REVIEW ARTICLE OPEN

Synthetic lethality in cancer: mechanisms, therapeutic exploitation and clinical translation

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Targeting synthetic lethal interactions has emerged as a promising strategy for cancer therapeutics, particularly by exploiting DNA damage response (DDR) pathways. A well-known example of this are PARP inhibitors, that selectively kill cancer cells compromised by mutations in DDR genes like *BRCA1/2*, while sparing normal cells with functional homologous recombination repair. These compounds have substantially improved clinical outcomes, especially in *BRCA1/2*-mutated ovarian cancer, enhancing both survival rates and quality of life. Their great clinical impact has been constrained by the appearance of resistance and safety concerns. New generation PARP inhibitors are being developed with enhanced selectivity and reduced side effects. Beyond PARP inhibition, several other drugs inhibiting key DDR components, such as ATR, ATM and DNA-PK, have progressed to clinical trials. These DDR inhibitors are being studied alone or in combination with chemotherapy, radiotherapy, immunotherapy or other targeted therapy, increasing efficacy and improving outcomes in resistant and advanced cancers. While most synthetic lethality-based clinical trials in oncology target DDR, an increasing trend in the preclinical and clinical setting is focused on inhibiting non-DDR pathways (e.g., PRMT5 and SMARCA4/2). However, challenges remain in determining the most effective combinations, identifying which patient populations will benefit the most from these therapies and overcoming resistance. Continued research is also essential to fully understand the intricate network of synthetic lethality and maximize the therapeutic potential of synthetic lethality-based therapies. Nonetheless, targeting synthetic lethal interactions with inhibitors represents an exciting frontier in precision oncology, offering the potential for more tailored, effective and less toxic cancer treatments.

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INTRODUCTION

Cells are constantly exposed to endogenous and exogenous sources of DNA damage that, if unrepaired, compromise cell viability. To overcome this, they rely on an intricate network of DNA damage response (DDR) pathways responsible for maintaining genomic stability by detecting DNA lesions, controlling the cell cycle and promoting accurate DNA repair. The dysregulation of these pathways can lead to tumorigenesis. In fact, DDR pathway gene alterations are amongst the most common genomic events observed in human cancers, making DDR components attractive targets for cancer treatment.

Despite the involvement of DDR defects in promoting cancer development, the dysfunction of these pathways also represents a specific vulnerability that can be exploited therapeutically. A promising approach gaining attention for cancer therapeutics in this context is synthetic lethality (SL), where the inhibition of a specific gene or pathway becomes toxic in cancer cells harboring mutations or deficiencies in other genes. By selectively killing cancer cells while sparing normal tissues, this strategy offers the potential for more precise and less toxic cancer treatments. This is exemplified by the success of Poly (ADP-ribose) Polymerase inhibitors (PARPi) in treating *BRCA1/2*-deficient tumors. *BRCA1/2*-deficient cells are impaired in homologous recombination repair (HRR), a high-fidelity mechanism for processing DNA double-strandtabl breaks (DSBs). The inhibition of PARP enzymes in these cells, which are involved in the repair of single-strand breaks (SSBs) by base excision repair (BER), results in the accumulation of DNA lesions that cannot be effectively repaired by HRR due to non-functional *BRCA1/2* proteins, ultimately leading to cancer cell death. The discovery of novel SL interactions within other DDR genes, coupled with the benefits of PARPi for cancer treatment and the advances in functional genomics, has led to extensive research into targeting other DDR components, such as the three primary phosphatidylinositol 3-kinase-like protein kinases ATR, ATM and DNA-PK, and their downstream effectors, CHK1/2. These proteins participate in the detection of DNA damage and the coordination of cell cycle progression in response to replication stress or DNA damage. Some other DDR targets that are being clinically explored are other cell cycle control kinases (WEE1, PKMYT1, CDKs and PLK1); proteins involved in DSB repair such as the polymerase POLQ (non-homologous end-joining) and the recombinase RAD51 (HRR); USP1, which deubiquitinates FANCD2/FANCI (FA/BRCA pathway) and PCNA (translesion synthesis); the WRN helicase, that mediates the choice between different DSB repair pathways; and APE1, an endonuclease involved in BER. Based on this, cancer cells containing high levels of replication

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stress or DNA damage often exhibit high dependency on these pathways, making them attractive targets for SL-based therapies.

In addition to monotherapy approaches, combining DDR inhibitors (DDRi) with conventional therapies, such as chemotherapy (CTx) and radiotherapy (RT), has shown promise in enhancing treatment efficacy and overcoming cancer drug resistance by exacerbating DNA damage beyond the repair capacity of cancer cells. Moreover, as DDRi are also able to modulate the tumor microenvironment (TME), increasing the tumor mutational burden and promoting immunogenic cell death, multiple clinical trials are testing their combination with immune checkpoint inhibitors (ICIs). Furthermore, DDR-targeting drugs are also being clinically associated with other targeted therapies, such as with the VEGF inhibitor bevacizumab, and with other DDRi featuring different mechanisms of action.

Although the vast majority of clinically advanced drugs targeting SL in oncology are DDRi, non-DDR agents, including metabolic enzymes (e.g., PRMT5, MAT2A), epigenetic regulators (e.g., SMARCA4, SMARCA2 and ALC1) and RNA helicases (e.g., DHX9), can also induce SL and some of them are undergoing preclinical and clinical evaluation, highlighting the broader applicability of SL across diverse cancer types and molecular contexts.

Based on these considerations, this review aims to provide a comprehensive overview of the mechanisms of SL in DDR and non-DDR pathways, focusing on the clinical development of novel therapeutic targets exploiting SL interactions in oncology. By integrating mechanistic insights with emerging clinical evidence, we discuss the opportunities and challenges associated with the translation of SL into effective cancer treatments, and we draw future directions for the rational design of targeted therapeutic strategies.

SYNTHETIC LETHALITY (SL)

The term synthetic lethality (SL), coined by Theodor Dobzhansky in 1946,[1] refers to the genetic interaction between two or more genes wherein their simultaneous alteration leads to severe loss of cell viability and death, while each of them is non-lethal alone[2] (Fig. 1). This phenomenon had been previously described at the beginning of the 20th century by Calvin Bridges, who noticed that certain combinations of gene mutations in *Drosophila melanogaster* were lethal, while the homozygous parents were viable.[3]

Although SL interactions have most commonly been associated with loss-of-function (LOF) alleles, an alternative SL situation, also called synthetic dosage lethality, may involve gain-of-function (GOF) alleles. In this case, a GOF mutation may be lethal only in the presence of a second-site mutation.[4] This concept may also be extended to the so-called "synthetic sick" interactions where the combination of mutations in two genes results in non-lethal impairment of cellular fitness more than mutation of either gene alone.[5] Combinations of other types of perturbations may also result in SL, including the action of chemical compounds or changes in the TME.[6,7]

Cancer is considered a disease of the genome. Recent advances in genome sequencing and the use of large-scale genetic CRISPR screens have allowed the rapid identification of genetic and epigenetic changes that distinguish tumor cells from non-tumor cells, revealing vulnerabilities that may be exploited to selectively target the tumor with therapeutics.[8,9] In the cancer therapy context, SL has been used as an innovative strategy to design drugs that inhibit one gene product that is lethal in the presence of a mutation in another specific gene, often occurring in tumors.[10] A well-known case of drugs targeting SL interactions is PARPi, used for the treatment of HRR-deficient (HRD) tumors. Furthermore, the term SL has not only been used in cancer therapeutics to target LOF alterations in cancer cells via inhibition of a gene product, but also for GOF alterations that may not be targeted directly, such as the case of KRAS-targeted therapies.[11] There are additional factors that influence drug-induced SL, such as the TME, metabolic networks, the control of the cell cycle, epigenetic regulation and the DDR pathways.[12] Therefore, SL increases selectivity towards the killing of tumor cells that harbor mutations in 'undruggable' proteins, including LOF mutations, hence enhancing the therapeutic index between the tumor and normal tissue. Moreover, combination therapy with these drugs might not only increase the efficacy of conventional therapies, allowing to decrease doses and, consequently, adverse effects, but also to overcome drug resistance[13] (Fig. 1).

DNA DAMAGE RESPONSE (DDR) AS ANTICANCER TARGET

Cells are constantly exposed to a variety of endogenous and exogenous sources of DNA damage. To mitigate these threats, they rely on different mechanisms to repair DNA damage, maintain genomic stability and promote cell survival (Fig. 2). SSBs are mainly repaired by BER, DNA replication errors by MMR, DNA adducts and covalent crosslinks between bases in the same DNA strand are repaired by NER, and the correction of abasic sites and damaged bases and the removal of uracil are performed by BER. The pathway that cells use to process DSBs depends on multiple variables, including the cell cycle stage during which they are generated, whether the DSB itself is one-ended or two-ended and chemically "clean" or "dirty".[14] Eukaryotic cells utilize two main mechanisms for DSB repair: error-prone non-homologous end-joining (NHEJ) and error-free HRR. The NHEJ pathway may be divided into canonical non-homologous end joining (c-NHEJ) or the alternative pathway for non-homologous end joining (alt-NHEJ), which is also termed as microhomology-mediated end-joining (MMEJ). These last two pathways, as the name end-joining indicates, involve the direct ligation of two-ended DSB ends with little or no sequence homology required. Since no repair template is required, it may occur at any phase of the cell cycle. Both c-NHEJ and alt-NHEJ typically cause short deletions or insertions at the DSB site, and besides, they may generate large deletions or chromosomal rearrangements.[15,16] In contrast, HRR requires a homologous sequence as a template, which allows the recombination machinery to accurately restore any missing genetic information in the vicinity of the break site.[17] Therefore, HRR may only take place in cell cycle stages with an available sister chromatid, which includes the S and G_2 phases, and hence a strict control mechanism is needed.[16] Another important type of DNA damage vital for cells are interstrand crosslinks (ICLs). ICLs result extremely toxic because they covalently link both DNA strands, preventing their separation during replication and transcription, and if left unrepaired, activate cell apoptosis.[18] A well-reported class of ICL-inducers is chemotherapeutic agents such as mitomycin C, cisplatin, nitrogen mustard, nitrosourea, and their derivatives. In non-proliferating cells or during G_1 phase of the cell cycle, ICLs are recognized and removed by the NER pathway, followed by excision by XPF-ERCC1 and translesion synthesis (TLS).[19,20] In contrast, in replicating cells, the DNA replication machinery serves as a sensor for ICLs, triggering DNA damage checkpoint activation, transient G_2 arrest and DNA damage repair by the Fanconi anemia/BRCA (FA/BRCA) pathway.[21] The resulting DNA duplex with a DSB may be finally repaired by multiple DSB repair sub-pathways, with HRR the preferential one, thanks to the readily available HRR-compatible template that occurs at ICL sites.[21]

Defects in these pathways may cause gene mutations and increase genomic instability that not only alter gene function but may also induce uncontrolled cellular growth and cancer,[22,23] for example, by the activation of oncogenes or inactivation of tumor suppressor genes.[23] Actually, many proteins involved in DDR, such as BRCA1/2, have been found altered in different tumor types and have been related to cancer initiation, development, metastasis

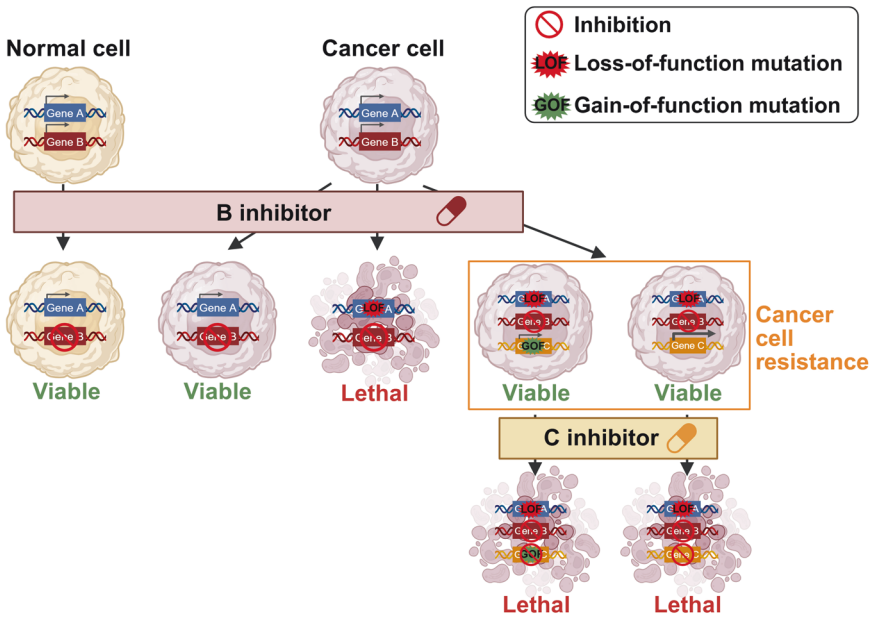


Fig. 1 Overcoming cancer drug resistance using a double-synthetic lethality approach. In the presence of a normal or cancer cell with 2 functional synthetic lethal genes (genes A and B), if only one of the genes is inhibited (gene B), cells remain viable. However, if this cancer cell has already a mutation on one of the genes (gene A) that impairs its function and the other gene is inhibited this results in cancer cell death. When cancer resistance appears due to for example the mutation or over-expression of an additional gene (gene C), it may be possible to overcome this resistance by designing an inhibitor that targets gene C, thereby restoring cancer cell lethality through this double-SL approach. Figure created with BioRender

and resistance to anticancer drugs.[24–27] The disruption of a specific DDR pathway frequently enhances the dependency of cancer cells on compensatory pathways for their survival. As previously described, these compensatory pathways can be disrupted using the SL concept to specifically target tumors with lower toxicities than conventional therapies. Moreover, a large number of studies have shown that DDR inhibition leads to significantly enhanced sensitivity of cancer cells to CTx and RT.[28–32] Dysfunction of several DDR pathways may also trigger the activation of the host's immune system,[33] contributing to the sensitization of tumors to ICIs. This finding suggested a potential treatment strategy for combining DDR-targeting agents with ICIs.[34] Preliminary results from different clinical trials have shown that combining DDR-targeting drugs with ICIs represents a promising therapeutic strategy for cancer therapy.[35,36] Consequently, accurate recognition and repair of DNA damage is essential to maintain genomic integrity and prevent genomic instability and tumorigenesis. Additionally, the identification of specific alterations in DDR genes in tumors can serve as a biomarker for the selection of the most suitable DDR-targeting drug to treat specifically these tumors, exemplified by the use of PARPi in tumors with *BRCA1/2* mutations. To add even more complexity, the reported sensitization effect of DDRi to conventional CTx and RT, and the reported link between DDR pathways and immunotherapy, encourages the study and design of DDRi-based combination treatments to circumvent cancer drug resistance.

THE CASE OF PARP INHIBITORS (PARPI)

Mechanism of action of PARPi

The success of PARPi as anticancer agents for *BRCA1/2*-deficient tumors provided a proof-of-principle example of the substantial promise of SL for cancer treatment. The discovery in 2005 of a SL interaction between the inhibition of PARP and mutations in *BRCA1* or *BRCA2* marked a milestone in cancer therapeutics.[37,38] *BRCA1* and *BRCA2* are tumor suppressor genes that confer a higher risk of cancer in mutation carriers, including breast, ovarian, pancreatic and prostate cancer.[39,40] Functional BRCA1/2 proteins are crucial to repair DSBs by HRR. When cells acquire HRR deficiency (HRD), driven by defects in *BRCA1*, *BRCA2* or other pathway components, such as *PALB2, ATM* or *ATR*,[41,42] non-conservative forms of DNA repair, like NHEJ, predominate. These other processes either fuse broken DNA ends at the DSB without using a homologous DNA sequence as a template or fuse regions of DNA close to the site of damage that display short regions of DNA sequence homology, deleting the intervening DNA sequence. The lack of use of homologous sequences as repair templates leads to error-prone repair, which causes DNA alterations and, in turn, cancer initiation or progression[43,44]; this explains in part the increase in cancer risk related to *BRCA1/2* mutations.[45] These tumors have frequently arisen in individuals with a germline (g) *BRCA1/2* mutation that have developed a somatic LOF aberration in the wild-type *BRCA1/2* allele.[46]

Upon DNA damage, members of the PARP family bind the DNA lesion and modify several proteins with ADP-ribose using NAD^+ as a substrate, rapidly recruiting other DNA repair factors.[47] PARP1 or 2 and tankyrase 1 (PARP5A) or 2 (PARP5B) generate PARylation, while other PARP members instead attach mono-ADP-ribose onto target proteins and seem to have cancer-relevant functions, being possible future targets for cancer therapy.[48,49] However, evidence to date suggests that only PARP1, 2 and 3 are activated by DNA breaks and catalyze ADP-ribosylation after DNA damage, with PARP1 responsible for 80–90% of the global PAR synthesis following DSBs.[48,50] PARP1 is the best-characterized member of the PARP family, and apart from regulating cell proliferation and differentiation by repairing SSBs and DSBs, it also participates in the stabilization of DNA replication forks and the modification of chromatin structure.[51] Its structure comprises three zinc finger domains for DNA binding, a BRCA-C-terminal domain, a catalytic domain containing a conserved ADP-ribosyl transferase fold, and a WGR (Trp-Gly-Arg) domain, which participates in DNA interaction and regulates the catalytic activity in response to DNA damage.[52] Binding to damaged DNA leads to an increase of the PARylation activity and the binding of NAD^+ stabilizes the catalytic domain in its unfolded conformation and strengthens the interaction

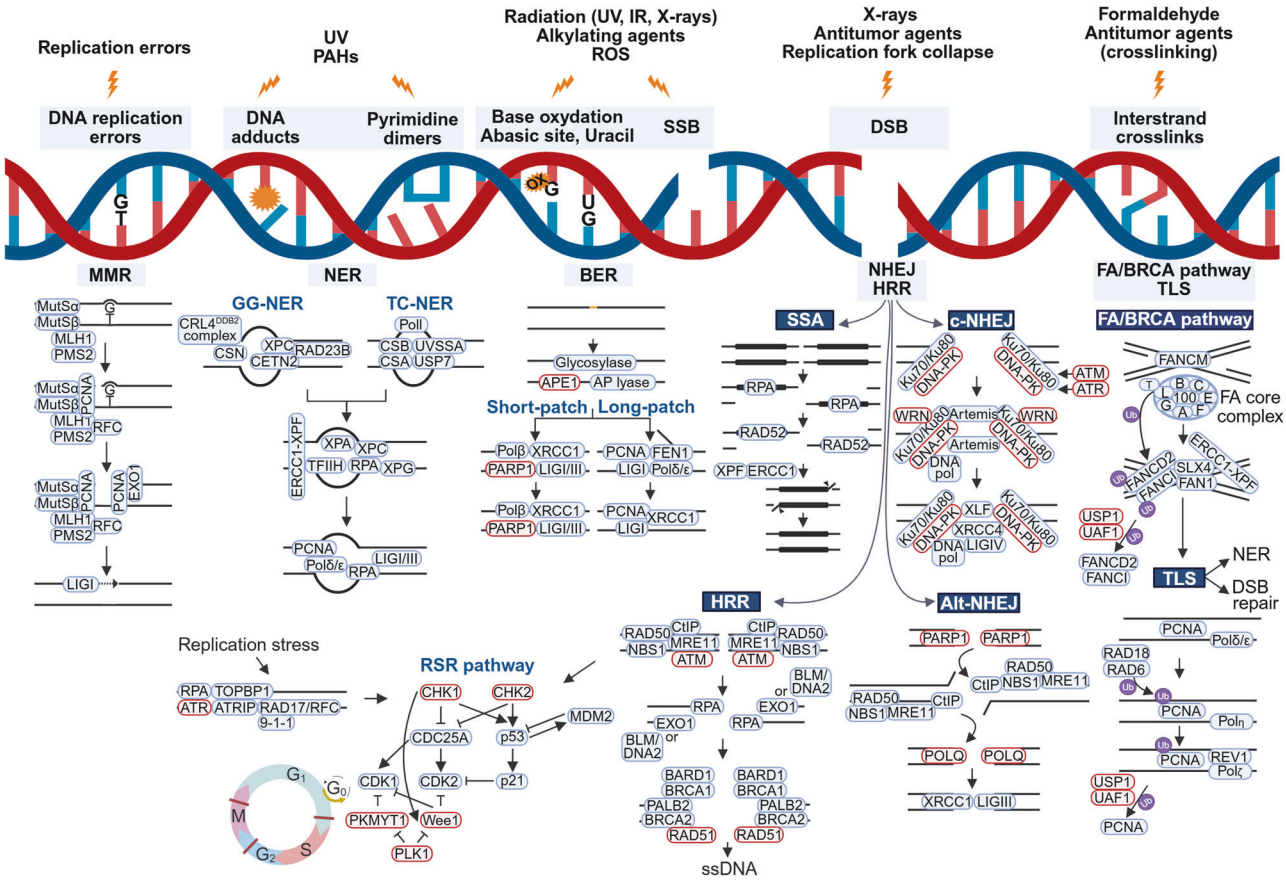


Fig. 2 Major DNA repair pathways that are being targeted clinically using the SL approach. Cells rely on multiple mechanisms to repair DNA damage. DNA replication errors are repaired by MMR and DNA adducts and pyrimidine dimers resulting from UV and polycyclic aromatic hydrocarbons (PAHs) by NER. The repair of abasic sites and damaged bases and the removal of uracil as well as SSBs, caused by radiation, alkylating agents or reactive oxygen species (ROS), are performed by BER. DSBs that can arise from X-rays, antitumor agents or replication fork collapse are repaired by error-prone non-homologous end-joining (NHEJ) and error-free homologous recombination repair (HRR). The NHEJ pathways may be divided into canonical non-homologous end joining (c-NHEJ) or the alternative pathway for non-homologous end joining (alt-NHEJ). ICLs, which can be caused by chemotherapeutic agents (e.g., MMC and cisplatin) amongst others, covalently link both DNA strands preventing their separation during replication and transcription. In non-proliferating cells or during G_1-phase this type of damage is recognized and removed by the NER pathway, followed by excision by XPF-ERCC1 and TLS. In replicating cells, DNA damage checkpoint is activated and damage is repaired by the FA/BRCA pathway. The other DNA duplex with a DSB may be finally repaired by multiple sub-pathways, being HRR the preferential one. Colored in red are the proteins for which selective drug inhibitors have been identified and have progressed to clinical trials. Figure created with BioRender

between the regulatory domains and DNA.[53] Short base lesions and SSBs that maintain DNA structure are mainly repaired by BER (Fig. 3). Damaged sites are first cleaved by glycosylase and APE1 and create a single-stranded DNA (ssDNA) nick. This is recognized as a SSB by members of the PARP family, being PARP1 the most relevant. PARP proteins generate PARylation of target proteins and themselves, using NAD^+ as a substrate.[47] Auto-PARylated PARP1 recruits downstream BER components, such as Polβ, XRCC1 and DNA ligase III to the DNA damage site.[54,55]

PARPi compete with NAD^+ for binding and are mostly selective for PARP1 and PARP2. Once bound, they prevent auto-PARylation of PARP and, therefore, its dissociation from the broken DNA. This causes the stabilization and trapping of PARP on the DNA and leads to DSB formation by stalling and collapsing replication forks[56,57] or by increasing the speed of fork elongation, what should be correctly repaired by HRR in the S/G_2-phase.[58] In cells with non-functional HRR, due to, for example, homozygous *BRCA1/2* mutations, the PARP1-dependent BER pathway compensates for the damaged DNA not repaired by HRR. Thus, in these cells, the pharmacological inhibition of PARP1 by PARPi causes the accumulation of SSBs, which during DNA replication form DSBs, leading to genomic instability, mitotic damage and cell death[59,60] (Fig. 4). Additionally, PARP1 seems to be essential for managing transcription-replication conflicts. Therefore, when it is inhibited, the head-on collision between transcription and replication machineries is left unresolved, creating a source of endogenous DNA stress that must be repaired by HRR.[61] Although it was long thought that the main mechanism for the hypersensitivity of *BRCA1/2*-deficient tumors to PARPi was the formation of unrepaired DSBs, recent findings suggest that ssDNA replication gaps are fundamental to the cytotoxicity of these agents. This hypothesis is based on the fact that *BRCA1/2*-deficient cells fail to restrain DNA replication in response to genotoxic stress and in consequence, accumulate ssDNA gaps. When these gaps are suppressed by either restored fork slowing or gap filling, these cells acquire chemoresistance. This suggests that the critical lesion that determines drug sensitivity to genotoxic chemotherapies, such as PARPi and cisplatin, are these ssDNA gaps instead of DSB.[62,63]

PARPi approved or in clinical trials

Six PARPi have been approved for cancer treatment: olaparib (FDA 2014, EMA 2014; Lynparza® from AstraZeneca), niraparib (FDA 2017, EMA 2017; Zejula® from GlaxoSmithKline), rucaparib (FDA

