (55 Gy, fraction size not stated), followed by niraparib	glioblastoma	6 month PFS	*14*	Well tolerated, OOR: 36 %, PFS−6 36 %	*NA* (NA)
	olaparib *(Lynparza, AZD2281, KU0059436, MK7339)*	0/II, recruiting	NCT04614909, (Kennedy et al., 2023)	Arm C: Olaparib + aRT (30×2 Gy), followed by olaparib	glioblastoma	PK, PD	6	Well tolerated, the median PFS was 3.8 months	0 (0)
		I, recruiting	NCT04550104, CONCORDE, (Horne et al., 2023)	olaparib + aRT (30×2 Gy)	NSCLC	MTD, R2PD	*10*	No dose limiting toxicities	*NA* (NA)
		I, completed	NCT01562210, (de Haan et al., 2021)	ARM A: olaparib + RT (24×2.75 Gy) + cisplatin ARM B: olaparib + RT (24×2.75 Gy)	NSCLC	MTD	ARM A: *10* ARM B: *18*	Severe oesophageal, hematologic and pulmonary toxicity	Control: *8* (80) 25 mg: *4* (57) 50 mg: *5* (45)
		I, completed	NCT03109080, RADIOPARP, (Loap et al., 2022)	olaparib + RT or aRT (28×1.8 Gy + 28×0.45 Gy boost)	TNBC	MTD	*24*	Well tolerated	*15* (33)
		I, completed	NCT01758731, (Karam et al., 2018)	olaparib + RT (33×2.1 Gy) + cetuximab, followed by cetuximab	head and neck cancer	MTD	*16*	Well tolerated, reduced dermatitis in the radiation field	*38* (69 %)
		Ib, follow-up	NCT02787642, RADIOSARP, (Sargos et al., 2022)	olaparib + nRT (33×1.8 Gy)	soft tissue sarcoma	MTD, DLT, pCR	*41*	Well tolerated, pCR 32 %, PR 3 (14 %), SD 12 (55 %)	*NA* (≥34.1)
		I, completed, no results reported	NCT02227082	olaparib + RT (23×2.03 Gy + 23×0.63 Gy tumour boost)	breast cancer	MTD	*7*	NA	*NA* (NA)
		I, completed	NCT01460888, ROCOCO, (Sheikh et al., 2023)	olaparib + RT (25×2 Gy)	oesophageal cancer	MTD, R2PD	*8*	Only the lowest dose was tolerated	*12* (75)
		I, completed	NCT02308072, ORCA−2, (Forster et al., 2021)	olaparib + RT (30×2 Gy) + cisplatin	HNSCC	DLT	*15*	Excessive acute toxicity, promising anti-tumour activity	8/15 DLT
		I, completed	NCT01390571, PARADIGM I, (Derby et al., 2024)	olaparib + RT (15×2.67 Gy), followed by adjuvant olaparib	glioblastoma	MTD, DLT	*16*	Very well tolerated, median OS 10.3 months	*1* (6)
		I, completed	NCT02229656, (Navran et al., 2024)	olaparib + RT (35×2 Gy or 30×2.33 Gy)	head and neck cancer	MTD	*9*	Standard dose were well tolerated, accelerated RT was highly toxic	Standard: *0* (0) Accelerated: *3* (75)
		I, recruiting	NCT03532880, (Rimner et al., 2023)	olaparib + RT (10×3 Gy)	ES-SCLC	MTD	*24*	Well tolerated, 12 month LR 27 %, PFS 3.6 months	*4* (17)
		I, recruiting	NCT01390571, PARADIGM II (Chalmers et al., 2018)	Arm A: olaparib + aRT (30×2 Gy) Arm B: olaparib + aRT (30×2 Gy) + temozolomide	glioblastoma	MTD, DLT	*14*	Very well tolerated	1 (7)
		I, recruiting	ISRCTN10361292, (Evans et al., 2020)	olaparib + RT (28×1.8 Gy) + capecetabine	pancreatic cancer	MTD	*18*	Very well tolerated	*2* (11)
		I/II, recruiting	NCT04711824, (Shen et al., 2023)	olaparib + RT (stereotactic 1–5 fractions), followed by durvalumab + physicians choice systemic therapy	breast cancer brain metastases	I: MTD II: efficacy, tolerability	*NA*	Well tolerated	*0 (NA)*
	fluzoparib *(AiRuiYi, SHR3162)*	I, recruiting	NCT05938374, NCC−4016, (Lu et al., 2024)	fluzoparib + RT (15×2.9 Gy)	soft tissue sarcoma	MTD	*49*	Systemically well tolerated, comparable wound complications	*2 (4)*
	iniparib *(BSI 201, SAR240550)*	I, terminated, no results reported	NCT01551680, RAPIBE	iniparib + WBRT (15×2.5 Gy)	brain metastases	MTD	*3*	NA	*NA* (NA)
		II, completed	NCT00687765, (Blakeley et al., 2019)	Iniparib + aRT (30×2 Gy), followed by temozolomide	glioblastoma	Median OS	*81*	Well tolerated, median OS 22 months, 2 year survival 38 %, 3 year survival 25 %	*67* (27)