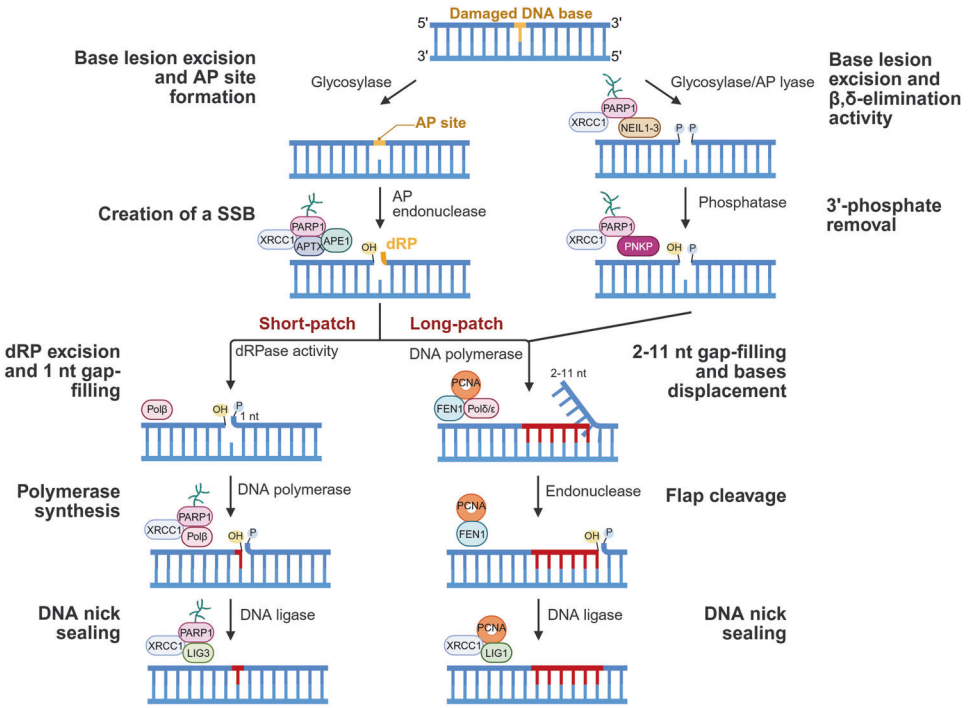


Fig. 3 Base excision repair (BER) pathway. BER is the major DNA damage repair pathway for correcting non-bulky forms of DNA damage (e.g., deamination, base oxidation or alkylation) that do not significantly distort the DNA helix. This process is performed in a series of successive reactions. A damage specific DNA glycosylase initially detects the lesion and excises the damaged base creating an abasic site (AP site), that is then cleaved by APE1 creating a SSB with 3′-hydroxyl (OH) and 5′-dRP ends. Alternatively, the NEIL1-3 glycosylase generates a 1-nucleotide (nt) gap through βδ-elimination flanked by 3′- and 5′-phosphate ends. The 3′ phosphate is removed by PNKP to produce a 3′-OH end. These DNA ends are processed by one of two sub-pathways: short-patch (single-nucleotide) or long-patch (more than one nucleotide) repair, during which a DNA polymerase fills the gap with the correct nucleotides and the repair mechanism is completed with the sealing of the nick by a DNA ligase. More concretely, the ssDNA nick is recognized by PARP1, which upon auto-PARylation, recruits downstream BER components. In short-patch BER, Polβ excises the dRP and fills the gap with a new nucleotide. The nick is then ligated by XRCC1-LIG3. In long-patch BER, Polδ/ε fill the gap with 2-11 nucleotides, creating a 5′-flap that is excised by FEN1 and finally ligated by LIG1 in a PCNA-dependent manner. Figure created with BioRender

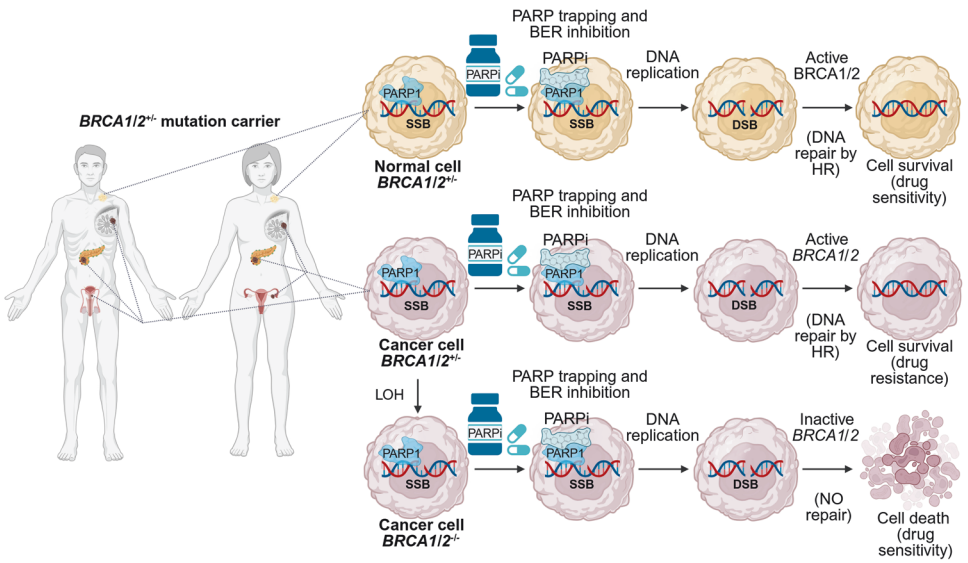


Fig. 4 Synthetic lethality in tumors from *BRCA1/2* mutation carriers treated with PARPi. PARPi induce PARP trapping and BER inhibition on sites with SSBs. SSBs in the cells are recognized by PARP1, that recruits downstream BER components to repair the damage. If the BER pathway is inhibited by PARPi in cells with heterozygous mutations in *BRCA1/2* (*BRCA1/2*$^{+/-}$), PARP1 becomes trapped on the DNA. This causes the stalling and collapse of replication forks and the formation of DSBs, that should be repaired by HRR using the functional *BRCA1/2* copy. The same happens in *BRCA1/2*$^{+/-}$ cancer cells, resulting in cancer cell survival and drug resistance. However, these cancer cells often lose the wild-type copy of *BRCA1/2* by loss of heterozygosity (LOH) and, in this case, when exposed to PARPi they can no longer repair the DSBs, leading to cancer cell death by SL between PARP1 (BER) and BRCA1/2 (HRR). Figure created with BioRender

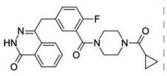
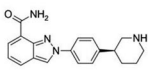
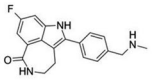
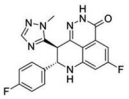
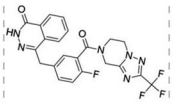
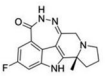
Drug name	Olaparib (Lynparza®)	Niraparib (Zejula®)	Rucaparib (Rubraca®)	Talazoparib (Talzenna®)	Fuzuloparib (AiRuiYi®)	Pamiparib (Partruvix®)
Structure						
Alternative name	AZD2281, KU0059436	MK-4827	AG014699, PF-01367338	BMN-673, MDV3800, PF-06944076	Fluzoparib, SHR-3162	BGB-290, Baihuize
Company	AstraZeneca	Tesaro (GlaxoSmithKline)	Pharmaand GmbH	Pfizer	Jiangsu Hengrui Pharmaceuticals	BeiGene
Approval	Ovarian, breast, pancreatic, prostate and endometrial cancer	Ovarian and prostate cancer	Ovarian and prostate cancer	Breast and prostate cancer	Ovarian cancer (only in China)	Ovarian cancer (only in China)
PARP trapping	++	+++	++	++++	++	++/+++

Fig. 5 PARPi approved for marketing. Six PARPi have been approved for cancer treatment: olaparib (Lynparza® from AstraZeneca), niraparib (Zejula® from GlaxoSmithKline), rucaparib (Rubraca® from Pharmaand GmbH), talazoparib (Talzenna® from Pfizer), and only in China, fuzuloparib (AiRuiYi® from Jiangsu Hengrui Pharmaceuticals) and pamiparib (Partruvix® from BeiGene). These drugs, except fuzuloparib and pamiparib, are currently approved by the FDA and the EMA for treating cancers such as breast, ovarian, prostate and pancreatic cancer. Fuzuloparib (formerly fluzoparib) received approval in 2021 by the NMPA for the treatment of ovarian cancer (including fallopian tube cancer or primary peritoneal cancer). Also in 2021, pamiparib was approved by the NMPA for g*BRCA1/2*m recurrent advanced ovarian, fallopian tube or primary peritoneal cancer previously treated with two or more lines of chemotherapy. Several clinical trials of these drugs directed to the expansion of their indications are ongoing. The different PARPi display distinct degrees of PARP trapping: talazoparib » niraparib > olaparib = rucaparib. Although backed by less evidence, fuzuloparib harbors similar trapping capacity compared to olaparib, and pamiparib similar or higher level. Figure created with BioRender

2016, EMA 2018; Rubraca® from Pharmaand GmbH), talazoparib (FDA 2018, EMA 2019; Talzenna® from Pfizer), and only in China, fuzuloparib (NMPA 2020; AiRuiYi® from Jiangsu Hengrui Pharmaceuticals) and pamiparib (NMPA 2021; Partruvix® from BeiGene). The different PARPi display large variable levels of cytotoxicity by causing distinct degrees of PARP trapping: talazoparib » niraparib > olaparib = rucaparib » veliparib[57,64] (Fig. 5). Although the trapping ability of PARPi depends on catalytic inhibition and the resulting dissociation rates, other factors such as reverse allosteric effects may also play a significant role.[65,66]

The clinical journey of PARPi began in 2003 with the introduction of rucaparib (then under the name AG014699) into human trials in combination with the chemotherapeutic agent temozolomide.[67] This milestone opened a new chapter in oncology, which was soon followed by a breakthrough Phase I trial for olaparib in *BRCA1/2*-carriers with advanced solid tumors. This study revealed that 63% of these patients experienced antitumor response with less side effects than conventional CTx (NCT00516373[68]). Soon afterwards, a Phase II trial showed that olaparib as maintenance treatment (MT) significantly improved median progression-free survival (mPFS) among patients with PtS recurrent ovarian cancer with a *BRCA1/2*m (NCT00753545[69]). This led to the approval of olaparib (Lynparza®) in 2014 by the EMA and the FDA for advanced *BRCA1/2*m ovarian carcinoma. This drug had been developed and taken into the first clinical trials by the UK-based biotech, KuDOS Pharmaceuticals, which was acquired by AstraZeneca in 2006. Subsequently, in 2017, the PARPi niraparib (Zejula®), originally developed by Tesaro and later acquired by GlaxoSmithKline, was approved as MT for recurrent ovarian cancer in complete/partial response (CR/PR) to Pt irrespective of *BRCA1/2*m status, based on data from the NOVA trial (NCT01847274). This trial found significantly longer mPFS in patients with PtS recurrent ovarian cancer treated with niraparib compared to those receiving placebo, regardless of the g*BRCA1/2* mutation or HRD status.[70] Following results from the Phase II QUADRA trial (NCT02354586[71]), niraparib also won approval in 2019 by the FDA as monotherapy for HRD relapsed ovarian cancer treated with three or more prior CTx regimens. Consequently, the therapeutic scope of PARPi expanded beyond *BRCA1/2*m tumors, requiring the improvement of the available tests for determining HRD in order to correctly identify eligible patients.

Thanks to the significant PFS benefit shown in the OlympiAD trial (NCT02000622[72]), the indications of olaparib were further expanded in 2018 (FDA) and 2019 (EMA) for g*BRCA1/2*m HER2- metastatic breast cancer previously treated with an anthracycline and a taxane (in the (neo)adjuvant or metastatic setting). Talazoparib (Talzenna®), another PARPi originally discovered by BioMarin Pharmaceutical, followed by acquisition by Medivation and subsequently acquired in 2016 by Pfizer, also received approval by the FDA (2018) and EMA (2019) for locally advanced or metastatic g*BRCA1/2*m HER2- breast cancer. This was based on the Phase III EMBRACA study (NCT01945775), where talazoparib as a single agent provided significant benefit in terms of PFS compared to standard CTx.[73] Similar to what happened with olaparib in the OlympiAD trial for breast cancer,[74] final overall survival (OS) data from the EMBRACA study did not show a significant improvement with talazoparib compared with CTx, although authors considered this lack of OS significance was likely confounded by high rates of post-progression crossover.[75]

Furthermore, the PARPi developed by Clovis Oncology and afterwards sold to Pharmaand GmbH, rucaparib (Rubraca®), received accelerated approval by the FDA in 2016 and conditional approval by the EMA in 2018 for g/s*BRCA1/2*m ovarian cancer progressed after 2 or more prior CTx lines, based on the better PFS data observed in patients with *BRCA1/2* mutation in the ARIEL 2 trial (NCT01891344[76]). In addition, following outcomes of the Phase III ARIEL3 trial (NCT01968213), rucaparib was also approved in 2018 by the FDA and the EMA for MT of recurrent ovarian cancer in CR/PR to Pt. This trial documented a statistically significant improvement in mPFS for patients with recurrent PtS ovarian cancer receiving MT with rucaparib vs placebo.[77] This was confirmed in subsequent exploratory analyzes (median follow-up of more than 2 years) showing that MT with rucaparib provided a meaningful delay in starting further therapy, without negatively impacting the efficacy of subsequent treatments administered after the first progression event.[78] After reviewing the final data provided by the ARIEL4 study (NCT02855944[79]) in 2024, both the EMA and the FDA considered that rucaparib was not as effective as CTx at prolonging patients' lives for g/s*BRCA1/2*m ovarian cancer that progressed after 2 or more prior CTx lines. Consequently, the agencies revoked the initial accelerated/conditional approvals granted to rucaparib, while the MT indication remains unaffected.

As soon as the benefits of PARPi in recurrent disease became clear, especially by increasing PFS,[69,80–82] clinical research focus shifted toward preventing recurrence through first-line MT. The SOLO1 study, which tested olaparib as MT for *BRCA1/2*m advanced ovarian cancer, detected an improvement in mPFS of around 42 months compared to the placebo group (NCT01844986[83]). Based on these findings, both the FDA (2018) and the EMA (2019) approved olaparib for MT of *BRCA1/2*m ovarian cancer in CR/PR to first-line Pt. However, after the approval, results from the final analysis of the SOLO1 study were published and reported a clinically meaningful, albeit not statistically significant, improvement in OS.[84] With the goal to broaden these benefits, in the following step researchers investigated in three clinical trials whether MT of PARPi alone or in combination could be beneficial as first-line treatment of newly diagnosed ovarian cancer irrespective of *BRCA1/2* status. PAOLA1 (NCT02477644), which was the first of these trials, showed that olaparib combined with the antiangiogenic agent bevacizumab provided continued PFS benefit for ovarian cancer beyond first progression, especially in patients with HRD-positive tumors.[85] This was translated to a clinically meaningful OS in patients with HRD-positive ovarian cancer[86] and led to the approval in 2020 of the combination of olaparib and bevacizumab as MT treatment for advanced HRD ovarian cancer in CR/PR to Pt by both the EMA and the FDA. Moreover, the PRIMA trial (NCT02655016) studied niraparib in newly diagnosed patients with advanced ovarian cancer in response to Pt. This study reported that those receiving niraparib exhibited significantly longer PFS, regardless of the HRR status,[87] although no differences in OS were found between the niraparib and placebo arm in the final analysis.[88] However, niraparib was approved by the EMA and FDA in 2020 for MT of advanced ovarian cancer in CR/PR to first-line Pt, regardless of the biomarker status. Finally, the VELIA trial (NCT02470585) tested veliparib plus CTx (carboplatin and paclitaxel) followed by MT with veliparib in ovarian cancer patients. This approach led to significantly longer PFS than carboplatin and paclitaxel induction therapy alone,[89] although benefit in OS was also not detected in the final analysis.[90] This trial also found that veliparib had a lower incidence of toxic effects, such as anemia and thrombocytopenia, than the other PARPi,[89] allowing a better safety profile when combined with CTx, which itself has a myelosuppressive effect. However, as described previously, veliparib displays markedly less trapping ability than the other PARPi, which may cause lower efficacy, especially in monotherapy[91] and has not been approved to date. Other side effects of PARPi reported in clinical trials include fatigue, nausea and hypertension.[89,92,93] In addition, the 5-year follow-up SOLO2 trial (NCT01874353), which tested oral MT with olaparib in recurrent disease, found a high risk for developing myelodysplastic syndrome or acute myeloid leukemia (AML). This association between olaparib and blood cancers is being further explored in an additional long-term follow-up of the patients.[94]

All these studies (SOLO1, PAOLA1, PRIMA and VELIA) showed a significant improvement in PFS of MT with a PARPi. However, all patients did not manifest the same magnitude of response: people with *BRCA1/2*m tumors benefited the most, followed by those with cancers with HRD not related to *BRCA1/2* mutations, and finally those that did not harbor any kind of HRD. Only the PRIMA trial with niraparib demonstrated significant benefit in the last group, although it was just beyond 3 months.[87] Moreover, the incongruency found in several trials exploring MT with PARPi (SOLO1, PRIMA and VELIA) between the PFS and the final OS results should be interpreted with caution and may be due to different factors, such as the long follow-up required, the subsequent lines of anticancer therapies (including PARPi) that receive these patients in the broad post-progression survival period and also the impact of prior treatments that can lead to PARPi and/or Pt resistance,[95] amongst others. Finally, the results from the OReO/ENGOT-Ov-38 Phase IIIB trial (NCT03106987) evaluating olaparib as MT in patients with relapsed ovarian carcinoma previously treated with a PARPi and at least two lines of Pt have recently been published. This trial assessed patients who relapsed after ending the initial treatment with a PARPi, but not those whose cancer relapsed during the treatment because of PARPi resistance. MT with olaparib provided these patients a modest significant improvement in mPFS over placebo of around 2 months regardless of *BRCA1/2*m status, with a proportion of them remaining progression-free at 1 year. The accelerated disease progression in a subset of patients from this trial suggests that they may have acquired PARPi resistance during prior MT with PARPi.[96] Therefore, this study was the first to demonstrate that maintenance olaparib rechallenge in heavily pretreated ovarian cancer patients may improve, albeit modestly, PFS, regardless of *BRCA1/2*m status.

Another great advance in the adjuvant setting was the approval in 2022 by both the EMA and the FDA of olaparib as adjuvant treatment of patients with deleterious or suspected deleterious g*BRCA1/2*m HER2- high-risk early breast cancer previously treated with neoadjuvant or adjuvant CTx. This was based on the international OlympiA Phase III trial (NCT02032823) studying 1836 patients with high-risk g*BRCA1/2*m HER2- early breast cancer receiving 1 year of adjuvant olaparib after completion of definitive local treatment and neoadjuvant or adjuvant CTx. Results showed that patients treated with olaparib exhibited significantly longer distant disease–free survival than those with placebo.[97] In 2024, the first PARPi/immunotherapy combination was approved in the EU: olaparib associated with durvalumab for MT of primary advanced or recurrent MMR-proficient endometrial cancer not progressed on first-line treatment with durvalumab plus carboplatin and paclitaxel. This approval was based on the results from the Phase III DUO-E/GOG-3041/ENGOT-EN10 trial (NCT04269200). In this study, the combination of carboplatin/paclitaxel plus durvalumab followed by durvalumab MT with olaparib demonstrated a significant PFS benefit in advanced or recurrent endometrial cancer patients.[98]

Apart from the different approvals for ovarian, breast and endometrial cancers (Fig. 6), the therapeutic landscape with PARPi has continued to expand into new indications and combinations. In the realm of metastatic castration-resistant prostate cancer (mCRPC), olaparib was approved in 2020 by the FDA for g/sHRD mCRPC and by the EMA for g/s*BRCA1/2*m mCRPC progressed to prior treatment with enzalutamide or abiraterone. This was based

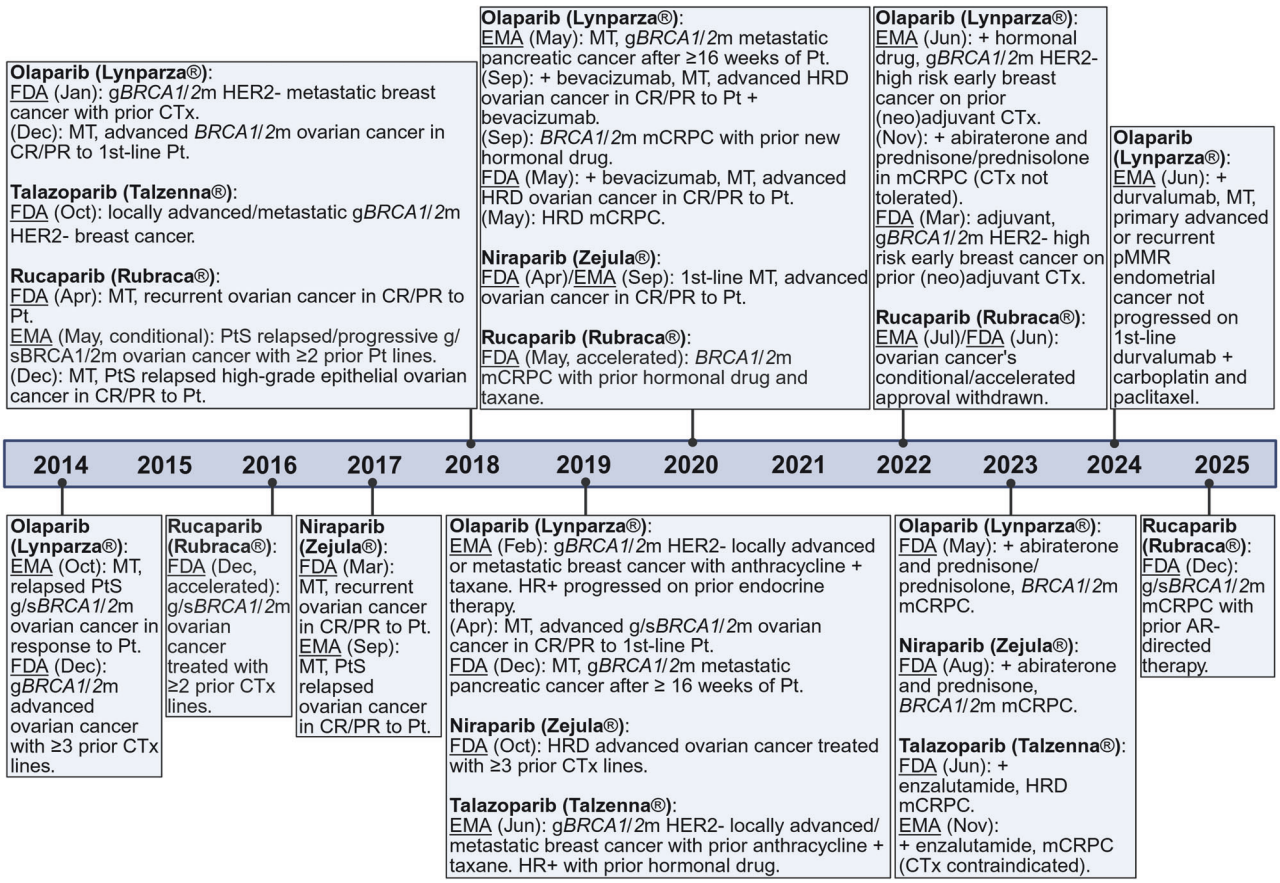


Fig. 6 Timeline of PARPi approvals by the EMA and FDA. Olaparib (Lynparza®) was the first PARPi to receive regular approval by both agencies in 2014 for ovarian cancer, followed by niraparib (Zejula®) in 2017. In 2018, olaparib's indications expanded to breast cancer (FDA), while talazoparib (Talzenna®) and rucaparib (Rubraca®) received approvals for breast and ovarian cancer, respectively. Subsequent years saw a rapid expansion of indications: olaparib for pancreatic cancer (FDA, 2019; EMA, 2020) and the first approvals for metastatic castration-resistant prostate cancer (mCRPC) for both olaparib (FDA and EMA) and rucaparib (FDA) in 2020. Notably, the timeline reflects a recent shift toward combination therapies, including olaparib with bevacizumab for ovarian cancer (FDA and EMA, 2020) and multiple PARPi combinations with androgen receptor-signaling inhibitors (abiraterone, enzalutamide) for mCRPC (2022–2023). Most recently, in 2024, olaparib was approved in combination with durvalumab for endometrial cancer (EMA), highlighting the ongoing integration of PARPi into immuno-oncology regimens. Figure created with BioRender

on the PROfound clinical trial (NCT02987543) that studied men with mCRPC harboring at least one alteration in *BRCA1/2* or *ATM* and whose disease had progressed during previous treatment with a next-generation hormonal agent. In this study, patients initially assigned to the olaparib group displayed significantly longer OS than those receiving enzalutamide or abiraterone plus prednisone as control therapy, despite substantial crossover from control therapy to olaparib.[99] Also in 2020, the FDA granted accelerated approval to rucaparib for g/s*BRCA1/2*m mCRPC previously treated with androgen receptor (AR)-directed therapy and a taxane-based CTx, thanks to the antitumor activity reported in the Phase II TRITON2 trial (NCT02952534[100]). In 2025, thanks to the efficacy data from the Phase III TRITON3 trial (NCT02975934) showing significantly longer duration of imaging-based PFS with rucaparib than with control medication in *BRCA1/2*m patients,[101] rucaparib received regular approval for g/s*BRCA1/2*m mCRPC previously treated with AR-directed therapy. Furthermore, the combinations olaparib/niraparib plus abiraterone and talazoparib plus enzalutamide have established new standards for treating mCRPC. This started in 2022 when the EMA extended the indication of olaparib to its combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom CTx is not clinically indicated, based on the results of the Phase III PROpel study (NCT03732820). This trial evaluated the efficacy and safety of olaparib plus abiraterone in the first-line mCRPC setting and found significantly prolonged imaging-based PFS compared with abiraterone and placebo irrespective of HRR mutation status.[102] This was followed by approval in 2023 of this same combination by the FDA for patients with deleterious or suspected deleterious *BRCA1/2*m mCRPC, thanks to an exploratory subgroup analysis suggesting that the benefit was higher in patients with *BRCA1/2* mutations.[103] Also in 2023, the FDA approved the fixed-dose combination of niraparib and abiraterone acetate, with prednisone, for patients with deleterious or suspected deleterious *BRCA1/2*m mCRPC, as determined by an FDA-approved companion diagnostic, based on results from the MAGNITUDE trial (NCT03748641). This study showed a significant improvement in radiographic PFS (rPFS)[104] and a trend toward longer OS with this combination in the HRD population and the *BRCA1/2* subgroup.[105] In the case of talazoparib, both the EMA and FDA extended its indications in the same year to the combination with enzalutamide for HRD mCRPC based on results from the TALAPRO-2 (NCT03395197) trial. This study detected a clinically meaningful and statistically significant improvement in rPFS with talazoparib plus enzalutamide versus standard-of-care (SOC) in men with HRD mCRPC.[106] This benefit has been further supported by the clinically meaningful improvement in OS observed in the final analysis results.[107] Finally, a new indication for olaparib was added as MT for metastatic g*BRCA1/2*m pancreatic cancer after receiving more than 16 weeks of Pt, by both the FDA (2019) and EMA (2020). This was based on the longer PFS with olaparib than with placebo

Table 1. Recent Phase I/II, II, III and/or IV clinical trials for approved PARP inhibitors: monotherapy and combination therapy

Target	Agent	Intervention	Cancer type	Phase	Clinicaltrials.gov identifier
PARP	Olaparib	Olaparib	*BRCA1/2*m CRPC	IV	NCT05457257
		Optimal dosing of oral anticancer drugs (e.g., Olaparib)	Renal cell, ovarian, thyroid, breast and endometrial carcinoma	IV	NCT05949424
		Olaparib	Breast and ovarian cancer	IV	NCT04330040
		Olaparib (adjuvant)	HER2- *BRCA1/2*m breast cancer	III	NCT02032823
		Olaparib	HRD-mCRPC	III	NCT02987543
		Olaparib + Abiraterone	mCRPC	III	NCT03732820
		Olaparib (MT)	Ovarian cancer	III	NCT01844986 NCT01874353 NCT03106987
		Olaparib + Bevacizumab	Ovarian, fallopian tube or peritoneal cancer	III	NCT02477644
		Olaparib + Durvalumab	Proficient-MMR endometrial cancer	III	NCT04269200
		Olaparib + Alpelisib	PtR ovarian cancer	III	NCT04729387
	Niraparib	Niraparib (MT)	Ovarian cancer	IV	NCT05187208 NCT06412120 NCT03752216 NCT04861181
		Niraparib (MT)	PtS ovarian cancer	III	NCT02655016 NCT01847274 NCT03705156 NCT03709316
		Niraparib vs Placebo	HER2- *BRCA1/2*m breast cancer or TNBC	III	NCT04915755
		RT vs Brachytherapy (vaginal) vs Observation vs Niraparib	Serous or *TP53*-mutated endometrial cancer	III	NCT04159155
		Niraparib or Temozolomide	Glioblastoma	III	NCT06388733
		Abiraterone + Prednisone ± Niraparib	HRD-CRPC	III	NCT04497844 NCT03748641
		Niraparib + CTx ± Bevacizumab	Ovarian cancer	III	NCT05009082
		Niraparib ± Pembrolizumab (MT)	NSCLC	III	NCT04475939
		Niraparib ± Dostarlimab vs CTx	Endometrial or ovarian carcinosarcoma	II/III	NCT03651206
		Niraparib + Dostarlimab vs CTx	Ovarian, fallopian tube or peritoneal cancer	III	NCT04679064
		SOC ± Niraparib ± Dostarlimab	Ovarian cancer	III	NCT03602859
		Carboplatin-Paclitaxel + Dostarlimab/ Placebo ± Niraparib	Endometrial cancer	III	NCT03981796
		CTx + Niraparib ± Atezolizumab	Ovarian cancer	III	NCT03598270
		Molecular targeted therapy (e.g., Niraparib) vs CTx	Biliary cancer	III	NCT05615818
		Niraparib + Heated Intraperitoneal CTx	Ovarian, fallopian tube or peritoneal cancer	III	NCT05659381
		SOC vs SOC+3 treatments (SBRT, radioactive material or Niraparib)	Castration-sensitive prostate cancer	III	NCT06320067
		Biomarker-driven therapy (e.g., Niraparib + Abiraterone + Prednisone) vs SOC	Metastatic prostate cancer	III	NCT03903835
		Atezolizumab + other (e.g., Niraparib)	Rollover study	III	NCT03768063
	Rucaparib	Rucaparib (MT)	Rollover study	III	NCT04676334
		Rucaparib (MT)	PtS ovarian, fallopian tube or peritoneal cancer	III	NCT01968213
		Rucaparib (MT) post-Bevacizumab	Ovarian, fallopian tube or peritoneal cancer and clear cell carcinoma	III	NCT04227522
		Rucaparib vs CTx	*BRCA1/2*m ovarian, fallopian tube or peritoneal cancer	III	NCT02855944
		Rucaparib vs Abiraterone or Enzalutamide or Docetaxel	HRD-mCRPC	III	NCT02975934
		Rucaparib + Nivolumab/Placebo (MT)	Ovarian cancer	III	NCT03522246
		Rucaparib/Placebo + Enzalutamide	mCRPC	III	NCT04455750
		Atezolizumab + other (e.g., Rucaparib)	Rollover study	III	NCT03768063
	Talazoparib	Talazoparib vs Capecitabine/Eribulin/ Gemcitabine/ Vinorelbine	*BRCA1/2*m breast cancer	III	NCT01945775
		Talazoparib + Enzalutamide vs Enzalutamide	mCRPC	III	NCT03395197
		Talazoparib + Enzalutamide vs Placebo		III	NCT04821622

Table 1. continued

Target	Agent	Intervention	Cancer type	Phase	Clinicaltrials.gov identifier
			DDR-deficient castration-sensitive prostate cancer		
		Avelumab vs Avelumab + other (e.g., Talazoparib)	Solid tumors	III	NCT05059522
	Fuzuloparib	Fuzuloparib (MT)	Ovarian cancer	III	NCT03863860
		Fuzuloparib + Abiraterone + Prednisone	CRPC	III	NCT04691804
		Fuzuloparib/Capecitabine + Camrelizumab	TNBC	III	NCT06533384
		Fuzuloparib ± Apatinib (MT)	Ovarian cancer	III	NCT06188455 NCT04229615 NCT06539091
		Fuzuloparib ± Apatinib vs CTx	*BRCA1/2*m HER2- breast cancer	III	NCT04296370
		Fuzuloparib + Apatinib vs CTx	HRD/HER2- breast cancer	III	NCT06255392
		Fuzuloparib + Dalpiciclib + Fulvestrant	HR+/HER2- breast cancer	III	NCT06612814
		Fuzuloparib + Endocrine therapy	HR+/HER2- SNF3- early breast cancer	III	NCT05891093
	Pamiparib	Pamiparib (MT)	Ovarian cancer	III	NCT03519230
		Pamiparib + Tislelizumab or Temozolomide	Advanced malignancies	III	NCT04164199
		Pamiparib	SCLC	II	NCT05483543
		Pamiparib	Ovarian cancer	II	NCT05489926
		Pamiparib	HRD-mCRPC	II	NCT05327621
		Pamiparib	HER2- breast cancer	II	NCT03575065
		Pamiparib	Gastric cancer	II	NCT03427814
		Pamiparib	Rare tumors	II	NCT06692491
		Pamiparib + Surufatinib	Ovarian cancer	II	NCT05652283
		Pamiparib + Tamoxifen	Ovarian cancer	II	NCT05669768
		Pamiparib + Tislelizumab	HRD-advanced malignancies	II	NCT04985721
		Pamiparib + Abiraterone (neoadjuvant)	Prostate cancer	II	NCT05376722
		Rezvilutamide + Goserelin + Pamiparib	Prostate cancer	II	NCT06387056
		Pamiparib + Bevacizumab	Ovarian cancer	II	NCT05044871
		PARPi (e.g., Pamiparib) + Androgen deprivation therapy ± Abiraterone	Prostate cancer	II	NCT05406999
		Pamiparib	Ovarian cancer and TNBC	I/II	NCT03333915
		Pamiparib + Surufatinib	Ovarian cancer	I/II	NCT05494580
		Pamiparib + Temozolomide	*IDH1/ 2*-mutated gliomas	I/II	NCT03914742

Data extracted from clinicaltrials.gov up until November 2025

reported in the Phase III POLO trial (NCT02184195[108]), although final OS results did not reach statistical significance.[109]

The role of PARPi is also expanding into earlier treatment settings. Historically, PARPi were reserved for recurrent disease, where acquired Pt resistance, frequently associated with secondary mutations restoring HRR function, often confers cross-resistance to PARP inhibition.[110,111] To circumvent these resistance mechanisms and maximize therapeutic impact, recent clinical trials have explored PARPi in the neoadjuvant setting. For instance, a Phase II trial (NCT02624973) testing olaparib monotherapy in primary treatment-naïve triple-negative breast cancer (TNBC) found high response rates in tumors with HRD, particularly in g*BRCA1/2*m tumors, but also in those with g*PALB2* or somatic *ATRX*, *BRCA1*, *EMSY*, *MEN1*, *PTEN* and *SETD2* mutations.[112] The high pathological CR rates from olaparib, alone or in combination with durvalumab in the Phase II OlympiaN trial (NCT05498155) provided additional encouraging evidence supporting further investigation of olaparib in the neoadjuvant setting for early-stage *BRCA1/2*m breast cancer.[113] These same outcomes were not observed in the PARTNER trial (NCT03150576) exploring neoadjuvant olaparib added to CTx in patients with TNBC cancer without g*BRCA1/2*m. Although these results need further confirmation in larger cohorts, they indicate that olaparib monotherapy could be useful to debulk big HRD early-stage breast cancer before surgery or treatment with CTx.[114]

PARPi are continuously included in novel clinical trials alone or associated with different chemo- or radiotherapeutic regimens, immunotherapy or targeted therapy (Table 1). PARP inhibition increases the collapse of replication forks after ionizing radiation (IR), generating persistent DNA DSBs that should be repaired by HRR.[115] Preclinical studies suggested that PARPi can act as radiosensitizers to improve the therapeutic outcomes of RT, especially in *BRCA1/2*m tumors.[28,31,116] Several clinical trials have explored this combination together with other agents for solid tumors (e.g., NCT04037254 and NCT01908478) with inconsistent results.[117–119] PARPi are also being clinically explored in combination with several ICIs, such as durvalumab (NCT04269200), camrelizumab (NCT06533384) and tislelizumab (NCT04164199), with positive results.[35,98] This is due to recent studies that have reported that PARPi mitigate resistance and enhance the efficacy of ICIs by increasing immune priming and TME modification.[120] In fact, PARP inhibition in *BRCA1/2*-defficient TNBC cells reduced DDR and induced neoantigens and cytosolic DNA, activating the IFN pathway via STING, resulting in the tumors' sensitization to ICIs.[121] Moreover, as PARPi cause the upregulation of PD-L1 expression, the combination of PARPi and anti-PD-L1 antibodies sensitized

cancer cells to PD-L1 blockade.[122] Based on preclinical findings suggesting the potentiation of PARPi effects by VEGFRi,[123] the synergy between these drugs is also being clinically analyzed in ovarian cancer with promising results (e.g., NCT02477644). Regarding CDK4/6i, the association of the CDK4/6i, dalpiciclib, with the estrogen receptor (ER) antagonist fulvestrant demonstrated significant clinical benefit in HR+ and HER2- advanced breast cancer (NCT03927456[124]). This combination is being studied in a Phase III trial associated with fuzuloparib (NCT06612814). Talazoparib is also being evaluated in a Phase I trial in association with the CDK4/6i palbociclib (NCT04693468). Preclinical data showed that abemaciclib and talazoparib synergistically suppressed the growth of TNBC cells and overcame talazoparib resistance through cell cycle arrest and apoptosis.[125] This synergy was also demonstrated in non-small cell lung cancer (NSCLC) xenografts.[126] Besides, the combination of talazoparib and palbociclib also reduced tumor growth in an in vitro bladder cancer model.[127] Results from a bioinformatics analysis in osteosarcoma also revealed potential sensitivity to combination therapy with CDK4/6i and PARPi.[128] PARPi are also included in clinical trials associated with: inhibitors of the PI3K/AKT/mTOR pathway, such as the α-selective PI3K inhibitor alpelisib (NCT04729387) or the pan-PI3K inhibitor buparlisib (NCT01623349), that are both being analyzed combined with olaparib; inhibitors of RAS/RAF/MEK, such as the MEK inhibitor selumetinib combined with olaparib (NCT03801369); the BET inhibitor ZEN003694 associated with talazoparib (NCT05071937 and NCT05327010); c-MET inhibitors, such as crizotinib, tested in combination with talazoparib (NCT04693468), and cabozantinib being combined with pamiparib (NCT05038839) and niraparib (NCT03425201); and drugs targeting EGFR/HER2, such as the dual EGFR/HER2 inhibitor, lapatinib, that was studied with the PARPi veliparib (not yet approved) in TNBC (NCT02158507) and the pan-EGFR inhibitor neratinib (NCT04502602), the EGFR inhibitor osimertinib (NCT03891615), the HER2-directed agent trastuzumab (NCT03368729 and NCT04508803 also adding the anti-PD-1 HX008) and the HER2-targeting antibody–drug conjugate comprised of trastuzumab bound to a linker drug containing duocarmycin, SYD985 (NCT04235101), that are all being clinically studied associated with niraparib.

This global momentum for PARPi is further evidenced by the approval of new PARPi such as fuzuloparib and pamiparib in China, which are currently being tested in diverse combinations with VEGFR inhibitors and PD-1 blockers to tackle Pt-resistant cancers. Fuzuloparib (AiRuiYi®), formerly fluzoparib, is an oral small molecule being developed by Jiangsu Hengrui Pharmaceuticals that received first approval in 2020 by the China National Medical Products Administration (NMPA) for the treatment of g*BRCA1/2*m recurrent ovarian cancer in patients who have received two or more lines of chemotherapy. Its indications have since expanded to include MT for PtS advanced ovarian cancer regardless of *BRCA1/2*m status (2022), and treatment for g*BRCA1/2*m, HER2- metastatic breast cancer (2025). The efficacy of fuzuloparib as MT for PtS recurrent ovarian cancer was confirmed in the Phase III FZOCUS-2 study (NCT03863860). In this trial, MT with fuzuloparib demonstrated a statistically significant and clinically meaningful improvement in PFS in these patients regardless of g*BRCA1/2* status, with a manageable safety profile.[129] Preclinical data suggested that fuzuloparib in combination with the VEGFR inhibitor (VEGFRi) apatinib or with apatinib and paclitaxel could exhibit significant efficacy without additive toxicity.[130] Based on these findings, several clinical trials exploring this combination in the maintenance setting are being conducted (e.g., NCT04229615 and NCT06539091). However, recent data from the Phase III FZOCUS-1 trial (NCT04229615) indicated that the addition of apatinib to fuzuloparib did not show an improvement in PFS compared to fuzuloparib alone, as first-line MT for newly diagnosed advanced ovarian cancer.[131] In contrast, a Phase II study (NCT04517357) reported a trend toward improved overall response rate (ORR) with the combination in patients with Pt-resistant (PtR) ovarian cancer or those naïve to VEGFRi,[132] suggesting that the benefit of the combination may be specific to later-line or resistant settings. Several other Phase II or III trials of fuzuloparib in combination with adjuvant endocrine therapy (NCT05891093), PD-1 inhibitors (NCT06533384) or abiraterone and prednisone (NCT04691804), amongst others, or as MT (NCT06188455) are ongoing.

In 2021, the China NMPA granted conditional approval to the PARPi pamiparib (Partruvix®) from Beigene for the treatment of g*BRCA1/2* mutation-associated recurrent advanced ovarian cancer previously treated with two or more lines of CTx. This approval was supported by the pivotal Phase II portion of a Phase I/II trial in subjects with g*BRCA1/2*m epithelial ovarian cancer (NCT03333915[133]). Currently, Phase III clinical trials are evaluating pamiparib in combination with temozolomide or the PD-1 inhibitor tislelizumab for advanced malignancies (NCT04164199), alongside its use as MT for PtS recurrent ovarian cancer (NCT03519230). Beyond ovarian cancer, a Phase II study demonstrated promising efficacy and a tolerable safety profile for pamiparib in patients with advanced and metastatic *BRCA1/2*m HER2- breast cancer (NCT03575065[134]). Conversely, the Phase II PARALLEL-303 study (NCT03427814) failed to show a significant benefit from MT with pamiparib in patients with inoperable gastric cancer who responded to Pt.[135] More recently, preliminary results from a prospective Phase II trial (Chinese Clinical Trial Register information number: CTR2200059119) indicated that the combination of pamiparib with neoadjuvant CTx and bevacizumab showed promising efficacy and acceptable toxicity for newly diagnosed advanced ovarian cancer.[136] Beyond its primary indications, pamiparib is distinguished by its unique pharmacokinetic profile. Unlike several other PARPi, it is not a substrate for the P-glycoprotein (P-gp) efflux pump, suggesting a potential to overcome specific mechanisms of acquired resistance. Additionally, its high blood-brain barrier penetration has expanded its clinical investigation into CNS-involved malignancies.[137] The Phase IB/II POST-PARPi trial (NCT05494580) demonstrated that pamiparib in combination with the multi-kinase inhibitor surufatinib, provides a potential therapeutic avenue for patients with heavily pre-treated PtR ovarian cancer previously treated with PARPi.[138]

BRCAness phenotype

When seeking additional SL uses besides *BRCA1/2* for these PARPi, the concept "BRCAness" showed up. "BRCAness" is a term used to define a subset of tumors that lack g*BRCA1/2* mutations but share other molecular features with *BRCA1/2*m tumors, such as HRD, effectively acting as phenocopies of *BRCA1/2*m tumors.[139] Increasing preclinical and clinical evidence suggests that defects in specific tumor suppressor genes involved in HRR and/or associated DDR pathways, especially *PALB2*, but also *ATM*, *ATR* or *CHK2*, amongst others, also influence the sensitivity to PARPi.[46,140] Genetic screens have shown that other defective genes in cancer, such as *CDK12*, *RAD51B* and *RAD51C*, might also cause a "BRCAness" phenotype, although solid clinical data have not yet been provided.[141–143] Apart from alterations in key DDR factors, alterations in chromatin regulators, such as *ARID1A*[144] and *BAP1*,[145,146] have also been associated with in vitro increased sensitivity to olaparib.

Clinical data indicate that the efficacy of PARPi in tumors exhibiting BRCAness or HRD varies according to the specific gene alteration and the tissue of origin. As for advanced pancreatic cancer, two parallel nonrandomized Phase II clinical trials of olaparib monotherapy in patients with BRCAness phenotype and lack of the g*BRCA1/2* variant, found significantly longer PFS and OS in those with PtS tumors harboring alterations in the following genes: *ATM* ($n = 14$, 50% germline and 50% somatic), g*PALB2*

Table 2. Clinical trials for novel PARP and PARG inhibitors: monotherapy and combination therapy

Target	Agent	Intervention	Cancer type	Phase	Clinicaltrials.gov identifier
PARP	Veliparib	Veliparib + Carboplatin	TNBC	III	NCT02032277
		Veliparib + Carboplatin + Paclitaxel vs CTx	NSCLC	III	NCT02264990
		Veliparib + Carboplatin + Paclitaxel	HER2- *BRCA1/2*m breast cancer	III	NCT02163694
		Veliparib + Carboplatin + Paclitaxel	Ovarian cancer	III	NCT02470585
		Veliparib + Carboplatin + Paclitaxel	NSCLC	III	NCT02106546
		Veliparib + Temozolomide	Glioblastoma	II/III	NCT02152982
		Veliparib + Temozolomide	Breast cancer	II	NCT01009788
		Veliparib + Temozolomide	CRC	II	NCT01051596
		Veliparib + Temozolomide	Solid tumors	II	NCT01193140
		Veliparib + Temozolomide	Melanoma	II	NCT00804908
		Veliparib ± Temozolomide	SCLC	II	NCT01638546
		Veliparib + RT + Temozolomide	Glioma without H3 K27M or BRAFV600 mutations	II	NCT03581292
		Veliparib + Temozolomide/Carboplatin + Paclitaxel	*BRCA1/2*m breast cancer	II	NCT01506609
		Veliparib + Temozolomide vs Pegylated Liposomal Doxorubicin	Ovarian cancer	II	NCT01113957
		Veliparib + Gemcitabine + Carboplatin	Testicular germ cell cancer	II	NCT02860819
		Veliparib + Cyclophosphamide	*BRCA1/2*m breast, ovarian, primary peritoneal or fallopian tube cancer, TNBC or low-grade NHL	II	NCT01306032
		Veliparib	Ovarian, fallopian tube or primary peritoneal cancer	II	NCT01540565
		Veliparib ± Carboplatin ± Paclitaxel	NSCLC	II	NCT01560104
		Topotecan + Carboplatin ± Veliparib	Advanced myeloproliferative disorders, AML or CML	II	NCT03289910
		Veliparib ± whole brain RT	NSCLC with brain metastases	II	NCT01657799
		Veliparib ± Cisplatin	TNBC, *BRCA1/2*m breast cancer ± brain metastases	II	NCT02595905
		Veliparib ± FOLFIRI ± Bevacizumab	CRC	II	NCT02305758
		Veliparib + Temozolomide	Solid tumors	II	NCT01827384
		Abiraterone + Prednisone ± Veliparib	CRPC	II	NCT01576172
		Veliparib + Topotecan + Filgrastim	Cervical cancer	II	NCT01266447
		Veliparib ± Gemcitabine and Cisplatin	Pancreatic cancer	II	NCT01585805
		Veliparib ± FOLFIRI	Pancreatic cancer	II	NCT02890355
		Veliparib ± Carboplatin	Breast cancer	II	NCT01149083
		Veliparib + FOLFOX + RT ± Pembrolizumab	Rectal cancer	II	NCT02921256
		Veliparib	Breast cancer	II	NCT01042379
	Senaparib	Senaparib (MT)	Ovarian cancer	III	NCT04169997
		Senaparib	*BRCA1/2*m recurrent PtS ovarian cancer	II	NCT04089189
		Senaparib	HRR-mutated CRPC	II	NCT04822961
		Senaparib + Temozolomide	Advanced solid tumors and SCLC	I/II	NCT04434482
	Venadaparib	Venadaparib + XELOX/Irinotecan	Gastric cancer	I/II	NCT04725994
		Venadaparib	HRD solid tumors	I/II	NCT04174716
	Stenoparib	Stenoparib	Ovarian cancer	II	NCT03878849
		Stenoparib	Breast cancer	II	NCT03562832
		Stenoparib + Temozolomide/ Carboplatin + Paclitaxel	Solid tumors and B-cell malignancies	I/II	NCT01618136
	Saruparib	Saruparib ± Durvalumab	SCLC	II	NCT06769126
		Saruparib + AZD5335	Solid tumors	I/II	NCT05797168
		Saruparib + AZD8205	Solid tumors	I/II	NCT05123482
		Saruparib + Ceralasertib	Solid tumors	I/II	NCT02264678
	AZD9574	AZD9574 ± Temozolomide/Deruxtecan	Solid tumors	I/II	NCT05417594
	SC10914	SC10914	Breast cancer	II	NCT04556292
		SC10914	Ovarian cancer	II	NCT04556539
		SC10914	*BRCA1/2*m CRPC	I/II	NCT04486937

Table 2. continued

Target	Agent	Intervention	Cancer type	Phase	Clinicaltrials.gov identifier
		SC10914	Solid tumors	I	NCT02940132
	Nesuparib	Nesuparib	Ovarian cancer	II	NCT05475184
		Nesuparib + FOLFIRINOX/Gemcitabine + Paclitaxel	Pancreatic ductal adenocarcinoma	I	NCT05257993
		Nesuparib	Solid tumors	I	NCT04335604
	TSL-1502	TSL-1502 vs CTx	*BRCA1/2*m breast cancer	II	NCT05420779
	AMXI-5001	AMXI-5001	Solid tumors	I/II	NCT04503265
	NMS-03305293	NMS-03305293 + Temozolomide	Glioblastoma	I/II	NCT04910022
	Simmiparib	Simmiparib	Solid tumors	I	NCT02993913
	RP12146	RP12146	Solid tumors	I	NCT05002868
	HWH340	HWH340	Solid tumors	I	NCT03415659
	TQB3823	TQB3823	Solid tumors	I	NCT05021367
	ABT-767	ABT-767	*BRCA1/2*m ovarian, fallopian tube or primary peritoneal cancer	I	NCT01339650
PARG	IDE161	IDE161	Advanced solid tumors	I	NCT05787587
	ETX-19477	ETX-19477 ± Pembrolizumab	Advanced solid tumors	I	NCT06395519