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Table 2 (*continued*)

DDR target	Drug	Phase, status	Trial identifier, name, ref	Treatment	Tumour type	Outcome measures	No of patients	Notable outcomes	Absolute no Grade 3–4 AE (% of patients affected)
	pamiparib *(Partruvix, BGB290)*	0/II, recruiting	NCT04614909, (Kennedy et al., 2023)	Arm A: pamiparib + aRT (30×2 Gy), followed by pamiparib Arm B: pamiparib + aRT (15×2.67 Gy), followed by pamiparib	glioblastoma	PK, PD	Arm A: *16* Arm B: *16*	Well tolerated, the median PFS was 5.4 (A), 6 (B) months	4 (13)
		Ib/II, completed, no final results	NCT03150862, SNO 2018, (Piotrowski et al., 2019)	Arm A: pamiparib + RT (33×1.8 Gy or 30×2 Gy) Arm B: pamiparib + RT (33×1.8 Gy or 30×2 Gy) + temozolomide	glioblastoma	DLT, MTD	A: *20* B: *9*	Well tolerated, ARM A DCR 65 %	A: *NA* (≥23) B: *NA* (≥11)
	talazoparib *(Talzenna, BMN 673, MDV3800)*	I, terminated, no results reported	NCT04690855, TARA	talazoparib + RT (8x3 Gy) atezolizumab	breast cancer	DLT	*23*	NA	*NA* (NA)
APE1	methoxyamine *(TRC102)*	I, completed	NCT02535325, (Biswas et al., 2022)	methoxyamine + RT (30×2 Gy) + pemetrexed + cisplatin	NSCLC	DLT, RP2D	*15*	CR 3 (20 %), PR 12 (80 %), 2-year PFS 49 %	*29* (NA)
		II, completed	NCT02395692, (Ahluwalia et al., 2018)	temozolomide + aRT (30×1.8–2 Gy)	glioblastoma	MTD	*19*	Well tolerated, but low response PFS−6 10.5 %.	*2* (NA)
ATM+ DNA-PK	XRD−0394	I, completed, no results reported	NCT05002140	XRD−0394 + RT (5×4 Gy)	solid tumours	MTD	*NA*	*NA*	*NA* (NA)
ATM	AZD1390	I, recruiting	NCT04550104, CONCORDE, (Horne et al., 2023)	AZD1390 + RT (30×2 Gy)	NSCLC	MTD, R2PD	*8*	Well tolerated	*NA* (NA)
ATR	berzosertib *(VE−822, VX−970, M6620)*	I, completed	NCT03641547, CHARIOT, (Mukherjee et al., 2022)	berzosertib + RT (15×2.33 Gy) + cisplatin + capecitabine	oesophageal cancer	DLT, RP2D	*16*	Well tolerated	*8* (31)
		I, completed	NCT02567422, 656MO, (Bhatia et al., 2022)	berzosertib + RT (70 Gy) + cisplatin	head and neck cancer	MTD	*43*	Well tolerated, 20 patients evaluable: CR: 30 %, PR 40 %, SD 15 %, PD 10 %	*NA (≥31)*
CHK1/2	prexasertib *(LY2606368)*	I, completed	NCT02555644, (Yang et al., 2021)	Arm A: prexasertib + RT (35×2 Gy) + cisplatin Arm B: prexasertib + RT (35×2 Gy) + cetuximab	head and neck cancer	MTD	Arm A: *7* Arm B: *18*	MTD not established, no safe doses	*Arm A: NA* (*86*) *Arm B: NA* (*83*)
WEE1	adavosertib *(AZD1775, MK1775)*	Ib, completed	NCT02585973, (Chera et al., 2021)	adavosertib + RT (35×2 Gy) + cisplatin	HNSCC	RP2D, 12 week OOR	*12*	12 week OOR 100 %, 1 year OS/PFS 90 %	*23* (100)
		I, completed	NCT02037230, (Cuneo et al., 2019)	adavosertib + RT (25×2.1 Gy) + gemcitabine, followed by adavosertib + gemcitabine	pancreatic cancer	MTD, OS, PFS	*34*	Median OS: 21,7 months, PFS 9.4	*27* (53)
		I, follow-up	NCT01849146, ABTC−1202, (Alexander et al., 2017)	Arm I: adavosertib + aRT (28×1.8 Gy) + temozolomide, followed by temozolomide	glioblastoma	RP2D	*51*	MTD was established, with acceptable tolerability	*NA* (NA)
		I, completed	NCT01922076, ADVL−1217, (Mueller et al., 2022)	adavosertib + RT (30×1.8 Gy)	diffuse intrinsic pontine gliomas	MTD, DLT	*46, 39* evaluable	Well tolerated, mainly grade 1/2 AE	*2* (NA)
		I, terminated	NCT03345784, (Gonzalez-Ochoa et al., 2023)	adavosertib + RT (45×2 Gy or 50×1.8 Gy) + cisplatin	cervical, upper vaginal and uterine cancer	MTD	*10*	Phase 2 dose could not be determined due to toxicity and early closure	*2* (20 %)
DNA-PK	peposertib *(M3814, nedisertib)*	Ia/Ib, completed,	NCT02516813, (Samuels et al., 2024)	Arm A: peposertib + RT (10×3 Gy) Arm B: peposertib + RT (33–35×2 Gy) + cisplatin	solid tumours	MTD	A: *34* B: *11*	Arm A was well tolerated, Arm B did not reach effective exposure	A: *3* (8.8) B: *2* (18.2)
		Ib, completed	NCT03770689, (Romesser et al., 2024)	nRT peposertib + (25×1.8 Gy + 3×1.8 Gy boost) + capecitabine	rectal cancer	MTD, RP2D	*19*	There were no improved complete response rates at tolerable dose levels.	*5* (26)