Data extracted from clinicaltrials.gov up until November 2025

($n = 2$), *ARID1A* ($n = 3$), s*BRCA* ($n = 1$), *PTEN* ($n = 1$), *RAD51* ($n = 1$), *CCNE* ($n = 1$), and *FANCB* ($n = 2$).[147] Similarly, in a Phase II trial (NCT02401347), single-agent talazoparib also demonstrated treatment-associated tumor regression in all HER2- advanced breast cancer patients with g*PALB2* mutations. Stable disease was detected in one patient with a g*CHK2* mutation (testicular cancer), in one patient with a g*ATM* mutation (colon cancer) and in three breast cancer patients with g*PALB2*, s*ATR* or s*PTEN* mutations.[148] In contrast, the Phase II TBCRC-048 (NCT02032823) trial that studied the efficacy of olaparib for HRD metastatic breast cancer found confirmed responses and improved survival only in patients with mutations in g*PALB2* (ORR, 82%; mPFS, 13.3 months) and s*BRCA1/2* (ORR, 50%; mPFS, 6.3 months). No responses were observed in patients with *ATM* or *CHK2* mutations alone.[149] Talazoparib also failed to show a sufficient level of efficacy in patients with advanced HRD (defined by deleterious mutations in genes such as *ATM*, *ATR*, *BRCA1/2*, *BARD1*, *PALB2*, amongst others) squamous cell lung cancer in another trial (NCT02154490).[150]

Concerning mCRPC, several clinical trials have shed more light to these biomarker-driven responses, especially in the case of *ATM*. The Phase II TOPARP trial (NCT01682772) evaluated the antitumor activity of olaparib in 2 serial parts, TOPARP-A and TOPARP-B, with the goal of identifying predictive biomarkers for response in this cancer type. In TOPARP-A, high response rates were found in patients with alterations in *BRCA1/2*, *ATM* (monoallelic mutations affecting the kinase catalytic domain), *PALB2* (one biallelic and the other monoallelic) or *HDAC2* (biallelic).[151] In the TOPARP-B, the greatest antitumor response was found in patients with g/s*BRCA1/2* alterations, but some antitumor activity was observed in other subgroups with DDR alterations, especially in the case of biallelic *PALB2* (but not in monoallelic), and to a less extend in those with *ATM* (g*ATM* and loss of ATM protein expression by immunohistochemistry), *FANCA*, or *CHK2* mutations.[152] The TRITON2 Phase II study that resulted in accelerated approval (FDA) of rucaparib for g/s*BRCA1/2* mCRPC also observed responses in patients with alterations in *PALB2*, *FANCA*, *BRIP1* (also known as *FANCJ*) and *RAD51B*, while no significant responses were detected in the *ATM*, *CDK12*, or *CHK2* subgroups (NCT02952534[153]). The same outcome was reported in the TRITON3 Phase III trial, where PFS was significantly longer with rucaparib compared to control among patients who had *BRCA1/2*m mCRPC, but not in those with alterations in *ATM* (NCT02975934[101]). A small retrospective observational study of patients with mCRPC who were prescribed off-label single-agent olaparib and were not reliably tested for the mutation type also found that patients with *ATM* mutations did not respond to PARPi as well as those with *BRCA1/2* mutations.[154] In contrast, *RAD51C* and *RAD51D* alterations have emerged as strong predictors of rucaparib sensitivity in ovarian cancer based on the Phase II ARIEL2 (NCT01891344[155]) and Phase III ARIEL3 (NCT01968213[156]) studies. Finally, niraparib monotherapy provided some disease stability in a proportion of patients with refractory solid tumors with mutations in *BAP1*, *ATM*, *CHEK2*, *PTEN*, *RAD50* and *ARID1A* in another Phase II trial (NCT03207347[157]). Promising activity with olaparib was also found in the Phase II ORCHID trial (NCT03786796) in metastatic renal cell carcinoma patients harboring *BAP1* mutations.[158]

Furthermore, as described before, some other clinical trials have found benefit with neoadjuvant PARPi for HRD breast cancers, such as with olaparib monotherapy in TNBC with germline *BRCA1/2*m or *PALB2* or somatic *ATRX*, *BRCA1*, *EMSY*, *MEN1*, *PTEN* and *SETD2* mutations (NCT02624973[112]). High response rates were also found with olaparib, alone or in combination with durvalumab for early-stage *BRCA1/2*m breast cancer (NCT05498155[113]), while no responses were reported with neoadjuvant olaparib plus CTx in TNBC cancer patients without g*BRCA1/2* mutations (NCT03150576[114]).

Altogether, these data indicate that factors such as the particular type of DDR gene alteration, whether it is somatic or germline, or monoallelic or biallelic and the Pt sensitivity status matter as biomarkers of response to PARPi. Additionally, it is worth noting that most of the studies lack significant numbers of individuals with mutations in specific DDR genes, especially in the less common ones, such as *RAD51C*, *RAD51D*, and *BARD1*, what limits their ability to adequately assess PARPi responses. Despite the need for further research in larger cohorts, these findings have opened new paths to broaden the indications of PARPi beyond *BRCA1/2* mutations.

Novel PARPi in clinical trials

Many other PARPi have progressed to clinical trials but currently lack regulatory approval (Table 2, and Supplementary Fig. S1).

Veliparib (AbbVie) has received several Orphan Drug Designations by the FDA for different cancers since 2008, but all of them

were later withdrawn or revoked. This drug demonstrated the ability to potentiate CTx and RT in different preclinical tumor models.[159,160] The randomized BrighTNess Phase III trial in TNBC (NCT02032277) suggested that the improvement observed in the pathological CR was due to carboplatin and not to veliparib, when adding veliparib to carboplatin and paclitaxel.[161] In the Phase III trial BROCADE3 (NCT02163694), oral treatment with veliparib in combination with paclitaxel and carboplatin seemed to significantly increase median progression-free survival (mPFS) in patients with HER2- metastatic *BRCA1/2*m breast cancer.[162] In contrast, OS was numerically but not significantly improved.[163] As described before, something similar occurred in the VELIA trial (NCT02470585), which found a significant prolongation in the mPFS of ovarian cancer patients treated with induction therapy with carboplatin, paclitaxel and veliparib followed by MT with veliparib,[89] but no improvement in median OS.[90] Regarding lung cancer, a specific informatic classifier, named LP52, was developed using independently derived RNA-seq data from 120 tumors representing a diverse set of NSCLC subtypes. Results from a Phase III trial (NCT02106546) in smokers with advanced squamous NSCLC could not demonstrate therapeutic benefit of adding veliparib to first-line CTx, but the LP52 signature seemed to identify a subgroup of patients likely to derive benefit from this combination.[164] Another Phase III study (NCT02264990) in patients with non-squamous NSCLC also employed this LP52 classifier. No significant improvement in OS was detected with veliparib + carboplatin/paclitaxel versus CTx alone, although a trend toward improved OS in the LP52-positive population suggested this subgroup may benefit from veliparib.[165] Recently, veliparib added to adjuvant temozolomide did not significantly prolong OS in patients with newly diagnosed *MGMT*-hypermethylated glioblastoma in a Phase III clinical trial (NCT02152982[166]). The same outcome was reported in the Phase II VERTU trial testing veliparib and RT, followed by adjuvant veliparib and temozolomide for newly diagnosed *MGMT*-unmethylated glioblastoma.[117] After failure of multiple late-stage clinical trials, the future of veliparib is uncertain and seems to have been removed from AbbVie's recent pipeline.

The PARPi senaparib (IMP4297) from Impact Therapeutics was included in a Phase III trial (NCT04169997) as MT following first-line CTx in patients with advanced ovarian cancer. Maintenance senaparib was well tolerated and significantly improved PFS irrespective of *BRCA1/2* mutation status.[167] Senaparib also demonstrated meaningful antitumor activity in a Phase II trial (NCT04089189) in *BRCA1/2*m recurrent PtS ovarian cancer patients.[168] In another Phase I/II study (NCT04434482), clinical survival benefit was observed for senaparib combined with intermittent low-dose temozolomide in relapsed small cell lung cancer (SCLC) patients with manageable hematological toxicity.

Venadaparib (IDX-1197) is a selective inhibitor of PARP1/2 developed by Idience Co. A Phase I/II study (NCT04725994) of this drug in advanced gastric cancer demonstrated promising efficacy in combination with irinotecan, particularly in those with HRD gene mutations.[169] A basket trial (NCT04174716) with this compound in patients with HRD solid tumors found strong potency of venadaparib in g/s*BRCA1/2*m metastatic breast cancer[170] and higher tumor response in pancreatic cancer patients with co-occurring *ATM* and *ASXL1* mutations.[171]

Stenoparib (E7449, 2X-121) is a dual inhibitor of PARP1/2 and of the regulators of canonical Wnt/β-catenin signaling, tankyrase1/2.[172] This compound originally developed by Eisai Co. and currently by Allarity Therapeutics is involved in two clinical trials: a Phase I/II as single agent for advanced solid tumors or B-cell malignancies and in combination with temozolomide or with carboplatin and paclitaxel for advanced solid tumors (NCT01618136), and a Phase II for advanced ovarian cancer selected by the 2X-121 DRP® biomarker of drug response (NCT03878849). Based on the clear clinical benefit detected in this last trial in terms of tumor shrinkage and long-term disease stability, Allarity Therapeutics has recently announced its early discontinuation to enable and accelerate the development of a follow-on trial with FDA regulatory purpose.[173]

AstraZeneca is developing two additional PARPi, saruparib (AZD5305) and AZD9574. Saruparib (AZD5305) is a selective non-trapping PARP2 inhibitor with strong PARP1 trapping ability that maintains the antitumor efficacy of first-generation PARPi with lower hematological toxicity, although it is not central nervous system (CNS)-penetrant.[174] This compound is included in two Phase III trials: in mCRPC receiving physician's choice new hormonal agents (NCT06120491) and associated with the ER antagonist camizestrant compared with CDK4/ 6i plus endocrine therapy or camizestrant in HR+, HER2-, *BRCA1/2*, or *PALB2*-mutated breast cancer (NCT06380751). Several Phase I/II clinical trials with saruparib for advanced solid tumors (e.g., NCT04644068 and NCT02264678) are ongoing and have shown a manageable safety profile and preliminary signs of efficacy.[175,176] AZD9574 is a CNS-penetrant PARPi that shows >8000-fold selectivity for PARP1 versus PARP2 and other members of the PARP family (PARP2, PARP3, PARP5A and PARP6) in biochemical assays.[174,177] The CNS profile makes it ideal for treating CNS malignancies or brain metastases that depend on PARP inhibition. A Phase I/II trial (NCT05417594) of AZD9574 as monotherapy and in combination with other anti-cancer agents for advanced solid malignancies is recruiting.

SC10914 is a compound from Jiangxi Qinfeng Pharmaceutical that, in a Phase I study in advanced solid tumors (NCT02940132), showed that it was safe and it was effective, particularly in g*BRCA1/2*m ovarian cancer participants.[178] Phase II studies of this compound in g*BRCA1/2*m prostate cancer (NCT04486937), breast cancer (NCT04556292) or ovarian cancer (NCT04556539) are ongoing.

Nesuparib (JPI-547/OCN-201) is another dual PARP1/2 and tankyrase1/2 inhibitor[179] developed by Jeil Pharmaceutical Co. in collaboration with Onconic Therapeutics. This drug is participating in a Phase II clinical trial for PtR advanced/relapsed ovarian cancer previously exposed to a PARPi (NCT05475184). Results from a Phase I trial (NCT04335604) suggested that nesuparib monotherapy was tolerable and effective in patients with advanced solid tumors harboring *BRCA1/2* or HRR mutations.[180] Also from Jeil Pharmaceutical Co. is amelparib (JPI-289 free base), a PARP1 inhibitor that, based on its neuroprotective effects,[181] is being evaluated for the treatment of acute ischemic stroke (NCT03062397, NCT02396069 and NCT01983358).

TSL-1502 is another PARPi that has been designed as a pro-drug whose metabolite (TSL-1502M) has higher localized concentration at cancer sites and, consequently, higher potency than current FDA/EMA approved PARPi, according to its developers (Tasly Pharmaceutical Group).[182] This drug showed preliminary anti-cancer activity in a Phase II trial (NCT05420779) for HER2- g*BRCA1/2*m breast cancer.[183]

AMXI-5001 is a dual PARP1/2 and microtubule polymerization inhibitor being studied in a Phase I/II (NCT04503265) sponsored by AtlasMedx for advanced malignancies.

The non-trapping, CNS-penetrant and selective PARP1 inhibitor from Nerviano Medical Sciences, NMS-03305293 (NMS-293), is included in a Phase I/II trial (NCT04910022) associated with temozolomide for glioblastoma, upon termination of another Phase I (NCT04182516) for solid tumors. Nerviano Medical Sciences has recently announced that the FDA has granted approval to proceed with two Phase I studies in the relapse setting for SCLC combined with temozolomide and for *BRCA1/2* wild-type ovarian cancer combined with DNA topoisomerase I inhibitor (TOP1i) topotecan.[184]

Several other PARPi remain in Phase I trials. Simmiparib (SOMCL-9112) is an orally bioavailable inhibitor involved in a first-in-human (FIH) trial (NCT02993913) sponsored by Shanghai

Acebright Pharmaceuticals for advanced solid tumors. The compound RP12146 from Rhizen Pharmaceuticals showed in a Phase I in solid tumors (NCT05002868) a differentiated safety profile in patients with mCRPC with limited hematological toxicities, as compared to first-generation PARPi, and with encouraging activity particularly in patients with *BRCA2* mutation.[185] HWH340, being developed by Hubei Biological Medicine Industrial Technology Institute is also being studied for *BRCA1/2*m or HRD advanced solid tumors (NCT03415659). Lerzeparib (TQB3823) is an orally available small molecule PARPi that was included in a Phase I/II study (NCT05405439) for prostate cancer that was prematurely terminated by the sponsor (Chia Tai Tianqing Pharmaceutical). Another Phase I (NCT05021367) for advanced solid tumors is ongoing. Finally, ABT-767 is another PARPi from AbbVie that exhibited an acceptable safety profile in a Phase I trial (NCT01339650) and a better efficacy in patients with *BRCA1/2* mutations, HRD positivity and Pt sensitivity.[186]

Limitations of PARPi: resistance and safety concerns

Despite the good initial response to PARPi, patients frequently develop resistance to these agents, resulting in disease relapse. Acquired resistance to PARPi may occur due to three general mechanisms. The first one consists of effects related to the drug target, such as the upregulation of drug efflux pumps,[187] mutations in PARP[188] or in the protein that removes PAR chains from target proteins, PARG.[189] Related to this, several PARG inhibitors (PARGi) are being developed and the compounds IDE161 from IDEAYA Biosciences and ETX-19477 from 858 Therapeutics (structures undisclosed) already entered clinical trials for advanced solid tumors (NCT05787587 and NCT06395519, respectively). A second mechanism of resistance may be the reactivation of HRR. This can be due to restoration of *BRCA1/2* function by the appearance of reversion mutations or epigenetic alterations inducing the re-expression of BRCA1/2 wild-type proteins or resulting in hypomorphic variants,[190–193] or owing to compensatory mutations (e.g., loss of the *53BP1-RIF1-REV7-shieldin* anti-resection signaling pathway) that result in re-wiring of the DDR.[192,194,195] And the last mechanism that may cause PARPi resistance is the loss of DNA end-protection and/or restoration of replication fork stability, and the subsequent suppression of lethal ssDNA gaps. While PRIMPOL initially creates these gaps to allow the replication fork to bypass trapped PARP-DNA complexes,[196] resistant tumors mitigate their lethality either through the restoration of fork protection or active gap-filling. Concerning the restoration of fork protection, the loss of factors like 53BP1, PTIP, EZH2, or MED12 prevents nucleases (primarily MRE11) from widening these gaps into DSBs.[197–199] Regarding gap-filling, the upregulation of POLQ allows the tumor to 'patch' the gaps created by PRIMPOL, effectively masking the HRD phenotype and allowing the cell to survive despite the presence of the PARPi.[200]

Further studies are required to develop therapeutic strategies that help to overcome acquired PARPi resistance and to determine the extent of cross-resistance between the different therapeutic options. In women with ovarian cancer, tumor debulking to remove or eliminate resistant clones may be one option.[201] Other potential strategies include combination therapies with the goal to amplify the antitumoral efficacy of PARPi, targeting the acquired mechanisms of resistance and/or delaying the appearance of resistance through suppression of the mutator phenotype, which arises in *BRCA1/2* m tumors.[202] It is important to remark, that non-HRD tumors are usually also resistant to Pt.[190,203,204]

Several combinational strategies aimed at overcoming PARPi resistance are being discussed, depending especially on the HRD status of the tumor at the time of treatment (Fig. 7). In these cases, therapeutic options to improve the durability of the treatment may direct to attack alternative vulnerabilities of the tumor, and the combination with therapies that prevent the acquisition of these resistance mechanisms.[205] PARPi-resistant tumors seem to accumulate high levels of replication stress, exemplified by, for instance, the acquisition of amplifications in the gene encoding the cyclin E protein, the *CCNE1* gene. In fact, HRR pathway mutations, such as the *BRCA1* mutation, and *CCNE1* amplification are nearly mutually exclusive, as these alterations provide different selective advantages for tumor development.[206–208] The *CCNE1* gene has also been found to be overexpressed in ovarian tumors resistant to CTx,[208,209] and therefore, these tumors exhibit high risk of treatment failure and represent an urgent unmet medical need. In cases of high replication stress, cells activate the replication stress response (RSR), rendering inhibitors of the key effector kinases of RSR (ATR, CHK1 and WEE1) promising candidates to treat these tumors.[210,211] In fact, combinations of these compounds with PARPi have shown great efficacy in clinical trials.[212,213] Because of the synergistic interaction between TOP1i and PARPi,[214] combinations of TOP1i and PARPi should also be considered as a way to increase efficacy in earlier lines of treatment, independently of the HRD status. As detected in sequence analyzes, error-prone DNA repair pathways, such as c-NHEJ and alt-NHEJ, may also be important for the acquisition of reversion events. Thus, another therapeutic approach to avoid restoration of HRR activity could be to combine PARPi with the c-NHEJ/alt-NHEJ inhibitors that are currently in clinical trials, such as DNA-PK and POLQ inhibitors (DNA-PKi and POLQi).[215,216] As previously described, beyond its role in alt-NHEJ, POLQ is essential for mitigating the lethality of ssDNA gaps, as it provides critical 'gap-filling' activity that masks the HRD phenotype.[200] Indeed, POLQ was found upregulated in HRD tumors, and the knockdown of POLQ in these tumors resulted in cancer cell death,[217,218] suggesting that POLQ could constitute a novel druggable target to treat HRD tumors. Besides, inactivating mutations in *53BP1-shieldin*, which cause acquired PARPi resistance, result in high in vitro and in vivo sensitivity to POLQi.[219] Moreover, in a patient-derived xenograft (PDX) model with a combined loss of *TP53BP1* and *BRCA1*, which was isolated from a patient with acquired PARPi resistance, novobiocin, a specific POLQi, was able to substantially reduce tumor growth.[220] Furthermore, the restored HRR functionality caused by *53BP1-shieldin* loss in *BRCA1*-mutated tumors seems to rely on sustained signaling through the ATR kinase.[205,221] This reinforces the evidence that combining PARPi with ATRi or POLQi could provide a comprehensive strategy to overcome multiple axes of resistance, by simultaneously disrupting the RSR, exhausting cell cycle checkpoints, and forcing the re-accumulation of lethal ssDNA gaps.

Concerning *BRCA1/2*m but HRR-proficient tumors, resistance is normally driven by *BRCA1/2*-hypomorphic expression or DDR rewiring events. In these cases, the use of a functional assay of HRD status, such as the RAD51 foci formation assay,[222] may increase the understanding of the level of HRD left in these tumors and therefore may help to predict the probability of response to PARPi.[223] However, this test is still being validated and, therefore, it is not yet available to be clinically implemented.[224] Currently, HRD status is being determined in the clinical setting by the identification of mutations in HRR genes, mutational signatures and/or genomic scars, through different centralized and in-house commercial tests and custom panels. However, as the HRD phenotype is dynamic and these tests reflect genomic history rather than the HRD status at the time of treatment, functional assays should be improved and clinically implemented in order to provide more real-time data on HRD status for prediction of response to PARPi and Pt-based CTx.[225]

Apart from the emerging resistance, safety concerns related to PARPi have also been raised. The different approved PARPi share several common adverse effects, such as hematological and gastrointestinal toxicities,[226] that may lead to treatment discontinuation and reduce combination possibilities with other drugs. PARP trapping on the DNA seems to contribute to PARPi cytotoxicity in healthy bone marrow and exhibits an inverse

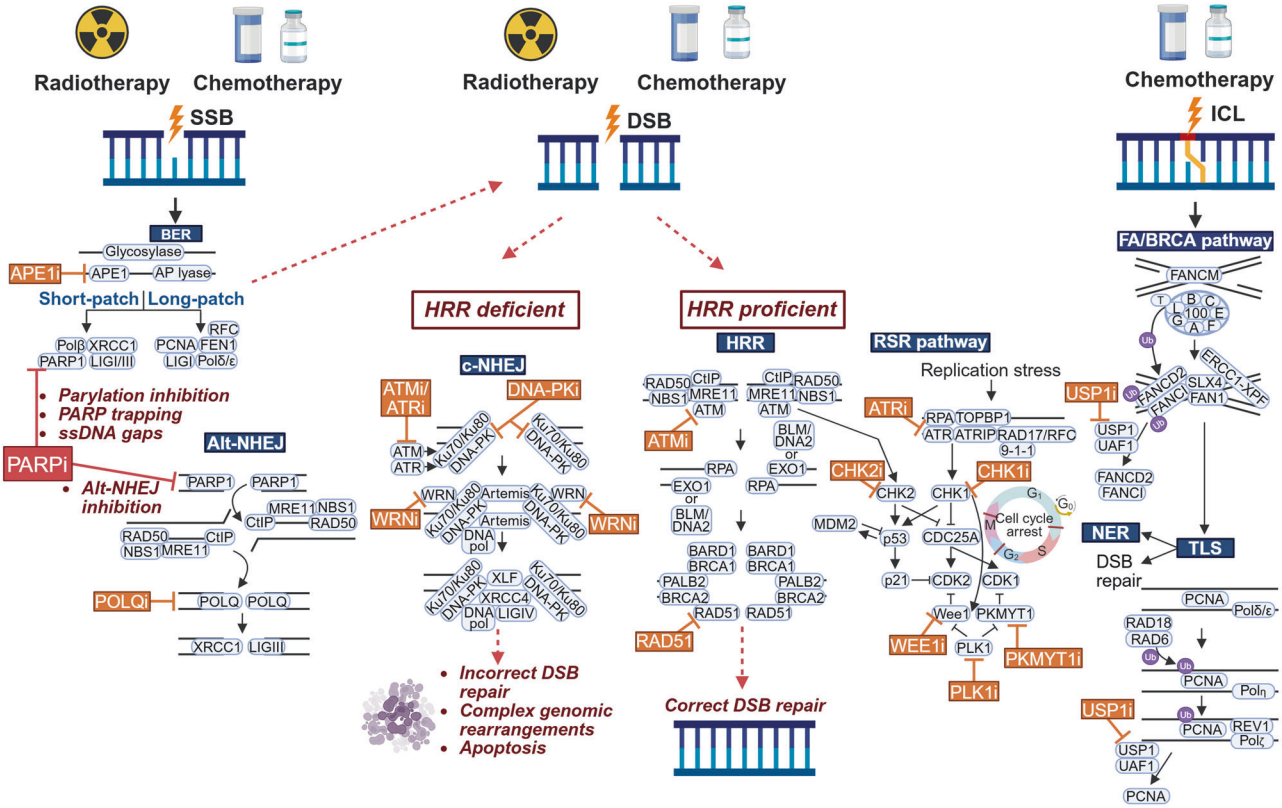


Fig. 7 Combination therapy strategies with PARPi. SSBs generated by CTx or RT are repaired by the BER pathway. PARPi inhibit PARylation and induce PARP trapping and the formation of ssDNA gaps, that may result in DSBs, which may also be caused directly by CTx or RT or by DSBs derived from ICLs first repaired by the FA/BRCA pathway in cooperation with TLS. Cancer cells with deficient HRR due to for instance *BRCA1/2* mutations, will repair these DSBs by the c-NHEJ pathway (as the alt-NHEJ will be inhibited by PARPi), resulting in incorrect DSB repair, the accumulation of genomic rearrangements and apoptosis. In contrast, cancer cells with proficient HRR will repair these DSBs leading to cancer cell survival and drug resistance. Moreover, alterations in other components of these involved pathways may allow cancer cells to repair DNA damage and become resistant to PARPi. In consequence, the combination with inhibitors of these altered components may resensitize cancer cells to PARPi. Figure created with BioRender

relationship with PARPi tolerability.[227] This should be taken into consideration when establishing combination regimens of PARPi with drugs with well-known bone marrow toxicity. Besides, recent data suggested that the SL effect of PARPi in cancer cells with HRD is due to PARP1 enzymatic activity and not to their capacity to trap PARP on DNA.[61] Moreover, the inhibition of PARP2 and tankyrase1/2 is believed to be associated with hematological[228,229] and gastrointestinal toxicities,[230] respectively. Overall, this makes it imperative that new-generation PARPi should be directed to the selective inhibition of PARP1 enzymatic activity without causing PARP trapping. The clinical emergence of highly selective PARP1i (e.g., saruparib) represents a promising step toward this goal, potentially allowing for the safer integration of the multi-axis combination strategies previously described.

Based on results obtained for PARPi, the implementation of successful SL-based therapies for cancer treatment should consider additional variables, apart from the resistance mechanisms. On the one hand, several features related to the altered gene should be analyzed, such as the zygosity of the target genetic alteration, the prevalence of its loss in a given cancer type or across cancers and whether this loss is essential for tumor promotion and/or maintenance. In fact, although GOF alterations in proto-oncogenes typically act dominantly, LOF alterations in tumor suppressor genes are usually recessive, requiring biallelic inactivation for tumorigenesis promotion, for instance via loss of heterozygosity (LOH).[143] It is also important to remark that a subset of tumor suppressor genes is known to be haploinsufficient, requiring only a single allele.[231] To add even more complexity, some other genes may be haploinsufficient for only specific related phenotypes, and some others (e.g., *TP53*) may harbor alleles with either LOF or dominant-negative activity depending on the specific mutation.[232,233] In consequence, the development of biomarkers that accurately assess LOH and zygosity would be helpful for the success of SL-based therapies. On the other hand, characteristics of the target gene to be inhibited therapeutically, such as the expression of the cell lineage and/or cancer type of interest and the toxicity impact of its inhibition in healthy tissue, should also be considered. Finally, the SL interaction itself should also be studied, for instance by determining the magnitude of the therapeutic index in preclinical models (effect size) and the penetrance of the SL interaction.[233] In fact, some SL interactions exhibit incomplete penetrance due to differential gene-regulatory and signaling networks across cell types and genetic and epigenetic heterogeneity within the tumor.[234] For instance, the varied expression of backup polymerases like POLQ or repriming factors like PRIMPOL across different genetic backgrounds may dictate the ultimate penetrance of PARPi-induced lethality.[196]

TARGETING SL INTERACTIONS IN DDR GENES BEYOND PARP INHIBITION

The discovery of new SL interactions in DDR genes and the success observed for PARPi has resulted in an increasing amount of oncologic research directed to targeting other components of the DDR pathway using the SL approach (Table 3). Many tumors

Table 3. Recent clinical trials for ATR, ATM, DNA-PK, CHK1, CHK2, WEE1, PKMYT1, CDKs, PLK1, POLQ, USP1, RAD51, WRN and APE1 inhibitors: monotherapy and combination therapy

Target	Agent	Intervention	Cancer type	Phase	Clinicaltrials.gov identifier
ATR	Ceralasertib	Ceralasertib + Durvalumab vs Docetaxel	NSCLC	III	NCT05450692
		Ceralasertib + Durvalumab	NSCLC	III	NCT06732401
		Ceralasertib	Advanced solid tumors	IIA	NCT04564027
		Ceralasertib	NSCLC	II	NCT03334617
		Ceralasertib + Olaparib	Gynecologic cancer	II	NCT04065269
		Ceralasertib + Olaparib	NSCLC	II	NCT02937818
		Ceralasertib + Olaparib	SCLC	II	NCT03428607
		Ceralasertib + Olaparib	Ovarian cancer	II	NCT03462342
		Ceralasertib ± Olaparib	Breast cancer	II	NCT03182634
		Ceralasertib ± Olaparib	TNBC	II	NCT03330847
		Ceralasertib + Durvalumab	Melanoma	II	NCT03780608
		Ceralasertib + Acalabrutinib	CLL	I/II	NCT03328273
		Ceralasertib ± Olaparib/ Durvalumab/Saruparib/Carboplatin	Advanced solid tumors	I/II	NCT02264678
	Berzosertib	Berzosertib + Topotecan	SCLC	II	NCT03896503
		Berzosertib + Topotecan	SCLC	II	NCT04768296
		Berzosertib + Sacituzumab govitecan	SCLC, extra-pulmonary small cell neuroendocrine cancer and PARPi resistant HRD-cancers	II	NCT04826341
		Cisplatin + Gemcitabine ± Berzosertib	Urothelial cancer	II	NCT02567409
		Gemcitabine ± Berzosertib	Ovarian, primary peritoneal or fallopian tube cancer	II	NCT02595892
		Gemcitabine ± Berzosertib	Leiomyosarcoma	II	NCT04807816
		Berzosertib + Irinotecan	*TP53*-mutant gastric or gastroesophageal junction cancer	II	NCT03641313
		Berzosertib + Carboplatin + Docetaxel	Prostate cancer	II	NCT03517969
		Berzosertib + Avelumab	Advanced solid tumors	II	NCT04266912
		Pembrolizumab + Gemcitabine + Carboplatin ± Berzosertib	NSCLC	I/II	NCT04216316
		Berzosertib + Lurbinectedin	SCLC and high-grade neuroendocrine cancers	I/II	NCT04802174
		Berzosertib + Topotecan	SCLC and extrapulmonary small cell cancers	I/II	NCT02487095
	Elimusertib	Elimusertib	Advanced solid tumors	I/II	NCT05071209
		Elimusertib	Advanced solid tumors and lymphoma	I	NCT03188965
		Elimusertib + SOC CTx	Advanced solid tumors	I	NCT04491942NCT 04616534NCT04514497
		Elimusertib + FOLFIRI CTx	Advanced cancers of the stomach and intestines	I	NCT04535401
		Elimusertib + Niraparib	Ovarian cancer and solid tumors (excluding prostate)	I	NCT04267939
		Elimusertib + Pembrolizumab	Advanced solid tumors	I	NCT04095273
		Elimusertib + Pembrolizumab	HNSCC	I	NCT04576091
	Camonsertib	Camonsertib	Solid tumors with *ATM* and *SETD2* LOF	II	NCT04589845
		Lunresertib + Camonsertib	Advanced cancer	II	NCT05605509
		Lunresertib + Camonsertib	CDK4/ 6i resistant ER+/ HER2- breast cancer	II	NCT05601440
		Camonsertib ± Talazoparib/Gemcitabine	Advanced solid tumors	I/II	NCT04497116
		Atezolizumab + Camonsertib ± Bevacizumab	NSCLC	I/II	NCT03337698
	Gartisertib	Gartisertib + Carboplatin	Advanced solid tumors	I	NCT02278250
	Tuvusertib	Tuvusertib	*SPOP*-mutant prostate cancer	II	NCT05828082
		Tuvusertib + Avelumab	Merkel cell skin cancer	II	NCT05947500
		Tuvusertib ± Avelumab	*ARID1A*-mutated endometrial cancer	II	NCT06518564
		Tuvusertib + Cemiplimab	NSCLC	II	NCT05882734
		Tuvusertib + Niraparib/Lartesertib	Ovarian cancer	II	NCT06433219
		Tuvusertib + Temozolomide	Advanced solid tumors and hematologic malignancies	I/II	NCT05691491
	ART0380	ART0380	Advanced solid tumors	II	NCT05798611
		ART0380 ± Gemcitabine ± Irinotecan	Advanced solid tumors	I/II	NCT04657068
	SC0245	SC0245 + Irinotecan	SCLC	II	NCT05731518
ATM	AZD0156	AZD0156 + Olaparib/Irinotecan/ Fluorouracil/ Folinic Acid	Advanced solid tumors	I	NCT02588105
	AZD1390	AZD1390 + RT	Brain cancer	I	NCT03423628

Table 3. continued

Target	Agent	Intervention	Cancer type	Phase	Clinicaltrials.gov identifier
		AZD1390 + RT ± Durvalumab	Soft tissue sarcoma	I	NCT05116254
		AZD1390 + SBRT	Advanced solid tumor	I	NCT05678010
		AZD1390 + RT	NSCLC	I	NCT04550104
		AZD1390	Healthy volunteers	I	NCT03215381
	WSD0628	WSD0628 + RT	Glioblastoma	I	NCT05917145
	Lartesertib	Tuvusertib + Niraparib/Lartesertib	Ovarian cancer	II	NCT06433219
		Lartesertib	Advanced solid tumors	I	NCT04882917
		Tuvusertib + Lartesertib/Avelumab	Advanced solid tumors	I	NCT05396833
ATM/ DNA-PK	XRD-0394	XRD-0394 + RT	Advanced solid tumors	I	NCT05002140
DNA-PK	CC-115	CC-115	Advanced solid tumors	I	NCT01353625
		CC-115 + Enzalutamide	Prostate cancer	I	NCT02833883
		CC-115 + Temozolmide	Glioblastoma	II	NCT02977780
	Peposertib	Peposertib + RT	Pancreatic cancer	I/II	NCT04172532
		Peposertib + Avelumab + RT	Advanced solid tumors and hepatobiliary malignancies	I/II	NCT04068194
		Peposertib + RT ± Avelumab	CRPC	I/II	NCT04071236
		Peposertib + Capecitabine	Rectal cancer	I/II	NCT03770689
		Peposertib + Avelumab + Temozolomide	Pediatric cancer	I/II	NCT02813135
	AZD7648	AZD7648 + Doxorubicin	Advanced solid tumors	I/IIA	NCT03907969
	M9831	VX-984	Advanced solid tumors	I	NCT02644278
	BY101298	BY101298	Advanced solid tumors	I	NCT06462716
DNA-PK/ mTor	Samotolisib	Samotolisib	Pediatric *TSC1/2* or *PI3K/ MTOR*-mutated advanced solid tumors, NHL or histiocytic disorders	II	NCT03213678NCT03155620
CHK1	Prexasertib	Prexasertib + Irinotecan	Desmoplastic small round cell tumor and rhabdomyosarcoma	I/II	NCT04095221
		Prexasetib	Ovarian cancer, endometrial adenocarcinoma and urothelial carcinoma	I/II	NCT05548296
		Prexasertib	SCLC	II	NCT02735980
		Prexasertib	Breast, ovarian and prostate cancer	II	NCT02203513
		Prexasertib	HRD-solid tumors or solid tumors with replicative stress	II	NCT02873975
		Prexasertib	Ovarian cancer	II	NCT03414047
		Prexasertib + low dose Gemcitabine	HNSCC	II	NCT06597565
		Prexasertib + LY3023414	TNBC	II	NCT04032080
	SRA737	SRA737	Advanced solid tumors or NHL	I/II	NCT02797964
		SRA737 + Gemcitabine + Cisplatin	Advanced solid tumors	I/II	NCT02797977
	BBI-355	BBI-355 ± Erlotinib/Futibatinib	*EGFR*- and *FGFR2*- amplificated tumors	I	NCT05827614
	LY2880070	LY2880070 ± Gemcitabine	Ewing sarcoma	I	NCT05275426
		LY2880070 + Gemcitabine	Advanced or metastatic solid tumors	I	NCT02632448
	PEP07	PEP07	Advanced or metastatic solid tumors	I	NCT05983523
		PEP07	AML and mantle cell lymphoma	I	NCT05659732
	SMP-3124LP	SMP-3124LP	Advanced solid tumors	I/II	NCT06526819
CHK2	PHI-101	PHI-101	Ovarian cancer	IA	NCT04678102
		PHI-101	AML	I	NCT04842370
WEE1	Adavosertib	Adavosertib	*SETD2*-amplificated advanced solid tumors	II	NCT03284385
		Adavosertib	*CCNE1*-amplificated advanced solid tumors	II	NCT03253679
		Adavosertib	*BRCA1/2*m advanced solid tumors and hematologic malignancies	II	NCT04439227
		Adavosertib	Uterine serous carcinoma or carcinosarcoma	II	NCT03668340
		Adavosertib	Uterine serous carcinoma	II	NCT04590248
		Adavosertib	Prostate cancer	II	NCT03385655
		Adavosertib	SCLC	II	NCT02593019
		Adavosertib	*BRCA1/2*m advanced solid tumors and hematologic malignancies	II	NCT02465060
		Adavosertib + Carboplatin	Advanced solid tumors	II	NCT01827384
		Adavosertib + Carboplatin	SCLC	II	NCT02937818
		Adavosertib + Carboplatin	*TP53*-mutated ovarian cancer	II	NCT01164995
		Adavosertib + Carboplatin + Paclitaxel	Squamous cell lung cancer	II	NCT02513563

Table 3. continued

Target	Agent	Intervention	Cancer type	Phase	Clinicaltrials.gov identifier
		Carbolatin + Paclitaxel ± Adavosertib	*TP53*-mutated ovarian cancer	II	NCT01357161
		Adavosertib + Cisplatin	Breast cancer	II	NCT03012477
		Adavosertib + Gemcitabine/Paclitaxel/ Carboplatin/ Doxorubicin	Ovarian, primary peritoneal and fallopian tube cancer	II	NCT02272790
		Adavosertib + Paclitaxel	*TP53*-mutated gastric adenocarcinoma	II	NCT02448329
		Gemcitabine ± Adavosertib	Ovarian, primary peritoneal and fallopian tube cancer	II	NCT02101775
		Cytarabine ± Adavosertib	AML and myelodysplastic syndrome	II	NCT02666950
		Adavosertib + Gemcitabine + RT	Pancreatic adenocarcinoma	II	NCT02037230
		Adavosertib ± Olaparib	Ovarian, primary peritoneal and fallopian tube cancer	II	NCT03579316
		Olaparib ± Adavosertib	TNBC	II	NCT03330847
		Adavosertib + Paclitaxel + Gemcitabine	Pancreatic cancer	I/II	NCT02194829
		Adavosertib + Irinotecan	Advanced solid tumors	I/II	NCT02095132
		Adavosertib + Carboplatin	Relapsed or refractory pediatric cancer	I/II	NCT02813135
	Azenosertib	Azenosertib	Ovarian, primary peritoneal and fallopian tube cancer	II	NCT05128825
		Azenosertib	Uterine serous carcinoma	II	NCT06369155NCT04814108
		Azenosertib + Gemcitabine	Pancreatic cancer	II	NCT06015659
		Azenosertib + Gemcitabine	Osteosarcoma	I/II	NCT04833582
		Azenosertib + Carboplatin + Pembrolizumab	TNBC	I/II	NCT06351332
	Debio-0123	Debio-0123 + Sacituzumab govitecan	TNBC and HR+/ HER2- advanced breast cancer	I/II	NCT06612203
		Debio-0123 + Temozolomide + RT	Glioblastoma and astrocytoma	I/II	NCT05765812
	Potrasertib	IMP7068	Advanced solid tumors	I	NCT04768868
	SY-4835	SY-4835	Advanced solid tumors	I	NCT05291182
	APR-1051	APR-1051	Advanced solid tumors	I	NCT06260514
WEE1/ PKMYT1	ACR-2316	ACR-2316	Advanced solid tumors	I	NCT06667141
PKMYT1	Lunresertib	Lunresertib + Gemcitabine/Camonsertib	CDK4/ 6i resistant ER+/ HER2- breast cancer	II	NCT05601440
		Lunresertib + Gemcitabine/FOLFIRI/Trastuzumab/ Camonsertib	*TP53*/*FBXW7*/PPP2R1A/*KRAS*-mutated or *CCNE1*-amplified advanced cancer	II	NCT05605509
		Lunresertib + Carboplatin + Paclitaxel	Recurrent *TP53*-mutated ovarian and uterine cancer	I	NCT06107868
		Lunresertib + XELOX	*CCNE1*-amplificated and *FBXW7*-mutant advanced gastrointestinal cancer	I	NCT05147350
		Lunresertib ± Camonsertib/Debio-0123	Advanced solid tumors	I	NCT04855656
CDK4/6	Palbociclib	Palbociclib + Fulvestrant	HR+/HER2- breast cancer	III	NCT01942135
		Palbociclib	Chordoma with *CDKN2A/B* LOF or *RB1-/CDK4/6*-positive	II	NCT03110744
		Palbociclib	Advanced cancer with *CDKN2A/B* LOF or *CDK4/ 6* amplifications	II	NCT02693535
		Palbociclib	*RB1*-positive anaplastic oligodendroglioma	II	NCT02530320
	Abemaciclib	Abemaciclib	*RB1*-positive TNBC	II	NCT03130439
		Abemaciclib	Thyroid cancer	II	NCT04552769
		Abemaciclib	*CDKN2A*-deficient mesothelioma	II	NCT03654833
		Abemaciclib ± Samotolisib ± Gemcitabine/ Capecitabine	Pancreatic ductal adenocarcinoma	II	NCT02981342
		Abemaciclib + Samotolisib + Fulvestrant vs Other	Metastatic breast cancer	IB	NCT02057133
CDK2	INCB123667	INCB123667 vs CTx	PtR ovarian cancer with cyclin E1 overexpression	III	NCT07214779
		INCB123667	PtR ovarian cancer with cyclin E1 overexpression	II	NCT07023627
		INCB123667 ± Palbociclib/Ribociclib±Fulvestrant/ Bevacizumab/Olaparib/Paclitaxel	Advanced solid tumors	I	NCT05238922
PLK1	Onvansertib	Onvansertib	Relapsed SCLC with *TP53*-mutation and *YAP1*- or *MYC* expression	II	NCT05450965
		Onvansertib ± FOLFIRI/FOLFOX+Bevacizumab	*KRAS*/*NRAS*-mutated mCRC (first line)	II	NCT06106308
		Onvansertib + FOLFIRI + Bevacizumab	*KRAS*-mutated mCRC (second line)	I	NCT03829410
POLQ	ART4215	ART4215 ± Talazoparib	Advanced solid tumors	I/IIA	NCT04991480
	ART6043	ART6043 ± Olaparib/Niraparib	Advanced solid tumors	I/IIA	NCT05898399
	GSK4524101	GSK4524101 ± Niraparib	Solid tumors	I/II	NCT06077877
	RP-3467	RP-3467 ± Olaparib	Advanced solid tumors	I	NCT06560632

Table 3. continued

Target	Agent	Intervention	Cancer type	Phase	Clinicaltrials.gov identifier
	SYN818	SYN818	Advanced solid tumors	I	NCT06666270
	Novobiocin	Novobiocin	Advanced solid tumors	I	NCT05687110
USP1	KSQ-4279	KSQ-4279 ± PARPi	Advanced solid tumors	I	NCT05240898
	XL309	XL309 ± Olaparib	Advanced solid tumors	I	NCT05932862
RAD51	Emzadirib	Emzadirib ± Gemcitabine/Capecitabine/ Rituximab and Bendamustine	B-cell malignancies and advanced solid tumors	I/II	NCT03997968
WRN	GSK4418959	GSK4418959 ± PD-1 inhibitor	MSI-H or MMR-deficient advanced solid tumors	I/II	NCT06710847
	HRO761	HRO761 ± Pembrolizumab/Irinotecan	MSI-H or MMR-deficient advanced solid tumors	I	NCT05838768
	RO7589831	RO7589831 ± Pembrolizumab	MSI-H or MMR-deficient advanced solid tumors	I	NCT06004245
APE1	APX3330	APX3330	Advanced solid tumors	I	NCT03375086
	TRC102	TRC102 + Pemetrexed + Cisplatin	Advanced solid tumors or mesothelioma	I/II	NCT02535312
		TRC102 + Temozolomide	Solid tumors and lymphomas	I/II	NCT01851369

Data extracted from clinicaltrials.gov up until November 2025

bypass genotoxic stress from CTx and RT by upregulating different DDR members, effectively 'rewiring' their signaling networks to enable DNA repair and checkpoint activation and ensure survival.

Some of the primary targets of DDRi are the phosphatidylinositol 3-kinase-like protein kinases (PI3KKs) ATR, ATM and DNA-PK because of their role as master regulators of the DDR.[235–237] Inhibitors of the downstream targets of ATR and ATM, CHK1 and CHK2, are also being developed. One of the hallmarks of cancer is uncontrolled sustained cell proliferation. The accumulation of genetic errors during cell division is surveilled by two major checkpoint-associated pathways: ATM-CHK2 and ATR-CHK1, which control G_1/S and G_2/M transitions through the DNA damage checkpoint and RSR, respectively. Functionally, this translates into the prevention of DNA damage accumulation and propagation (ATM-CHK2 axis) and the prevention of replication stress-induced DNA damage during cell division (ATR-CHK1 axis). Based on this, mutations in ATM-CHK2 may participate in cancer promotion and in ATR-CHK1 in cancer prevention.[238] Interestingly, while *ATM* gene is frequently mutated in cancer, what makes it appropriate for SL approaches, mutations in *ATR* and *PRKDC* (the gene that codes for DNA-PKcs) are only found in specific cases of cancer.[239–241] Moreover, although ATM and DNA-PK mediate the response to DSBs and ATR to SSBs and regions generated at stalled replication forks,[242] there is increasing evidence of crosstalk and functional redundancy between both pathways.[243] SL relationships have been reported between ATM and DNA-PKcs[244,245] and between ATM and ATR,[246] but apparently not between ATR and DNA-PKcs.[247] The inhibition of other DDR pathways such as the serine/threonine kinase WEE1 that leads to G_2/M arrest is also being explored. In fact, WEE1 has been found to be overexpressed in various malignancies, conferring resistance to anticancer drugs.[248–250] When combined with DNA-damaging CTx or RT, the inhibition of checkpoint-associated pathways results in the overwhelming of the repair capacity of resistant tumor cells and enhanced cytotoxicity and therapeutic sensitization.[29,30,32,251,252] Some other key DDR players that are being clinically targeted are the cell cycle regulating kinase similar to WEE1, PKMYT1, cyclin-dependent kinases (CDKs), PLK1, POLQ, RAD51, USP1, WRN and APE1.

ATR inhibitors (ATRi)

In response to genotoxic stressors affecting DNA replication, cells activate the RSR pathway, with the ultimate goal of slowing DNA synthesis and replication and allowing time for DNA repair.[23] ATR is a protein kinase from the family of the phosphoinositide-3-kinase-related kinases (PIKKs) that is a key player of the RSR pathway. LOF mutations in the *ATR* gene cause Seckel syndrome, characterized by severe growth retardation in utero, impaired intellectual delay, microcephaly and dwarfism. However, whereas hypomorphic ATR function is compatible with life,[253] the complete loss of ATR is embryonic lethal, underscoring its role as an essential gene.[254] This biological constraint requires a 'transient inhibition' strategy, through for instance small molecules, rather than the catastrophic consequences of permanent/complete loss that protein degraders or knockouts would cause.

ATR shares sequence and functional homology with two other DDR kinases, ATM and DNA-PK.[255,256] In human cells, the vast majority of ATR exists in complex with ATRIP,[257,258] and responds to different types of DNA damage and genotoxic stress[259]; many of them have in common a DNA structure formed at the replication fork that ATR can recognize. This structure consists of RPA-coated ssDNA that recruits ATR through binding to its partner, ATRIP.[257,260] CHK1 is a critical regulator of the G_2/M and intra-S cell cycle checkpoints that is phosphorylated by ATR.[261] Many cancer cells suffer dysregulation of G_1 checkpoints,[262,263] thereby creating a dependency on the S and G_2/M checkpoints and increased replication stress when entering S-phase.[264] This vulnerability may be further amplified in ALT+ tumors that rely on ATR to manage inherent telomeric replication stress.[265] In addition, CTx, RT and cancer-related inflammation also increase replication stress. Because ATR and CHK1 are S- and G_2-phase regulators, they are attractive targets for cancer therapeutics. Indeed, inactivating the ATR/CHK1 pathway in cancer cells results in the inhibition of DNA damage-induced G_2/M checkpoint arrest, leading to mitotic catastrophe and apoptosis. Moreover, the inhibition of the ATR/CHK1 axis causes the collapse of replication forks and renders cancer cells dependent on HRR to repair DSBs. Synergism between ATR, CHK1 and PARP inhibition has been reported in *BRCA1/2* m tumors.[266] Preclinical and clinical data have also shown that deficiency in the other cell cycle checkpoint kinase ATM sensitizes cancer cells to ATR inhibition.[267–269]

Clinical development of ATRi currently follows three primary axes: (i) SL in *ATM*-deficient or ALT+ tumors; (ii) potentiation of DNA-damaging CTx/RT; and (iii) reversal of resistance to PARPi or ICIs. Several ATRi progressed to clinical trials (Supplementary Fig. S2), with AstraZeneca's ceralasertib (AZD6738) having undergone the most extensive development. Berzosertib (VX-970/M6620/VE-822), gartisertib (M4344 or VX-803) and tuvusertib (M1774) from Merck, elimusertib (BAY1895344) from Bayer, camonsertib (RP-3500) from Repare Therapeutics, alnodesertib (ART0380) from Artios Pharma and SC0245 from Biocity Biopharmaceutics. Other ATRi that are still in preclinical phases are: VE-821, developed by Vertex/Merck; schisandrin B (isolated from Schisandra chinensis), AD1058; NU6027; dactolisib (NVP-BEZ235), EPT-46464, torin-2, AZ20 and Novartis' tetrahydropyrazolo[1,5-a] pyrazines lead and azabenzimidazole series lead.