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Table 2 (*continued*)

DDR target	Drug	Phase, status	Trial identifier, name, ref	Treatment	Tumour type	Outcome measures	No of patients	Notable outcomes	Absolute no Grade 3–4 AE (% of patients affected)
		I, recruiting	NCT04555577, (Majd et al., 2023)	peposertib + aRT (30×2 Gy) followed by temozolomide	glioblastoma	MTD	*15*	Well tolerated, one DLT, three transient G3 dermatitis	*4* (26)
		I, completed	NCT03724890, (Perez et al., 2024)	Only part B: peposertib RT (10×3 Gy) + avelumab	solid tumours	MTD, RP2D	*19*	Well tolerated but limited antitumor effect	*12* (NA)

AE, adverse events; APE1, apurinic/apyrimidinic endonuclease 1; ATM, ataxia-telangiectasia mutated; ATR, ataxia-telangiectasia and Rad3-related; CHK1, checkpoint kinase 1; CHK2, checkpoint kinase 2; CHK1/2, checkpoint kinase 1 and 2; CR, complete response; DCR, disease control rate; DDR, DNA damage response; DNA-PK, DNA-dependent protein kinase; DLT, Dose-limiting toxicities; FU, follow-up; Gy, Gray; HNSCC, Head and neck squamous cell carcinoma; MTD, maximum tolerated dose; NA, Not applicable; NAR, neoadjuvant rectal score; NSCLC, non-small cell lung cancer; OS, overall survival; PARP, poly (ADP-ribose) polymerase; pCR, pathological response rate; PFS, progression free survival; PR, partial response; QoL= quality of life; RP2D, recommended phase 2 dose; RT, radiotherapy; aRT, adjuvant radiotherapy; nRT, neo-adjuvant radiotherapy; LDFWAR, Low-dose fractionated whole abdominal radiation therapy; WBRT, whole brain radiotherapy.

with radiotherapy. Preliminary results indicate that the addition of fluzoparib was well tolerated, with only two grade 3 dose limiting toxicities (anaemia, skin reaction). Promising clinical outcomes were observed, with around a fifth of patients achieving pathological response and more than half having stable disease. Although one-third of patients developed major post-operative wound complications, complication rates were consistent with previous trials and literature (Lu et al., 2024).