Ceralasertib (AZD6738) is an orally bioavailable ATRi with antitumor activity demonstrated in several preclinical models.[270] Various Phase II clinical trials studied ceralasertib associated with olaparib. This was based on the finding that in *BRCA1/2*m tumors with acquired PARPi resistance, the inhibition of the ATR/CHK1 axis reverses restored HRR and compromises replication fork stability.[266] The CAPRI study (NCT03462342) in recurrent high-grade serous ovarian cancer showed good tolerability of this combination and a signal of activity in *BRCA1*m tumors.[271] A more thorough study of PtS patients within this study demonstrated clinical activity with an ORR of 48.5% and a mPFS of 8.3 months (95% CI: 5.9, 10.7). Remarkably, in patients with germline HRR gene alterations, ORR was 100% and mPFS was not reached.[272] The Phase II OLAPCO trial (NCT02576444) in patients with HRD relapsed or refractory cancers found preliminary activity in *ATM*-mutated tumors and in PARPi-resistant *BRCA1/2*m ovarian cancer.[273] Another Phase II trial in TNBC patients (NCT03182634) did not observe sufficient evidence of efficacy with the combination of olaparib and ceralasertib, but identified some biomarkers of potential benefit, such as functional HRD by RAD51 foci, *CCNE1* amplification (high cyclin E1 expression) and pathogenic mutations in HRR genes.[274] This was in line with data observed in the randomized Phase II VIOLETTE study (NCT03330847), where ceralasertib plus olaparib did not improve PFS compared to olaparib monotherapy as 2nd or 3rd line for metastatic TNBC.[275] The Phase II SUKSES-N2 trial (NCT03428607) in SCLC patients with predefined DDR gene alterations also showed that olaparib alone or combined with ceralasertib did not meet the predefined efficacy, although disease stabilization was more evident in the combination arm.[276] In contrast, ceralasertib associated with durvalumab exhibited promising antitumor activity in a Phase II study (NCT03780608) in patients with metastatic melanoma who had failed anti-PD-1 therapy[277] and with advanced gastric cancer refractory to CTx.[278] Consistent with this, the Phase II umbrella HUDSON study (NCT03334617) evaluating rational combination regimens for advanced NSCLC following failure of anti-PD-L1 and Pt-doublet therapy observed the greatest clinical benefit with durvalumab plus ceralasertib, especially in *ATM*-altered patients. Moreover, biomarker analyzes suggested that anti-PD-L1/ATR inhibition stimulated immune-mediated antitumor activity.[279] This synergy is likely driven by the accumulation of cytosolic DNA fragments following ATR inhibition, which activates the cGAS-STING pathway. This causes an increase in the production of Type I interferons and proinflammatory cytokines within the tumor, thereby enhancing T-cell recruitment and overcoming resistance to ICIs.[280] These findings resulted in the initiation of the Phase III LATIFY study associating ceralasertib with durvalumab in comparison to docetaxel in patients with NSCLC whose disease progressed on or after prior anti-PD-L1 therapy and Pt (NCT05450692). Another Phase III study is analyzing ceralasertib in addition to anti-PD-L1 immunotherapy to increase time without cancer for patients with NSCLC (NCT06732401). In relation to ATM, another Phase IIA study (NCT04564027) is assessing ceralasertib monotherapy in previously treated patients with *ATM*-altered tumors. Preliminary results have shown limited responses to ceralasertib monotherapy in these tumors, despite reaching target plasma levels. Alternative patient selection and combination treatment strategies are being explored.[281] Another Phase I/II trial is studying ceralasertib administered orally in combination with CTx and/or novel anti-cancer agents (olaparib, saruparib or durvalumab) to patients with advanced malignancies (NCT02264678). One of the combinations under study is ceralasertib and olaparib for *ATM*-proficient versus deficient gastric adenocarcinomas. Clinical activity from the Phase I part of this study was reported for ceralasertib and olaparib in HRD PtS relapsed ovarian cancer.[282] It is also important to remark that resistance mechanisms to ceralasertib have also been published. For instance, resistance was detected in gastric cancer cells with loss of the nonsense-mediated decay factor *UPF2*[283] and, as happens with PARPi,[187] in cancer cells with overexpression of the ATP-binding cassette transporters P-gp and BCRP.[284]

Berzosertib, formerly M6620, VX-970 or VE-822, is another ATRi that resulted in selective sensitization of pancreatic tumors to RT.[251] It also showed suppression of gastric cancer cells' proliferation and migration ability.[285] The structure of berzosertib is based on that of VE-821, which was identified by Vertex Pharmaceuticals during high-throughput screening.[286] An early Phase I trial (NCT02487095) found remarkable activity from the combination of berzosertib and the TOP1i topotecan in Pt-refractory SCLC patients, which tend not to respond to topotecan alone.[287] Meanwhile, in a Phase II trial (NCT03896503) in relapsed SCLC patients, it showed no effect on PFS compared to topotecan alone, but a significant improvement in OS.[288] The association of these two drugs was also explored in relapsed PtR SCLC patients (NCT04768296). Another Phase I/ II study (NCT04826341) is studying the anti-TROP2 antibody hRS7 conjugated to a TOP1i, sacituzumab govitecan, plus berzosertib in SCLC, extra-pulmonary small cell neuroendocrine cancer and HRD cancers resistant to PARPi. Response was observed in two patients with neuroendocrine prostate cancer and a patient with *EGFR*-transformed SCLC, but not in the other patients.[289] Another Phase I study (NCT03641547) showed good tolerability of berzosertib in combination with CTx and RT in esophageal cancer.[290] Moreover, in a Phase I study (NCT02157792) combining berzosertib with gemcitabine with or without cisplatin for advanced solid tumors, good tolerability and preliminary efficacy signs were observed.[291] In contrast, in a Phase II randomized clinical trial (NCT02567409) with metastatic urothelial cancer patients, the addition of berzosertib to cisplatin and gemcitabine did not prolong PFS and was associated with significantly higher hematologic toxicities.[292] More recently, in a randomized Phase II trial (NCT02595892) clinical benefit was observed with the addition of berzosertib to gemcitabine in PtR ovarian cancer patients stratified into the Pt-free interval below 3 months subgroup and in patients with *ATM*-mutated tumors.[293] In fact, *ATM* loss sensitized human prostate cancer lines to berzosertib,[269] what had already been reported for VE-821.[246] Another Phase II trial associating berzosertib with irinotecan in progressive, metastatic or unresectable *TP53*-mutant gastric or gastroesophageal junction cancer (NCT03641313) did not meet primary ORR endpoint, but the combination demonstrated anti-tumor activity compared to other agents (e.g., ramucirumab and paclitaxel or TAS-102).[294] Finally, it is also being studied in other Phase II trials in combination with avelumab for DDR-deficient metastatic or unresectable solid tumors (NCT04266912), with gemcitabine for soft-tissue sarcomas (NCT04807816) and with carboplatin with or without docetaxel in mCRPC patients (NCT03517969). Preliminary results from this last trial showed fewer ORRs and more adverse events in patients treated with carboplatin and berzosertib, compared to those treated with carboplatin and docetaxel.[295] Other Phase I/II studies are analyzing berzosertib added to CTx and pembrolizumab for advanced squamous cell NSCLC (NCT04216316), and to the DNA alkylating agent lurbinectedin for solid tumors, SCLC and high-grade neuroendocrine cancers (NCT04802174). Especially after not observing the expected results with berzosertib and topotecan in PtR SCLC, Merck has decided to switch focus to the other ATRi, tuvusertib (M1774).

Tuvusertib (M1774), a potent and selective orally administered ATRi, showed antitumoral activity as monotherapy and in combination with the PARPi niraparib in preclinical models with DDR pathway gene mutations.[296,297] Preliminary results of an FIH study (NCT04170153) of tuvusertib as monotherapy in patients with advanced solid tumors demonstrated a manageable safety profile and exposure-related target engagement.[298] Tuvusertib is also included in Phase I/II trials in combination with the anti-PD-1 cemiplimab in non-squamous NSCLC patients (NCT05882734) and

with temozolomide for metastatic solid tumors (NCT05691491). Some other Phase II studies that are currently recruiting analyze oral tuvusertib combined with the anti-PD-L1 avelumab for *ARID1A*-mutated endometrial cancer (NCT06518564) or merkel cell skin cancer (NCT05947500), alone for refractory *SPOP*-mutated prostate cancer (NCT05828082) and in association with the PARPi niraparib or the ATM inhibitor (ATMi) lartesertib in ovarian cancer patients (NCT06433219).

Elimusertib (BAY-1895344) is a highly selective, orally bioavailable ATRi, which exhibited strong monotherapy efficacy in cancer CDXs carrying certain DDR deficiencies. This compound was developed by lead optimization efforts focusing on potency, selectivity, and oral bioavailability starting from quinoline 2 that harbored weak ATRi activity.[299] When associated with certain DNA damage-inducing CTx, RT or other DDRi (PARP, ATM, CHK1, DNA-PK or WEE1 inhibitors), synergistic antitumoral activity was observed. Furthermore, elimusertib plus the next-generation nonsteroidal AR antagonist darolutamide significantly improved antitumoral efficacy compared with monotherapy in androgen-dependent prostate cancer models, and this efficacy was further enhanced when adding RT.[300] A FIH clinical trial exploring elimusertib as a single agent in advanced solid tumors and non-Hodgkin's lymphoma (NHL) detected antitumor activity against cancers with certain DDR defects, including deleterious *ATM* mutations (NCT03188965; EudraCT 2016-004484-39).[268] The durable stable disease observed in one patient with a *BRCA1* deleterious mutation provided the rationale for a Phase IB clinical trial associating elimusertib with niraparib in patients with advanced solid tumors and ovarian cancer (NCT04267939, EudraCT 2018-003930-34). However, this study was terminated due to lack of clinical benefit. This trial also found upregulation of PD-L1 expression in tumor tissues from patients treated with elimusertib. These findings, together with previous preclinical data indicating synergy between elimusertib and ICIs resulted in a Phase I trial (NCT04095273; EudraCT 2018-003420-36) assessing elimusertib in combination with pembrolizumab, which was recently completed. Several other Phase I studies testing in different solid cancers the combination of elimusertib and CTx or RT (e.g., NCT04616534, NCT04491942 and NCT04535401) are ongoing. A Phase I/II trial is also exploring oral monotherapy with elimusertib in patients with relapsed or refractory solid tumors (NCT05071209). Preliminary results from these trials showed that elimusertib-related toxicities were primarily hematologic.[301] Synergistic myelotoxicity was found when combined with CTx,[302] including the first case of AML.[303] Although several clinical trials with this drug are ongoing, elimusertib has been removed from Bayer's portfolio.

Camonsertib (RP-3500) is a selective oral inhibitor of ATR kinase with IC_{50} values of 1.0 and 0.33 nM in biochemical and cell-based assays, respectively.[304] A Phase I/II (NCT04497116) trial of camonsertib alone or in combination with talazoparib or gemcitabine for advanced solid tumors with ATRi-sensitizing mutations was recently completed. Preliminary data from the Phase I part of this trial demonstrated better clinical benefit in ovarian cancers with LOF alterations in *ATM* and other DDR genes.[305] A patient with alternative lengthening of telomeres-positive (ALT+) (driven by biallelic loss of *ATRX*) metastatic melanoma experienced clinical and molecular response with good oral tolerability upon treatment with camonsertib. This provides clinical evidence of SL between *ATRX*-deficient/ALT+ tumors and ATRi, probably due to the high replication stress and defects in genome maintenance present in these tumors.[306] Camonsertib is currently being included in several Phase I/II trials, including for advanced solid tumors associated with niraparib or olaparib (NCT04972110) and for metastatic NSCLC together with multiple immunotherapy-based drugs (NCT03337698). Three other Phase II trials that analyze camonsertib monotherapy in tumors with *ATM* or *SETD2* loss (NCT04589845), or in combination with the PKMYT1 inhibitor (PKMYT1i) lunresertib for CDK4/ 6i resistant ER+/ HER2- metastatic breast cancer (NCT05601440) or advanced cancer (NCT05605509) are recruiting. Following termination of its collaboration agreement with Roche, Repare Therapeutics has regained global rights to camonsertib.

Gartisertib (M4344 or VX-803), developed by Vertex and bought by Merck in 2017, is a potent inhibitor of ATR-driven CHK1 phosphorylation with an IC_{50} of 8 nM and good binding affinity ($K_i < 150$ pM). It displayed good antiproliferative activity in a selected set of cancer cell lines, showing synergy with several types of DDRi, including ATM, PARP and CHK1 inhibitors (CHK1i). For instance, synergy between gartisertib and the ATMi lartesertib was demonstrated in PDX models of TNBC.[307] Gartisertib also provided good in vivo results as monotherapy in ALT+ tumors or in combination with talazoparib in TNBC xenografts.[308,309] Another preclinical study also found that gartisertib enhanced the activity of TOP1i, gemcitabine, cisplatin, and talazoparib.[252] These data supported the use of gartisertib in Phase I clinical trials as monotherapy or associated with carboplatin for advanced solid tumors (NCT02278250), and in combination with niraparib against PARPi-resistant ovarian cancer (NCT04149145) and advanced solid tumors (NCT04655183), although the last two trials were withdrawn based on portfolio prioritization. Results from the first trial (NCT02278250) with gartisertib as a single agent or associated with carboplatin for advanced solid tumors showed good tolerability at lower doses, but unexpected liver toxicity that prevented further dose escalation, and limited antitumoral activity, leading to the discontinuation of its development.[310]

Alnodesertib (ART0380) is an orally available ATRi that is being evaluated in the Phase I/II STELLA trial as monotherapy or in combination with gemcitabine or irinotecan in patients with *ATM*-deficient metastatic solid tumors (NCT04657068). Based on promising preliminary results from the STELLA study,[311] alnodesertib has recently won FDA Fast Track status for *ATM*-negative CRC.[312] Another Phase II basket study as monotherapy in patients with biologically selected advanced solid tumors was terminated (NCT05798611).

Finally, SC0245 is a novel ATRi that displayed potent activity for ATR/ATRIP with IC_{50} of 14 nM,[313] and is being studied in a Phase IB/II trial in patients with relapsed SCLC associated with irinotecan (NCT05731518). Preliminary results showed favorable safety and pharmacokinetic characteristics and antitumor activity.[314]

The diverse clinical outcomes of these ATRi, ranging from dose-limiting toxicities to promising "unmasking" of HRD, underscore the necessity for more precise biomarker-driven patient selection and optimized intermittent dosing schedules. Beyond *ATM* and *ATRX* loss, identifying drivers of high replication stress, such as *CCNE1* amplification, may further refine the target population. Furthermore, the ability of ATRi to trigger cytosolic DNA-sensing pathways (cGAS-STING) and induce 'viral mimicry' provides a robust mechanistic rationale for their continued development in combination with ICIs.

ATM inhibitors (ATMi)

ATM is an active serine/threonine kinase responsible for the regulation of checkpoints during the cell cycle in response to DNA DSBs. More concretely, ATM is an important initiator of the DDR via the MRN complex at DNA DSBs sites.[315,316] Active ATM then uses its kinase activity to phosphorylate multiple downstream targets such as BRCA1, CHK2 and p53 that are essential for DDR, apoptosis, cell cycle arrest, and as cell-cycle checkpoints.[317,318] For this reason, *ATM* is often considered a major tumor suppressor gene. Biallelic g*ATM* mutations result in the development of ataxia telangiectasia, a rare hereditary autosomal recessive disorder characterized by cerebellar degeneration, telangiectasia, immunodeficiency, cancer susceptibility and radiation sensitivity.[319]

Somatic mutations in *ATM* are commonly seen in cancer, especially in lymphoid malignancies.[320,321] In addition, *ATM* LOH

may arise through deletion of the long arm of chromosome 11, which often causes the co-deletion of other genes present on this site, such as *MRE11*, *CHK1* and *H2AX*.[322,323] Nevertheless, a key mechanism of ATM deficiency is the hypermethylation of the *ATM* promoter region.[324] Mutations in the gene downstream from the ATM/CHK2/p53 pathway, *CHK2*, although less common, are also observed across cancer types including colon, kidney, breast and prostate cancer.[325] However, the most frequently mutated gene across cancer types is *TP53*, which may also suffer LOH through allelic deletion of chromosome 17p in cancer.[326] Overall, as aberrations in the ATM/CHK2/p53 axis frequently occur in cancer, targeting these specific defects could contribute to effective cancer treatments. Moreover, although *ATM* deficiency causes loss of DSB DNA repair and consequently genomic instability, it also increases the dependence of cancer cells on other repair mechanisms, such as repair of replication stress, particularly in dividing cells. Based on this, the inhibition of other kinases (e.g., ATR) involved in these alternative pathways has been considered a potential mechanism for SL in cancers lacking *ATM*,[241] justifying the clinical exploration of ATMi in combination with ATRi. Besides, ATM kinase inhibition sensitizes cancer cells to the cytotoxic effects of IR and DSBs-inducing agents, such as etoposide and doxorubicin.[327] Specifically, ATMi act as potent radiosensitizers that by blocking ATM-mediated DNA damage signaling and checkpoint activation, prevent the repair of radiation-induced DSBs and enhance cancer cell lethality.[328,329] Crucially, ATM inhibition also promotes the accumulation of micronuclei and cytosolic DNA, which, similar to ATRi, activate the cGAS-STING pathway and increase lymphocyte infiltration into the TME, providing evidence that ATM might be a promising target to enhance ICI therapy.[330] Preclinical models also demonstrated that the inhibition of ATM potentiated the effects of olaparib in different cancer cell lines[328,331] and breast cancer xenografts.[327,329] In fact, an SL interaction between PARP and ATM was found in trastuzumab-resistant cells.[332]

A few ATMi are currently undergoing clinical trials (Supplementary Fig. S3). Firstly, AZD0156, which is an orally bioactive ATMi ($IC_{50} = 0.58$ nM),[333] was evaluated in a Phase I clinical trial alone or in combination with other antitumoral treatments in patients with advanced cancer (NCT02588105). This compound was later discontinued by AstraZeneca to prioritize the development of their other ATMi, AZD1390. AZD1390 is another ATMi that demonstrated to cross the intact blood–brain barrier in a positron emission tomography study with healthy volunteers (NCT03215381) and in a Phase 0/IB study in glioma patients (NCT05182905), supporting its indication for glioblastoma or other brain malignancies.[334] Indeed, this CNS-penetrant profile is a critical differentiator for the current generation of ATMi, as it allows for the potentiation of RT in the treatment of primary brain tumors and brain metastases, where previous inhibitors failed due to poor permeability. For this reason, this drug is currently being evaluated in a Phase I trial associated with RT in patients with brain cancer (NCT03423628). Preliminary results indicated good tolerability for AZD1390 and encouraging efficacy as radiosensitizer.[335] Preclinical data showed that AZD1390 blocks ATM-dependent DDR pathway activity and combined with RT induces G_2 cell cycle phase accumulation, micronuclei, and apoptosis. It was also able to radiosensitize lung cancer and *TP53*-mutant glioma cell lines. In PDXs of glioma and lung cancer brain metastasis, it significantly induced tumor regression and increased animal survival compared to IR alone.[328] Its role as radiosensitizer is also being studied in several Phase I trials in solid tumors (NCT04550104, NCT05116254 and NCT05678010). In addition, another Phase II/III is evaluating AZD1390 in combination with the SOC (RT + temozolomide) in newly diagnosed *MGMT* methylated and unmethylated glioblastoma (NCT03970447).

Another CNS-penetrant ATMi, WSD0628, also entered a Phase I trial (NCT05917145) with RT for recurrent brain tumors. This compound had previously shown a promising role in combination with RT in glioblastoma multiforme and melanoma metastatic to the brain in preclinical models.[336]

Lartesertib (M4076) is an ATP-competitive ATMi ($IC_{50} < 1$ nM) that was able to sensitize tumor cell lines to radiation in vitro and in vivo.[337] In a FIH study (NCT04882917) of lartesertib in patients with advanced solid tumors the MTD of this compound was determined, and target exposure and engagement were achieved without significant hematological toxicity.[338] Besides, based on the described SL mechanism between ATM and ATR, a Phase II trial in epithelial ovarian cancer (NCT06433219) and a Phase I in solid tumors (NCT05396833) combining lartesertib with the ATRi tuvusertib are ongoing. These two clinical trials are also studying lartesertib associated with the PARPi niraparib (NCT06433219) or with the anti-PD-L1 avelumab (NCT05396833).

Multiple other small-molecule ATMi are still in preclinical phases, and some others are not further being developed. For instance, the ATMi M3541 ($IC_{50} = 0.25$ nM) was also studied in a Phase I study in combination with palliative RT in solid tumors (NCT03225105), but it was prematurely terminated based on the sponsor's decision.[339] Additionally, several compounds that are under clinical development demonstrated inhibition capacity over different DDR kinases. For instance, XRD-0394 is a novel dual ATM/DNA-PK inhibitor developed by XRad Therapeutics that in a FIH study trial, potently radiosensitized the tumors and suggested synergy with PARPi and TOP1i (NCT05002140[340]). Another Phase 0/I study is being held to assess the safety and tolerability of XRD-0394 in combination with RT in patients with high-grade gliomas (NCT06829173).

In summary, while preclinical models suggest broad synergy with various DNA-damaging agents, clinical translation is currently focused on high-precision strategies. Efforts are concentrated on localized radiosensitization for CNS malignancies and, to a lesser extent, on SL-based combinations with ATR or PARP inhibitors and ICIs (e.g., avelumab). This shift prioritizes mechanistically grounded synergy over the overlapping systemic toxicities often encountered with traditional CTx.

DNA-PK inhibitors (DNA-PKi)

DNA-PK responds to DSB and plays a pivotal role in the c-NHEJ repair pathway. The DNA-PK holoenzyme comprises DNA-PKcs, a catalytic subunit with kinase activity, and Ku70/80 heterodimer, which is activated upon binding to broken DNA ends. Recent studies have demonstrated that overexpression of DNA-PK is associated with resistance to CTx and/or RT by promoting DSB repair through c-NHEJ,[341–343] and with poor prognosis.[344] Actually, DNA-PKi have been shown to impair DNA repair and re-sensitize cancer cells to chemo- and/or radiotherapeutic agents.[345,346] Several DNA-PKi are currently undergoing clinical trials (Supplementary Fig. S4).

CC-115 is an oral CNS-penetrant dual inhibitor of mammalian target of rapamycin (mTOR) kinase and DNA-PK with IC_{50} of 21 nM and 13 nM, respectively.[347] This compound was studied in a FIH trial (NCT01353625) for advanced solid and hematologic malignancies, where it showed toxicities consistent with mTOR inhibitors and promising efficacy, especially in an endometrial carcinoma patient who remained in complete remission for more than 4 years.[348] Another Phase IB trial (NCT02833883) of CC-115 in combination with enzalutamide in mCRPC showed good tolerability and a significant trend towards improved prostate-specific antigen response in patients with PI3K/AKT/mTOR pathway alterations.[349] In a Phase II trial (NCT02977780) comparing temozolomide with CC-115 for glioblastoma, CC-115 did not demonstrate a significant benefit in PFS or OS, and it was associated with high toxicity characteristic of mTOR inhibition.[350]

Peposertib (M3814, MSC2490484A or nedisertib) is another orally bioavailable DNA-PKi that was able to sensitize a variety of cancer cell lines to DSB-inducing agents and IR.[351] A FIH study in

advanced solid tumors or chronic myeloid leukemia (CML) (NCT02316197) showed good tolerability but modest efficacy of peposertib monotherapy.[352] In other Phase I trials, peposertib plus palliative RT was also well-tolerated (NCT02516813[353]), and antitumor activity was found limited when combined with avelumab with or without palliative RT in patients with advanced solid tumors (NCT03724890[354]). Additionally, in a Phase IB/II study (NCT03770689) associating this drug with capecitabine and RT for locally advanced rectal cancer, peposertib did not improve CR rates at tolerable dose levels.[355] Another clinical study (NCT04702698) did not detect the influence of food on peposertib's pharmacokinetics but suggested that when combining this drug with CTx or RT, the delay in maximum concentration should be considered to optimize the sensitization effect.[356] Finally, initial data of the Phase I trial (NCT04555577) of peposertib and RT in adults with newly diagnosed *MGMT*-unmethylated glioblastoma showed favorable safety and preliminary signs of efficacy potentiating the effect of RT.[357] Currently, a large number of other Phase I (e.g., NCT05868174, NCT04750954 and NCT04092270) and Phase I/II (e.g., NCT04172532, NCT04068194 and NCT04071236) clinical trials with this compound as monotherapy or in combination with CTx, RT and/or the ICI avelumab for different solid tumors are ongoing. An early evaluation of the Phase I/II trial in advanced prostate cancer not responsive to hormonal therapy (NCT04071236) showed good tolerability and a significant decrease in PSA velocity with the triplet combination of RT, peposertib and avelumab compared to the doublet (RT plus peposertib),[358] suggesting that DNA-PKi might enhance the "immunogenic" effect of RT. A European proof-of-concept therapeutic stratification Phase I/II trial of molecular anomalies in relapsed or refractory tumors is also studying peposertib associated with avelumab and metronomic temozolomide (NCT02813135). This compound is also being explored in a Phase I study with the ATRi tuvusertib for advanced solid tumors (NCT05687136).