The PRIMA and SADDRIN-I are currently recruiting and without preliminary results. The PRIMA combines fluzoparib plus concurrent stereotactic body radiotherapy and camrelizumab. The SADDRIN-I combines the ATM inhibitor AZD1390 with preoperative radiotherapy of 50 Gy given in 25 fractions with or without durvalumab.

When considering other tumour types, multiple trials report that DDR inhibitors are generally well tolerated. However, the addition of DDR inhibitors demonstrated varying tolerability and effectiveness, and subsequent phase II trials failed to observe improved survival or response. Many of the identified trials included some form of systemic therapy alongside the combination of a DDR inhibitor and conventional dosed radiotherapy (Table 2).

In phase I studies, niraparib and veliparib showed promising short-term safety profiles, with a similar incidence of adverse events compared to radiation alone in breast, brain and peritoneal carcinomatosis (Keenan et al., 2022; Reiss et al., 2016; Mehta et al., 2015). However, some trials observed increased long-term toxicities such as severe fibrosis (Jagsi et al., 2018). Despite good tolerability in subsequent phase II trials, the addition of niraparib and veliparib resulted in no significant improvement in survival or clinical outcomes (Chabot et al., 2017; Baxter et al., 2020; Sim et al., 2021; Karajannis et al., 2022).

Similarly, trials involving olaparib also yielded mixed results. While generally well tolerated in breast, lung, pancreas and brain cancers, olaparib caused severe toxicities such as mucositis, perforations, dyspnoea and acute respiratory distress syndrome in oesophageal and head and neck cancers, especially when combined with higher irradiation doses or with accelerated schedules (Sheikh et al., 2023; de Haan et al., 2021; Navran et al., 2024; Derby et al., 2024; Loap et al., 2022). This suggest that the addition of DDR inhibitors to the irradiation of more vulnerable or rapidly proliferating normal healthy tissues might not be without risk, and may come at the cost of increased toxicity.

Comparable results and challenges have been reported in trials with other DDR-inhibitors, highlighting the challenges in achieving meaningful clinical benefits with these novel agents. Nevertheless, given the tolerability of DDR inhibitors and the widespread use of radiotherapy, the addition of DDR inhibitors to radiotherapy still provides opportunities for further research. Future trials should exercise caution with irradiating vulnerable and rapidly proliferating tissue, and incorporate adequate long-term follow-up to explore a potential increase in long-term toxicities. Especially as the majority of clinical trials have yet to report long-term outcomes.

STS may provide a unique opportunity to safely investigate the addition of DDR inhibitors to radiotherapy, as they frequently occur in the extremities, which lack vital organs, vulnerable tissues, and rapidly proliferating tissues other than skin and bone marrow, alleviating some of the toxicity concerns. Importantly, almost all of the identified trials prescribed the full recommended radiation dose in conventional fractionations. While this did not improve treatment outcomes, it may allow similar treatment results at a lower radiation dose through radiosensitization. In turn, this may allow for a safe radiation dose reduction while maintaining therapeutic efficacy and reducing morbidity.

6. Conclusion

Radiotherapy remains a cornerstone of sarcoma treatment. However, even with the combined treatment of radiotherapy and surgery, 5–15 % of STS patients relapse locally and 30–50 % distantly. This emphasises the need to further reduce relapses. Targeting the DDR pathway through

Table 3
Ongoing clinical trials investigating radiotherapy with DDR inhibitors.