AZD7648 is a DNA-PKi with IC_{50} value of 0.6 nM and >100-fold selectivity against mainly closely related kinases such as ATM, ATR and other PIKKs.[359] This compound enhanced RT, CTx and olaparib activity in xenografts.[216,360] A Phase I/IIA trial (NCT03907969) of AZD7648 alone or with doxorubicin in advanced cancer patients reported greater toxicity than expected with limited antitumor efficacy, what lead to early study termination. Proteomic analysis from this trial suggested that while target engagement was achieved at higher doses, it triggered compensatory activation of other DDR pathways, such as FA/BRCA and HRR, which may explain the limited efficacy.[361]

M9831 (VX-984) is a DNA-PKi that inhibits the repair of radiation-induced DNA DSB in glioblastoma cells and enhances the radiosensitivity of brain tumor xenografts.[362] This compound was studied in a Phase I trial in combination with CTx in advanced solid tumors (NCT02644278), but its development was discontinued during dose escalation due to business-related issues.[363]

BY101298 is an oral DNA-PKi from Chengdu Baiyu Pharmaceutical Co. that is currently undergoing a Phase I trial as a single agent or in combination with RT in patients with advanced solid tumors (NCT06462716). Preliminary results from a FIH trial (Chinese Clinical Trial Register information number: CTR20230997) reported that BY101298 exhibited a favorable safety profile and manageable toxicity for advanced solid tumors.[364]

Samotolisib (LY3023414, GTPL8918) is an oral ATP-competitive inhibitor of the class I PI3K isoforms, mTOR and DNA-PK that exhibits potent in vivo efficacy via intermittent target inhibition.[365] This compound demonstrated a manageable safety profile and single-agent activity in a FIH trial in patients with advanced cancers (NCT01655225[366]). Its pharmacokinetic profile was characterized by rapid absorption and elimination in another Phase I trial (NCT02536586[367]). A Phase IB/II (NCT02407054) study then investigated enzalutamide ± samotolisib for mCRPC with progression on prior abiraterone treatment, and found significantly improved PFS, and a clinically meaningful benefit in patients with *PTEN* intact and no androgen receptor splice variant 7.[368] In a Phase II study (NCT02549989) in patients with heavily pretreated advanced endometrial cancer prospectively selected for tumors with activating PI3K pathway mutations, samotolisib showed modest activity as monotherapy.[369] Moreover, in a Phase I trial (NCT02124148) associated with the CHK1i prexasertib, preliminary efficacy was detected in advanced cancer patients, although the combination led to some toxicity.[370] Based on this, another Phase II trial studied the efficacy of samotolisib plus prexasertib in patients with metastatic TNBC (NCT04032080), but results have not been published. Another Phase I trial is analyzing samotolisib and fulvestrant associated with the CDK4/6i abemaciclib for metastatic breast cancer (NCT02057133). However, in a Phase II trial (NCT02981342) testing this combination for pancreatic adenocarcinoma, abemaciclib-based therapy did not improve survival compared with SOC CTx.[371] In contrast, in a Phase I study (NCT02079636) for advanced NSCLC, stable disease as best response and acceptable safety were reported using combinations of abemaciclib and either samotolisib or pembrolizumab.[372] Samotolisib associated with abemaciclib ± letrozole is also being explored in a Phase II trial in endometrial or low-grade serous ovarian cancer patients (NCT03675893). Samotolisib has also been explored in a Phase II study (NCT02443337) in NSCLC patients associated with the FDA-approved EGFR antibody necitumumab, and although the combination was safe and tolerable, the study was terminated due to lack of efficacy.[373] Finally, a Phase II trial in pediatric patients with relapsed or refractory advanced solid tumors, NHL or *TSC1/2*- or PI3K/mTOR-mutated histiocytic disorders was completed, but results have not yet been reported (NCT03213678). Another Phase II pediatric study for treating patients with relapsed or refractory advanced solid tumors, NHLs or histiocytic disorders is ongoing (NCT03155620).

Despite the encouraging clinical progress of some DNA-PKi, the development of these compounds faces some challenges. Firstly, the difficulty in achieving good selectivity for DNA-PK over other closely related PI3K-family members due to high structural homology, often resulting in off-target mTOR-related toxicities (as seen with CC-115).[374,375] While recent Cryo-EM advancements have resolved the activated DNA-PK holoenzyme at near-atomic resolution, the protein's vast size and inherent conformational plasticity continue to hinder the discovery of inhibitors of this kinase using computer modeling.[374,376] Given the modest efficacy of DNA-PKi as monotherapy, it seems that the field is pivoting toward the identification of combination therapies that may improve the antitumoral effect of DNA-PKi.[377] As c-NHEJ is the primary mechanism for the repair of radiation-induced damage, lots of efforts are focused on the role of DNA-PKi as radiosensitizers.[378,379] However, emerging clinical strategies are exploring synergy with TOP1i (e.g., the dual ATM/DNA-PK inhibitor XRD-0394) and ATRi (e.g., peposertib plus tuvusertib in NCT05687136).

CHK1/2 inhibitors (CHK1/2i)

CHK1 and CHK2 are two serine/threonine-protein kinases that represent the key downstream effectors of the checkpoint-associated ATR-CHK1 and ATM-CHK2 pathways, respectively. While CHK1 is essential for HRR of DSBs and its expression is restricted to S and G_2 phases of the cell cycle, CHK2 is stably expressed all throughout the cell cycle, but inactive in the absence of DNA damage. Although structurally unrelated, these two kinases exhibit overlapping functions.[380]

Several CHK1/2i are being clinically evaluated (Supplementary Fig. S5). Firstly, prexasertib (LY2606368 or ACR-368) displays IC_{50} values of <1 nM for CHK1 and of 8 nM for CHK2.[381] In Phase II clinical trials, monotherapy with this drug showed modest activity in patients with *BRCA1/2* wild-type metastatic/recurrent TNBC

(NCT02203513[382]) and no activity in patients with extensive-stage SCLC (NCT02735980[383]). In contrast, prexasertib demonstrated durable single-agent activity regardless of clinical characteristics, *BRCA1/2* status, or prior therapies (including PARPi) in another Phase II trial (NCT03414047) for PtR or refractory recurrent ovarian cancer.[384] Besides, another Phase II (NCT02873975) explored the role of replication stress or HRR deficiencies (alterations in *BRCA1/2*, *PALB2*, *RAD51C/D*, *ATR*, *ATM*, *CHK2* or FA genes) in the response to prexasertib, but results have not been reported. Another Phase II study analyzed the efficacy of prexasertib plus the dual PI3K/mTOR and DNA-PK inhibitor, samotolisib (LY3023414), in patients with metastatic TNBC (NCT04032080), based on preclinical and clinical (Phase I, NCT02124148) data showing antitumor activity with this combination.[370] Two other Phase II of prexasertib combinations are ongoing: associated with irinotecan and temozolomide for desmoplastic small round cell tumor and rhabdomyosarcoma (NCT04095221) and with low-dose gemcitabine for HNSCC (NCT06597565). Preliminary results from the first trial with irinotecan showed promising activity with manageable adverse events.[385] Prexasertib is also being studied as monotherapy or with ultra-low dose gemcitabine in ovarian carcinoma, endometrial adenocarcinoma, and urothelial carcinoma (NCT05548296), using the phosphoproteomics ACR-368-tailored OncoSignature assay from Acrivon Therapeutics as a predictive biomarker of response.[386]

SRA737 (CCT245737) is another orally active CHK1i[387] that was found to be SL with members of the B-family of DNA polymerases (*POLA1*, *POLE*, and *POLE2*) in human lung and colorectal cancer (CRC) cells.[388] When associating SRA737 with PARPi this resulted in tumor regression in both PARPi-resistant and *CCNE1*-amplificated ovarian cancer PDX models.[211] This compound was studied in a Phase I/II clinical trial (NCT02797964) as monotherapy in patients with NHL or solid tumors, where it showed good tolerability, but no activity. Expansion cohorts in this study included patients with tumors harboring specific genetic alterations expected to confer sensitivity to CHK1 inhibition (e.g., in *TP53*, *PTEN*, *CDKN2A/B* and *ATM*). No differences in response in these subpopulations were observed.[389] Based on the lack of efficacy as monotherapy, another Phase I/II trial (NCT02797977) then explored SRA737 in combination with low-dose gemcitabine and cisplatin or gemcitabine alone in advanced cancer subjects. The combination of SRA737 and low-dose gemcitabine was well tolerated with lower myelotoxicity than in other similar trials, and partial tumor responses were identified in anogenital and other solid tumors, especially in patients with genomic alterations in the FA/BRCA pathway or in *CDK12/ARID1A*, and intermediate to high tumor mutational burden and possible increased replication stress.[390]

BBI-355 is a small molecule CHK1i ($IC_{50} = 16$ nM), developed as an extrachromosomal DNA (ecDNA)-directed therapy. Preclinical data showed synergistic antitumoral activity between oral BBI-355 and agents targeting amplified *EGFR* or *FGFR2* oncogenes in multiple ecDNA-positive gastric cancer CDXs and PDXs.[391] In consequence, this drug is being evaluated in a FIH clinical trial (NCT05827614) as a single agent or in combination with select targeted therapies (the ribonucleotide reductase inhibitor BBI-825, the EGFR inhibitor erlotinib and the FGFR1-4 inhibitor futibatinib) in patients with solid tumors with oncogene amplifications (e.g., *EGFR*, *FGFR2*). While the SL hypothesis between CHK1 inhibition and oncogene-amplified ecDNA was preclinically strong, the Phase I data revealed a narrow therapeutic index and significant hematological toxicity that prevented reaching the doses needed for robust antitumor activity. Based on this, monotherapy and combination arms of BBI-355 in this clinical trial have been recently discontinued.

The oral and selective ATP-competitive CHK1i ESP-001 (LY2880070) is being explored in two Phase I/II trials: in participants with advanced or metastatic solid tumors as monotherapy and in combination with gemcitabine (NCT02632448) and in a Phase II for Ewing sarcoma or Ewing-like sarcoma in combination with low-dose gemcitabine (NCT05275426). Preliminary results from the first trial (NCT02632448) reported generally good tolerability and promising efficacy in combination with low-dose gemcitabine in patients with advanced or metastatic ovarian cancer.[392] Strikingly, although no evidence of clinical activity was observed for pancreatic adenocarcinoma, in vitro efficacy was observed for the combination in patient-derived organoids.[393]

PEP07 (CASC-578) is an oral CNS-penetrant CHK1i that is being studied in two Phase I trials as a single agent for advanced or metastatic solid tumors (NCT05983523) and AML and mantle cell lymphoma (NCT05659732). PEP07 was active as monotherapy in lung cancer xenografts and displayed synergistic antitumoral activity in combination with the WEE1i AZD-1775 in multiple solid tumor cell lines and in NSCLC tumor xenografts.[394]

SMP-3124LP is a liposome-encapsulated CHK1i developed by Sumitomo Pharma America that showed tumor regression in PDX models of ovarian cancer,[395] leading to the initiation of a Phase I/II trial (NCT06526819) in patients with advanced solid tumors.

In recent years, several other clinical-stage CHK1i have been discontinued. GDC-0575 (ARRY-575, RG7741) is a potent CHK1i discovered by Array BioPharma and developed by Genentech (subsidiary of Roche) that demonstrated synergistic effect with CTx in cancer cells, PDX models and patient tumors.[396,397] In a Phase I study in combination with gemcitabine in patients with refractory solid tumors, antitumoral activity was observed but limited to a small number of patients (NCT01564251[398]). Rabusertib (LY2603618) is another CHK1i that in a Phase I trial (NCT01139775) in combination with pemetrexed and cisplatin, showed partial response in 2 NSCLC patients and stable disease in 8.[399] In the posterior Phase II part, an increased number of thromboembolic events were detected with this combination.[400] In contrast, no significant clinical activity was found of LY2603618 combined with pemetrexed in another Phase II study (NCT00988858) in patients with advanced NSCLC[401] and in a Phase I/II trial (NCT00839332) in combination with gemcitabine for pancreatic cancer.[402] In consequence, the development of this compound was discontinued. The same happened with AstraZeneca's CHK1i AZD7762 owing to the unpredictable cardiac toxicity detected in a Phase I study (NCT00413686[403]). As for another CHK1i, MK-8776 (SCH900776), despite evidence that augmented DNA damage in circulating leukemic blasts in a Phase II trial (NCT01870596) with cytarabine in relapsed AML patients,[404] it seems to have been discontinued by Merck. This compound was also included in a Phase I trial for participants with solid tumors or lymphoma with and without gemcitabine (NCT00779584).

PHI-101 is a CHK2i with additional activity against FLT3 tyrosine kinase that showed preclinical antitumoral activity in ovarian and breast cancer cell lines. Moreover, in vivo studies suggested a synergistic effect between PHI-101 and PARPi for breast and ovarian cancer treatment.[405] This drug is being studied in a Phase IA dose-escalation study for PtR ovarian, fallopian tube, and primary peritoneal cancer (NCT04678102). As mutations in *FLT3* are the most common genetic alteration in AML,[406] and PHI-101 also inhibits FLT3, it is being explored in a Phase I trial in AML (NCT04842370). Preliminary data showed good tolerability and significant efficacy, particularly in *FLT3*-mutant AML.[407]

The clinical landscape of CHK1/2i is increasingly defined by biomarker-driven stratification and the exploitation of replication stress. While broad application has been hindered by toxicities, exemplified by the recent discontinuation of the ecDNA-directed agent BBI-355 due to a narrow therapeutic window, the success of prexasertib in serous endometrial cancer validates the use of phosphoproteomic signatures to identify SL vulnerabilities. Furthermore, the field is pivoting toward 'induced SL' by pairing CHK1i with replication stressors (e.g., ultra-low dose gemcitabine associated with prexasertib in NCT05548296), as well as toward the inclusion of expansion cohorts with specific genetic

abnormalities expected to confer sensitivity to CHK1 inhibition (e.g., *CCNE1* amplification, *BRCA1/2* or *ATM* deficiency or GOF/amplification of *CHK1* or *ATR*, amongst others) due to high replication stress.

WEE1, PKMYT1, CDKs and PLK1 inhibitors

WEE1 is a nuclear-localized protein kinase that inhibits both CDK1 and CDK2 in response to DNA damage, thereby activating the G_2/M checkpoint of the cell cycle to allow time for DNA repair.[408] Cancer cells with dysregulated G_1/S cell cycle checkpoints rely on functional G_2/M checkpoints to prevent excessive DNA damage.[409] Since p53-deficient cells lack a functional G_1 checkpoint, they become uniquely and broadly dependent on the WEE1-regulated G_2/M arrest to maintain genomic stability. Therefore, blocking G_2/M checkpoints with WEE1i results in loss of genomic integrity due to increased replication stress.[410] Several preclinical studies have confirmed that this dependency creates a 'classic' SL interaction, where WEE1i causes mitotic lethality specifically in p53-deficient cells and sensitizes them to RT and DNA-damaging agents.[30,32] Moreover, using the knowledge of the SL interaction between *ATRX* and *WEE1*, researchers reported that the proliferation of glioma and hepatocellular cells with *ATRX* mutations was selectively inhibited with the WEE1i adavosertib.[411] Furthermore, cyclin E1, encoded by the *CCNE1* gene, interacts in normal cells with CDK2 to drive the transition from G_1 to S phase, where DNA replication occurs. Upon DNA damage, WEE1 phosphorylates and inactivates the cyclin E1/CDK2 complex to halt cell cycle progression and allow time for repair. In many malignancies (e.g., gynecological cancers) *CCNE1* amplifications cause CDK2 hyperactivation, accelerating G_1/S cell cycle progression and inducing massive replication stress.[412] Mutations in other regulators of G_1/S transition, such as *TP53* and *CDKN2A*, exacerbate the effects of *CCNE1* amplification. In this high replication stress state, cancer cells become "addicted" to the S and G_2/M checkpoints to prevent premature and lethal entry into mitosis before DNA replication is completed.[413,414] Consequently, these tumors are highly susceptible to WEE1 inhibition, which forces a "mitotic catastrophe" driven by premature CDK1/cyclin B complex activation in the presence of CDK2-mediated replication stress. This mechanism provides a robust framework for SL, where WEE1i synergize with different DNA-damaging agents to overwhelm the cell's repair capacity. Several of these agents have progressed to clinical trials (Supplementary Fig. S6).

Adavosertib (AZD1775 or MK-1775) is a potent WEE1i that was able to induce apoptosis and arrest at G_2/M in trastuzumab-resistant breast cancer cells.[415] *CCNE1* overexpression was able to sensitize TNBC cells and PDX to adavosertib.[416] Adavosertib also led to tumor inhibition and enhanced gemcitabine efficacy in sarcoma cells.[417] Several Phase I clinical trials for cancer treatment were performed with this compound as monotherapy or in combination with CTx/RT (e.g., NCT00648648 and NCT02037230) and found that adavosertib was in general safe and tolerable.[418,419] Several Phase II studies are ongoing or have already been completed. Clinical benefit was observed in a Phase II trial of adavosertib plus paclitaxel and carboplatin in women with PtS *TP53*-mutant ovarian cancer (NCT01357161[420]). Subsequently, in Phase II clinical trials, adavosertib also enhanced carboplatin (NCT01164995[421]) and gemcitabine (NCT02101775, also known as NCT02151292[422]) efficacy in *TP53*-mutated tumors. Moreover, adavosertib demonstrated clinical potential in *RAS*/*TP53*-mutant metastatic CRC in another Phase II trial (EUDRACT 2012-005111-12[423]). In a biomarker-driven SCLC umbrella study, no objective response was found with adavosertib monotherapy, but stable disease was observed in 25% of the patients without selected biomarker and in 43% of the participants with *MYC* family amplification or *CDKN2A* and *TP53* co-alteration (NCT02593019[424]). In another study (NCT02513563) with the same cancer type, the primary endpoint (mPFS of 4.8 months) was met with the combination of adavosertib with carboplatin and paclitaxel, but response rates and mPFS of Pt-doublet combination were similar to historical data from other trials.[425] No ORRs were observed in another Phase II trial in SCLC combining adavosertib plus carboplatin (NCT02937818[426]). These results underscore the necessity of improved combinatorial approaches or stringent biomarker selection in SCLC. Based on data indicating that TNBC models harboring *CCNE1* amplification exhibited higher sensitivity to adavosertib,[416] a Phase II study was designed to assess adavosertib in patients with *CCNE1*-amplified, advanced refractory solid tumors (NCT03253679). Adavosertib monotherapy showed promising clinical activity in *CCNE1*-amplified solid tumors, especially in ovarian cancer,[427] as well as in uterine serous carcinoma (NCT03668340[428]). Antitumor activity was also observed in patients with the same cancer type previously treated with Pt (NCT04590248[429]), and when combined with CTx in patients with PtR ovarian cancer (NCT02272790[430]). Contrarily, adavosertib combined with cisplatin in metastatic TNBC missed the pre-specified cutoff of >30%. The finding of immune-infiltrated tumors in patients experiencing clinical benefit suggested further study of the combination between WEE1i and PD-1/PD-L1 inhibitors (NCT03012477[431]). Meaningful response was not detected when combining adavosertib with carboplatin for advanced solid tumors (NCT01827384[432]). However, when combined with gemcitabine and RT for pancreatic cancer in a Phase I/II trial (NCT02037230), OS was substantially higher than prior results of gemcitabine with RT.[419] Finally, results from the first Phase II study of adavosertib in pediatrics with irinotecan demonstrated that the association was of sufficient activity to support further study in neuroblastoma, and possibly other pediatric tumor types with recurrent *ATRX* mutation (NCT02095132[433]). The increased level of hematologic toxicity reported for adavosertib as a single agent or in combination has become a challenge in several clinical trials and should be further studied to optimize the treatment with this drug.[430]

Azenosertib (ZN-c3) is another selective, and orally bioavailable WEE1i that has progressed to clinical trials. A Phase I study of this compound for solid tumors (NCT04158336) showed early signal of clinical activity and appeared to be safe and tolerable as a single agent.[434] Particularly, azenosertib demonstrated clinical activity in subjects with recurrent or advanced uterine serous carcinoma,[435] which is currently being validated in a Phase II study in these patients (NCT04814108). Also ongoing is the Phase II DENALI trial (NCT05128825) of azenosertib in PtR ovarian cancer, which consists of a first part enrolling patients without considering biomarker status, and a second one testing patients for cyclin E1 overexpression. Preliminary results reported clinically meaningful response rates and duration of response with azenosertib monotherapy in women with cyclin E1-positive tumors.[436] Another Phase II biomarker trial of azenosertib for uterine serous carcinoma is ongoing (NCT06369155). Azenosertib was tested in combination with niraparib in a Phase I trial (MAMMOTH trial) in subjects with PtR ovarian cancer who had failed PARPi MT (NCT05198804), but as efficacious drug exposures were not reached, this combination is not further being studied.[437] Azenosertib plus CTx or bevacizumab is being explored in a Phase IB trial in patients with PtR or refractory ovarian cancer (NCT04516447). Preliminary data indicated that the association was well-tolerated and exhibited encouraging clinical activity, with durable responses. Remarkably, patients with cyclin E1 overexpressing tumors demonstrated significantly higher improvement in ORR and PFS.[438] This compound is also being explored in another Phase I in participants with metastatic *BRAF* V600E mutant CRC in association with the BRAF inhibitor (BRAFi) encorafenib and cetuximab (NCT05743036). While the results in BRAFi-naïve patients were encouraging, the sponsor decided not to proceed with the dose expansion phase due to resource prioritization and an evolving treatment landscape.[437] Regarding pancreatic cancer,

a Phase I trial (NCT04005690) aiming to identify biomarkers of response, and a Phase II (NCT06015659) testing the association of azenosertib and gemcitabine are also enrolling. Two Phase I/II studies are testing azenosertib plus carboplatin and pembrolizumab for metastatic TNBC (NCT06351332), and plus gemcitabine in both adult and pediatric subjects with relapsed or refractory osteosarcoma (NCT04833582). Preliminary results showed greater event-free survival than historical control cohorts of salvage therapy in these patients.[439] Finally, a Phase I trial is analyzing azenosertib associated with trastuzumab for stomach cancer or other solid tumors (NCT06364410). Based on the positive results, azenosertib was granted FDA Fast Track status in January 2025 for patients with PtR epithelial ovarian, fallopian tube or primary peritoneal cancer with cyclin E1 overexpression.[440]

Debio-0123 is an orally available CNS-penetrant ATP-competitive WEE1i that has progressed to clinical trials. A Phase I trial of Debio-0123 with carboplatin in advanced solid tumors (NCT03968653) showed a manageable safety profile and observable preliminary antitumor activity.[441] This compound also elicited strong synergy with the PKMYT1i lunresertib in preclinical models of *CCNE1*-overexpression and in a tumor xenograft using intermittent Debio-0123/lunresertib dosing at subtherapeutic monotherapy doses.[442] Based on these data, a Phase I study (NCT04855656) of lunresertib alone or in combination with Debio-0123 in patients with *CCNE1*-amplified or *FBXW7*-/*PPP2R1A*-mutant advanced solid tumors is ongoing. Preliminary results showed that the combination is safe and effective in these patients.[443] This strategy, targeting both WEE1 and PKMYT1, aims to maximize CDK1 hyperactivation while preventing compensatory survival mechanisms. In another Phase I (NCT05815160), Debio-0123 in combination with carboplatin and etoposide has led to promising antitumor activity with good tolerability in participants with recurrent SCLC previously treated with standard Pt.[444] Preliminary data from another Phase I (NCT05109975) have reported that continuous dosing of Debio-0123 as monotherapy exhibits a manageable safety profile and linear pharmacokinetics for advanced solid tumors.[445] Moreover, in preclinical models of glioblastoma, Debio-0123 demonstrated significant efficacy as monotherapy and improved response to CTx or RT.[446] This evidence supported the design of a Phase I/II study in combination with temozolomide for recurrent glioblastoma, and with temozolomide and RT for newly diagnosed glioblastoma (NCT05765812). Additionally, based on synergistic antitumoral activity of Debio-0123 associated with sacituzumab govitecan in preclinical models of breast cancer,[447] a Phase I/II evaluating this combination in TNBC or HR+/ HER2- advanced breast cancer has recently started (NCT06612203).

The other WEE1i that are currently undergoing clinical trials are potrasertib, SY-4835 and APR-1051. Potrasertib (IMP7068) is a potent and selective WEE1i being tested in a Phase I study for advanced solid tumors (NCT04768868). Preliminary results showed that IMP7068 was well-tolerated and exhibited a meaningful pharmacodynamic effect and preliminary antitumor activity.[448] SY-4835 (NCT05291182) and APR-1051 (NCT06260514) are other WEE1i being studied in FIH studies in patients with advanced solid tumors.