DDR target	Drug	Phase	Trial identifier	Treatment (DDRi plus)	Tumour type
PARP	AZD5303	I	NCT04550104	RT	NSCLC
	pamiparib *(Partruvix, BGB290)*	I	NCT05526924	RT + tislelizumab + 5-FU	head and neck cancer
	niraparib *(Zejula, MK4827, ZL2306)*	I/II	NCT03644342	induction carboplatin + paclitaxel followed by RT + niraparib	cervix cancer
		I/II	NCT04926324	RT + dostarlimab	rectal cancer
		I/II	NCT05784012	RT + cisplatin + dostarlimab	HNSCC
		I/II	NCT04194554	RT	prostate cancer
		II	NCT04037254	RT + androgen deprivation therapy	prostate cancer
		II	NCT05162196	RT + toripalimab	recurrent SCLC
		II	NCT05700721	RT + dostarlimab	brain metastases
		II	NCT04837209	RT + dostarlimab	TNBC
	olaparib *(Lynparza, AZD2281, KU0059436, MK7339)*	I/II	NCT04728230	RT + durvalumab ± carboplatin/etoposide	ES-SCLC
		I	NCT06197581	RT	breast cancer
		I	NCT03923270	RT + durvalumab ± tremelimumab	ES-SCLC
		I	NCT05411094	RT + durvalumab	pancreatic cancer
		I/IIa	NCT03212742	RT + temozolomide	glioma
		I	NCT06217757	low dose RT + cisplatin + etoposide + sugemalimab	ES-SCLC
		II	NCT03598257	RT	breast cancer
		II	NCT05623319	RT + pembrolizumab	ES-SCLC
		II	NCT04683679	RT + pembrolizumab	breast cancer
		II	NCT05366166	RT + pembrolizumab	HNSCC
		II	NCT05568550	RT + pembrolizumab	prostate cancer
		II	NCT05379972	RT + olaparib, followed by olaparib + prembrolizumab	gastric cancer
		II	NCT04748042	RT + abiraterone, androgen deprivation therapy	prostate cancer
	talazoparib *(Talzenna, BMN 673, MDV3800,)*	I	NCT04170946	RT	ES-SCLC
	rucaparib *(Rubraca, PF01367338, AG−014699)*	I	NCT03542175	RT	TNBC
	fluzoparib *(AiRuiYi, SHR3162)*	I	NCT06074692	RT + Camrelizumab	sarcoma
		II	Zhang et al., 2022	RT + temozolomide	glioblastoma
APE1	methoxyamine *(TRC102)*	II	NCT05198830	methoxyamine + RT + pemetrexed, cisplatin followed by durvalumab	non-squamous NSCLC
ATM	AZD1390	Ib	NCT04550104	RT	NSCLC
		I	NCT05678010	RT	solid tumours
		I	NCT05182905	RT	glioma
		I	NCT05116254	RT and RT + durvalumab	sarcoma
ATR	berzosertib (VE−822, VX−970, M6620)	Ib	NCT04052555	RT	TNBC
		I	NCT02589522	RT	brain and lung cancer
	camonsertib (RP3500)	I/II	NCT05566574	RT	solid tumours
	elimusertib (BAY1895344)	I	NCT04576091	RT + pembrolizumab	HNSCC
	ceralasertib *(AZD6738)*	I	NCT02223923	RT	solid tumours
		I	NCT04550104	RT	NSCLC
WEE1	adavosertib (AZD1775, MK1775)	I	NCT04460937	RT	oesophageal and gastroesophageal junction cancer
		I	NCT03028766	RT + cisplatin	head and neck cancer
DNA-PK	etidaligide *(AsiDNA)*	I/II	NCT05394558	RT	recurrent high-grade glioma
	peposertib *(M3814, nedisertib)*	I/II	NCT04172532	RT	pancreatic cancer
		I	NCT04533750	RT	head and neck cancer
		I/II	NCT04068194	RT + avelumab	hepatobiliary cancer

ATM, ataxia-telangiectasia mutated; ATR, ataxia-telangiectasia and Rad3-related; DDR, DNA damage response; DNA-PK, DNA-dependent protein kinase; ES-SCLC, extensive stage small-cell lung cancer; HNSCC, Head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; PARP, poly (ADP-ribose) polymerase; RT, radiotherapy; SCLC, small cell lung cancer; TNBC, triple negative breast cancer.

key proteins like PARP, ATM, ATR and DNA-PK appears a promising strategy to enhance radiosensitivity in STS, especially in genetically complex subtypes.

This review highlights the potential of targeting DDR pathways to sensitize STS to radiation. Preclinical data demonstrates that targeting DDR pathways is a promising strategy to enhance the radiosensitivity of tumour cells while having minimal effect on normal cells. While phase I and II trials have demonstrated that DDR inhibitors are generally well tolerated, some trials observe an increase in severe adverse events, and most phase II trials report limited to no increase in disease control or overall survival. However these data, are still very fragmented.

Enhancing radiation efficacy through DDR inhibitors may enable safe reduction in irradiation dose, decreasing toxicity while maintaining clinical effectiveness. Therefore, efforts should be made to either improve efficacy by developing more effective DDR inhibitors or to reduce radiation doses through DDR inhibitor-mediated radiosensitization while maintaining efficacy. Future trials in STS are warranted and they should primarily focus on extremity STS to alleviate the majority of observed toxicities associated with this combined treatment approach. The results of ongoing trials, like the RADIOSARP, NCC-4016, PRIMA and SADDRIN-I are eagerly awaited and will provide critical insights into this new treatment strategy in STS.

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Declaration of Competing Interest

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Appendix A. Supporting information

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