PKMYT1, also named Myt1, is a cell cycle-regulating kinase similar to WEE1 that acts by negatively regulating CDK1 through its phosphorylation and cytoplasmic sequestration.[449] *CCNE1* amplification is SL with PKMYT1 inhibition. In fact, the overexpression of *CCNE1* disrupts CDK1 homeostasis.[450] WEE1 and PKMYT1 were also found to be SL,[451–453] as simultaneous WEE1 and PKMYT1 inhibition synergistically promoted CDK1/2 activation, aggravating DNA replication stress and fork replication collapse, providing a potential approach for cancer treatment. Upregulation of PKMYT1 promoted acquired resistance of cancer cells to the WEE1i adavosertib, an effect that was reversed by PKMYT1 knockdown.[454] Repare Therapeutics has developed a first-in-class PKMYT1i, lunresertib (RP-6306), that is currently undergoing Phase I and II clinical trials (e.g., NCT05601440, NCT05605509 and NCT06107868) for different solid tumors alone or in combination with CTx, the ATRi camonsertib or the WEE1i Debio-0123 in patients with specific mutation profiles (e.g., *TP53*/*KRAS*/*FBXW7*/*PPP2R1A* mutations or *CCNE1* amplifications). This is based on preclinical data reporting synergy of lunresertib and the ATRi camonsertib to induce cytotoxicity and durable antitumor activity in *CCNE1*-amplified ovarian and endometrial cancer cell lines, CDXs and PDXs, especially in those carrying genomic biomarkers predictive of lunresertib sensitivity (*CCNE1* amplification and *FBXW7* and *PPP2R1A* LOF).[455] Results from the Phase I MINOTAUR study (NCT05147350) showed that the combination of lunresertib and FOLFIRI was well tolerated and demonstrated promising efficacy in heavily pretreated patients with *CCNE1*-amplificated and *FBXW7*-mutant advanced gastrointestinal cancers.[456] A strong response was also reported from the MYTHIC Phase I clinical trial (NCT04855656) evaluating the combination of lunresertib and camonsertib in patients with endometrial cancer and PtR ovarian cancer harboring lunresertib-sensitizing biomarkers (*CCNE1* amplifications and mutations in *FBXW7* or *PPP2R1A*).[457]

To address the limitations of monotherapeutic checkpoint targeting, ACR-2316 has emerged as a potential first-in-class, dual WEE1/PKMYT1 inhibitor. Unlike combinatorial approaches that use two separate drugs, ACR-2316 is a single small molecule rationally designed to prevent the compensatory PKMYT1 signaling that typically results in WEE1i resistance.[458] Preclinical data using Acrivon's Predictive Precision Proteomics (AP3) platform demonstrated that ACR-2316 induces superior DNA damage and mitotic catastrophe compared to selective WEE1i.[459] This drug is currently being evaluated in a Phase I study (NCT06667141) for advanced solid tumors.

Inhibitors of the different CDKs have also entered clinical trials. The most clinically advanced are the CDK4/6 inhibitors (CDK4/6i), palbociclib (Ibrance®), ribociclib (Kisqali®), and abemaciclib (Verzenio®), which have received global approvals for metastatic breast cancer and are also included in Phase III clinical trials (eg., NCT04966481, NCT04862663 and NCT02152631). Newer generations of inhibitors are directed to other CDK family members, such as CDK2 (e.g., AVZO-021, INCB123667, PF-07104091 and INX-315), CDK7 (e.g., samuraciclib, Q-901 and SY-5609) and CDK9 (e.g., PRT2527). Some pan-CDK inhibitors (e.g., seliciclib and milciclib) are also being developed, although the trend is toward more selective therapeutics. Sensitivity to these agents has been related to reduced expression of the genes *CDKN2A*,[460] which codifies for the CDK4/6 inhibitors $p16^{INK4a}$ and $p14^{ARF}$, *CCNE1*[461] and *TP53*,[462] and to increased expression of MYC,[463] *CCND1* and the retinoblastoma tumor suppressor gene (*RB1*).[461] As for CDK4/6i, palbociclib demonstrated antitumor activity in patients with *CDKN2A* alterations in Phase II trials in chordoma (NCT03110744) and head and neck cancer (NCT02693535).[464,465] Additional alterations in *PIK3CA*, *PTEN*, *MTAP*, or *MET* genes related to response were identified.[465] Resistance to palbociclib was detected in tumors with high *CCNE1* mRNA expression in a Phase III trial (NCT01942135) testing palbociclib plus fulvestrant.[466] While the other CDK4/6i abemaciclib, showed better outcomes in patients with anaplastic thyroid cancer (NCT04552769[467]) and mesothelioma (NCT03654833[468]) with *CDKN2A* loss, some other clinical trials failed to identify sufficient activity with this drug in *CDKN2A*-deficient tumors.[469,470] Palbociclib and abemaciclib monotherapy did not demonstrate clinical activity in two trials in patients with pretreated *RB1*-positive anaplastic oligodendroglioma (NCT02530320[471]) or metastatic TNBC (NCT03130439[472]), respectively. Amongst the different hypotheses for this lack of response, the authors of the last study suggested this could be due to the rewiring of the cell cycle machinery in these tumors rendering them non-dependent on CDK4/6.[472] In addition,

abemaciclib-based therapy (e.g., associated with the PI3K/mTOR/DNA-PK inhibitor samotolisib) did not show clinical benefit in a Phase II trial (NCT02981342) in pancreatic ductal adenocarcinoma patients.[371] A Phase IB clinical trial (NCT02057133) is currently analyzing the combination of abemaciclib, samotolisib and fulvestrant in metastatic breast cancer patients. Meanwhile, the CDK2 inhibitor INCB123667 showed encouraging antitumor activity in a Phase I study (NCT05238922) in patients with advanced PtR and refractory ovarian cancer and cyclin E1 overexpression,[473] which is currently being explored in Phase II (NCT07023627) and III (NCT07214779) trials. Based on the inconsistent clinical outcomes with CDK inhibitors, further studies on the mechanisms of response and resistance to these drugs should be performed.

PLK1 is another serine/threonine kinase that displays a key role as a regulator of mitosis by participating in the cell cycle G_2/M checkpoint. After being activated by AURKA, PLK1 inhibits WEE1 and PKMYT1 via their phosphorylation, resulting in the consequent activation of CDKs.[474,475] *PLK1* has been found to be overexpressed in cancer, often associated with poor outcomes.[476] The clinical progression of PLK1 inhibitors has been constrained by the appearance of resistance and by lack of PLK1 selectivity, which causes low efficacy and dose-limiting toxicities.[477] PLK1 contains two main domains, the kinase domain and the polo-box domain.[478] According to this, the different PLK1 inhibitors can be classified as ATP competitors (e.g., volasertib and onvansertib), which compete with ATP for binding the kinase domain, and non-ATP competitors (e.g., allopole), which target the polo-box domain. The discovery of SL interactions between *PLK1* and *KRAS*,[479] *BRCA1*,[480] *CCND1*,[481] *TP53*,[482] *MYC*[483] and FA/BRCA pathway genes,[484] amongst others, has opened a new path to the clinical application of PLK1 inhibitors for tumors with specific alterations in these genes. In fact, onvansertib was granted the Fast Track Designation by the FDA for its development as second-line treatment in patients with *KRAS*-mutated metastatic CRC associated with FOLFIRI and bevacizumab.[485] Significant activity was reported in the Phase IB/II trial (NCT03829410) analyzing this combination, particularly in patients without prior exposure to bevacizumab.[486] This led to the exploration of the combination in the first-line setting (NCT06106308). Another Phase II trial is assessing whether onvansertib is useful in patients with relapsed SCLC carrying *TP53* mutations or *MYC* overexpression (NCT05450965).

In summary, the clinical landscape of cell cycle inhibitors is undergoing a paradigm shift from broad applications toward biomarker-driven precision strategies and multi-node checkpoint disruption. While first-generation WEE1i inhibitors like adavosertib provided proof-of-concept, their clinical utility was constrained by a narrow therapeutic window and hematologic toxicities. The emergence of more selective agents, such as the WEE1i azenosertib and the first-in-class PKMYT1i lunresertib, and of the next-generation dual WEE1/PKMYT1 inhibitor ACR-2316, represents a new frontier in the exploitation of SL in this context. The clinical success of these next-generation therapeutics increasingly relies on the identification of robust predictive biomarkers (most notably *CCNE1* amplification and *FBXW7*/*PPP2R1A* mutations) and the implementation of combinatorial strategies that prevent bypass signaling. However, maximizing the utility of these biomarkers will require overcoming clonal heterogeneity, potentially through the integration of liquid biopsies (ctDNA) to monitor real-time SL dependencies and guide adaptive treatment strategies. The FDA's recent regulatory milestones for these compounds underscore a growing confidence in targeting G_2/M and S-phase dependencies. Future efforts must focus on optimizing intermittent dosing schedules and identifying mechanisms of acquired resistance to fully integrate these cell cycle modulators into the standard of care for refractory solid tumors.

POLQ inhibitors (POLQi)

Another target being explored within the end-joining pathway, in particular the alt-NHEJ, is Polθ, also called POLQ. The helicase domain of POLQ is responsible for annealing small sequences of microhomology flanking the DSB that are then repaired by the polymerase domain.[487] *POLQ* is upregulated in numerous cancers and its overexpression is associated with poor prognosis.[488,489] Several preclinical studies showed that *POLQ* deficiency is SL with various DDR pathway genes, including *BRCA1/2*, *ATM*, *ATR*, *XRCC6* (encoding the Ku70 protein), *RAD52* and *FANCD2*.[215,217,490–493] Furthermore, as HRD cancer cells seem to overexpress POLQ and be hypersensitive to POLQ knockdown,[217] an inhibitor of POLQ could constitute a promising drug to be associated with PARPi to avoid the acquisition of reversion mutations and restoration of HRR-activity in these tumors.

The availability of crystal structures for both the helicase and the polymerase domain of POLQ has helped in the development of potent inhibitors of this protein,[494,495] since both domains contain druggable sites.[494] Four main biotech companies have developed POLQi that are currently in clinical trials: Artios Pharma (Cambridge, UK), IDEAYA Biosciences (San Francisco, USA), Repare Therapeutics (Montreal, Canada) and Synrx Therapeutics (Hangzhou, China). The structure of these compounds has not yet been disclosed. It has been reported that POLQ might contribute to the acquisition of PARPi resistance,[219] which may occur via loss of *53BP1*, an SL gene with *POLQ*.[491,496] This leads to the conclusion that using POLQi in combination with PARPi, or as second-line therapy, might prolong drug response and delay the acquisition of resistance.

Artios Pharma is clinically evaluating two POLQi, ART4215 and ART6043, as monotherapy and in combination with other drugs. ART4215 is a highly selective, oral small molecule inhibitor targeting the POLQ polymerase domain, which is included in a Phase I/IIA trial as monotherapy and in combination with the PARPi talazoparib in advanced or metastatic solid tumors (NCT04991480). ART6043 is another selective, orally bioavailable, small-molecule inhibitor of POLQ that is being explored in a Phase I/IIA study for advanced/ metastatic solid tumors as monotherapy or in combination with PARPi olaparib or niraparib (NCT05898399). Based on encouraging clinical activity and good tolerability reported in this trial,[497] the FDA has recently granted Fast Track Designation to ART6043 in combination with olaparib for g*BRCA1/2*m HER2- locally advanced or metastatic breast cancer not priorly exposed to a PARPi.

GSK4524101 (GSK-101 or IDE705) is being developed by IDEAYA Biosciences as a POLQi in combination with niraparib in a GSK-sponsored Phase I/II clinical trial for solid tumors (NCT06077877).

The SYN818 from Synrx Therapeutics entered clinical trials with a Phase I study (NCT06666270) administered orally for advanced solid tumors and showed a preliminary favorable safety profile.[498]

Repare Therapeutics is developing the POLQ ATPase inhibitor RP-3467. This compound is being studied in a FIH trial alone and in combination with olaparib for advanced solid tumors (NCT06560632).

Similar to RP-3467, the antibiotic novobiocin was identified in a high-throughput screen as a specific POLQ ATPase inhibitor that selectively kills HRD tumor cells in vitro and in vivo (Supplementary Fig. S7).[220] A Phase I trial (NCT05687110) sponsored by the National Cancer Institute is studying novobiocin in patients with solid tumors carrying HRR or DDR alterations that are PARPi-naïve or exhibit resistance to these drugs.

Collectively, the rapid clinical progression and regulatory support for POLQi underscore their potential to transform the treatment landscape for HRD malignancies, particularly as a strategy to circumvent or overcome the limitations of current PARPi therapies.

USP1 inhibitors (USP1i)

USP1, which is associated with UAF1, is a deubiquitinating enzyme involved in regulating both the FA/BRCA pathway and TLS by

deubiquitinating the FANCI/FANCD2 complex and PCNA, respectively.[499,500] *USP1*-deficient mice harbor genomic instability and are highly sensitive to DNA damage, resembling the FA phenotype. Meanwhile, *USP1*$^{-/-}$ cells exhibit impaired FANCD2 foci assembly and a defect in HRR and induced growth arrest at G_2/M.[501,502] The inhibition of USP1 by different USP1i also sensitized cancer cells to chemotherapeutic agents, including Pts, doxorubicin, PARPi and TOPI/II inhibitors.[502–504]

USP1i are another class of inhibitors that have recently entered clinical trials with the orally bioavailable compound KSQ-4279 from KSQ Therapeutics (Supplementary Fig. S8). Mechanistic studies indicated that the accumulation of ubiquitinated PCNA was the likely cause of SL in *BRCA1/2*/HRD cell lines. Synergistic activity was frequently observed with PARPi across a large panel of cancer cell lines, and especially in those with *BRCA1/2* alterations.[505] More concretely, RO7623066 (KSQ-4279 or RG6614) is a potent and selective USP1i that was identified using the CRISPRomics platform from KSQ Therapeutics. In 2023, the compound entered a worldwide license and collaboration agreement with Roche. Preclinical data demonstrated the capacity of this compound to induce durable tumor regression of PARPi–resistant tumors when dosed in combination with PARPi.[504] Based on this data, RO7623066 is being tested in a Phase I clinical trial alone and in combination with PARPi in patients with advanced solid tumors (NCT05240898).

XL309 (previously ISM3091) is another orally bioavailable USP1i identified through Insilico Medicine's artificial intelligence platform that has been recently licensed to Exelixis for its global development and commercialization. In vitro data revealed synergistic activity between XL309 and olaparib in HRD cell lines. Dose-dependent single-agent inhibitory activity was also observed in multiple CDX and PDX models. The antitumoral response was more robust and durable when combining XL309 and olaparib in a *BRCA1/2* wild-type ovarian PDX model with acquired resistance to this drug.[506] Based on these findings, a Phase I study (NCT05932862) of XL309 alone and in combination with olaparib in patients with advanced solid tumors is recruiting.

Overall, USP1i represents a promising strategy to bypass PARPi resistance by disrupting PCNA-mediated TLS and the FA/BRCA pathway. The clinical entry of RO7623066 and XL309 marks a shift toward targeting these pathways in HRD tumors. As these Phase I clinical trials progress, the key challenge will be identifying the optimal therapeutic window and robust biomarkers to maximize the efficacy of these combinations in the refractory setting.

RAD51 inhibitors (RAD51i)

RAD51 recombinase is a major component of HRR, fundamental for maintaining genomic stability. HRR provides error-free repair of DSBs during S and G_2 phases of the cell cycle. Initially, CtIP associates with the MRN complex (MRE11, RAD50 and NBS1) and stimulates bidirectional DNA end resection.[507] DNA resection of the DSB 5′-ends, generates 3′-ended ssDNA overhangs that are first coated by RPA, which is then replaced by RAD51, forming a nucleoprotein filament, a process mediated by BARD1, BRCA1/2, PALB2 (FANCN) and RAD51 paralogs (RAD51B, RAD51C, RAD51D, XRCC2 and XRCC3).[508] Then the filament of RAD51-ssDNA initiates the search for complementary sequences, strand invasion and DNA polymerization, processes by which the sequence surrounding the break site is resynthesized, via the formation of a D-loop that serves as a primer and template for DNA synthesis.[509] DNA DSB induction and recognition lead to nuclear accumulation of RAD51, which is detectable as nuclear foci. These foci serve as a surrogate marker of HRR functionality that can be used as a biomarker to select cancer patients for drug response, such as with PARPi.[192] RAD51 has been detected as overexpressed in several malignancies,[510,511] which has been associated with enhanced DNA repair and increased resistance to anti-cancer treatments.[512,513] Based on these findings, RAD51 inhibition is considered a promising strategy for the treatment of these tumors.

Emzadirib (CYT-0851) is a potent, selective and oral first-in-class inhibitor of RAD51-mediated DNA repair that in a Phase I/II clinical trial (NCT03997968) showed good tolerability and promising and broad clinical activity in advanced hematologic malignancies and solid tumors.[514] However, Cyteir Therapeutics announced in 2023 the discontinuation of the development of emzadirib, due to a lack of overall clinical efficacy according to the company's criteria.

Several other RAD51i are still in preclinical stages. B02 is a RAD51i discovered by researchers from the National Cancer Institute that has demonstrated promising results in preclinical studies, particularly in combination with other chemotherapeutic agents or CHK1i.[515,516] The structure of this compound has served as a starting point to design other RAD51i with enhanced potency, selectivity, and pharmacokinetic properties.[516,517] SAT-122 from Satya Pharma was able to disrupt RAD51-BRCA2 interaction and attenuated RAD51 foci formation and tumor progression in different cancer cell lines.[518] The RAD51i SCR-6992 developed by Simcere Pharmaceutical also showed encouraging antitumoral activities, including synergy with chemotherapeutic drugs, in cancer cell lines and animal models.[519]

To sum up, while the clinical progress of RAD51i has been hampered by the discontinuation of its most advanced candidate, the biological rationale for targeting RAD51 remains robust. The current focus is shifting toward developing next-generation inhibitors with higher binding affinity, identifying predictive biomarkers of response and exploring combinatorial regimens designed to sensitize HRR-proficient tumors to PARPi.

WRN inhibitors (WRNi)

Werner syndrome ATP-dependent helicase (WRN) is a member of the RecQ DNA helicase family, encoded by the *WRN* gene, that participates in DNA replication and repair, transcription, and telomere maintenance. More specifically, WRN mediates the choice between different DSB pathways by promoting c-NHEJ while suppressing alt-NHEJ; additionally, it facilitates HRR through its roles in DSB resection and CHK1-mediated RAD51 loading.[520] Mutations in this gene cause the autosomal recessive disorder Werner syndrome, characterized by the appearance of premature aging (progeria) and aging-related disorders, including increased cancer incidence, due to impaired DNA damage repair and telomeric shortening.[521] Preclinical data identified a SL relationship between WRN and microsatellite unstable (MSI) cancers. In MSI-high (MSI-H) cells, the genome is characterized by the accumulation of unstable TA nucleotide repeats, which tend to form non-canonical DNA secondary structures (such as cruciforms or large loops) that cause replication fork collapse. WRN is uniquely required to unwind these structures and maintain fork progression; therefore, WRN inactivation causes DSBs and activated DSB responses, leading to apoptosis and G_1 or G_2/M cell cycle arrest preferentially in MSI cells. Based on this finding, WRN was considered a promising drug target for MSI cancers, such as a subtype of colorectal, endometrial, gastric and ovarian cancers.[522,523] Several WRNi have recently entered clinical trials (Supplementary Fig. S9).

GSK4418959 (IDE275/GSK959) is an oral WRNi discovered by IDEAYA in collaboration with GlaxoSmithKline that is undergoing a Phase I/II study (NCT06710847) alone or in combination with a PD-1 inhibitor in MMR-deficient or MSI-H solid tumors.

HRO761 from Novartis is a potent, allosteric WRNi that was identified through an innovative hit-finding and lead-optimization strategy. Preclinical data showed the ability of this compound to lead to WRN degradation and inhibit tumor cell growth selectively in MSI cells in a p53-independent manner. Additionally, it caused dose-dependent DNA damage induction and tumor growth inhibition in MSI CDX and PDX.[524] This oral WRNi is being studied in a Phase I clinical trial alone or combined with pembrolizumab or

irinotecan in patients with solid cancer with MSI or MMR-deficiency (NCT05838768).

RO7589831 (VVD-133214) is another oral allosteric WRNi that was discovered by Vividion Therapeutics and later licensed to Roche. This compound binds WRN and causes DNA DSBs, nuclear swelling and cell death selectively in MSI-H cells, compared to microsatellite-stable cells. In MSI-H CRC cells and PDXs, it also resulted in robust reduction of tumor growth.[525] A Phase I study (NCT06004245) of this compound alone and associated with pembrolizumab for MMR-deficient or MSI solid tumors is recruiting. Preliminary results have shown that RO7589831 is generally safe and well tolerated and exhibits promising clinical responses in these patients.[526]

In summary, the WRN-MSI axis represents a highly selective SL vulnerability that has translated from discovery to clinical evaluation. By targeting the unique dependency of MSI-H cells on WRN to resolve replication-stalling non-canonical DNA structures, WRNi offer a potent, precision-oncology approach for MMR-deficient tumors, particularly for patients who have exhausted SOC immunotherapy.

APE1 inhibitors (APE1i)

The reduction-oxidation (redox) factor 1 - apurinic/apyrimidinic endonuclease (Ref-1/APE1) is the main apurinic/apyrimidinic endonuclease in eukaryotic cells, participating in the removal of non-bulky DNA lesions in the BER pathway and in redox signaling. This endonuclease cleaves abasic sites and generates ssDNA nicks 5′ to the abasic site, which are then processed by short- or long-patch BER. Ref-1/APE1 also functions as a redox signaling protein that modulates the activity of critical transcription factors, such as NF-κB, AP-1, HIF-1α and STAT3.[527,528] Ref-1/APE1 expression is upregulated in many tumors, which has been associated not only with increased cancer cell proliferation, migration and survival, but also with chemoresistance.[529,530] Several small-molecule inhibitors of the endonuclease activity of APE1 involved in DDR have been described (e.g., CRT0044876, AR03) but none of them have entered clinical trials.

APX3330 (Supplementary Fig. S10) is an orally bioavailable inhibitor of Ref-1/APE1's redox function that showed signs of clinical activity in a Phase I trial (NCT03375086) with an unselected population of patients with advanced solid tumors.[531] However, this compound acts as a selective antagonist of the Ref-1 redox signaling domain by disrupting transcriptional co-activation while sparing APE1 endonuclease activity. Consequently, its therapeutic potential in the DDR landscape lies more in its ability to suppress adaptive stress signaling rather than direct BER inhibition.[532] In contrast, TRC102 (also known as methoxyamine) covalently binds to the reactive aldehyde of abasic sites, effectively blocking APE1 endonuclease from recognizing and processing BER intermediates. Clinical trials with this drug aim to exploit an induced SL state caused by several DNA-damaging agents (e.g., temozolomide, pemetrexed) that overwhelm the cell's DNA repair capacity. A Phase I/II study (NCT02535312) showed a tolerable safety profile and antitumor activity of TRC102 in combination with cisplatin and pemetrexed for advanced solid tumors, and of TRC102 with pemetrexed for malignant mesothelioma progressed to prior pemetrexed therapy.[533] Promising durable disease control was also reported when combining it with temozolomide in another Phase I/II trial (NCT01851369) in patients with granulosa cell ovarian cancer.[534]

Altogether, the APE1-BER axis represents a complex therapeutic target where the distinction between disrupting oncogenic redox signaling (APX3330) and blocking DDR (TRC102) allows for precise, context-dependent strategies to overcome chemoresistance in solid tumors.

TARGETING SL INTERACTIONS BEYOND DDR GENES

Although more than 70% of clinical candidate drugs targeting SL focus on DDR, other emerging drugs that have progressed to the clinical setting target other pathways outside DDR,[535] such as metabolic enzymes (e.g., PRMT5, MAT2A), chromatin regulators (e.g., SMARCA4, SMARCA2, ALC1) or RNA helicases (e.g., DHX9).

Regarding metabolic SL, MTAP, MAT2A, and PRMT5 participate in the methionine/S-adenosyl-L-methionine (SAM) cycle, whose regulation is critical for maintaining cellular homeostasis. Loss of the *MTAP* gene, which often occurs in cancer (e.g., gliomas, NSCLC) due to its proximity to the frequently deleted *CDKN2A/B* locus,[536,537] was found to be SL with the inhibition of MAT2A and PRMT5.[538] This SL was enhanced when combining MAT2A and PRMT5 inhibitors (MAT2Ai and PRMT5i), leading to a more potent antitumoral effect.[539] In fact, upon *MTAP* depletion, an accumulation of the MTAP substrate MTA, which is a PRMT5 potent and selective inhibitor, occurs. This results in reduced PRMT5 activity and increased sensitivity to PRMT5i. Moreover, MAT2A produces the PRMT5 substrate SAM, and therefore, the inhibition of MAT2A also causes a reduction in PRMT5 methylation activity and, in turn, a reduction of tumor growth in *MTAP*-depleted cells.[540] GSK3326595 (EPZ015938) is a FIH PRMT5i optimized from GSK3235025 (EPZ015666). The analog GSK3235025 showed antiproliferative activity in TNBC cells and PDX, as well as synergy with the EGFR inhibitor erlotinib.[541] It also showed activity in AML preclinical models, especially in those with *MLL* rearrangements.[542] In a Phase I/II trial (NCT03614728) GSK3326595 monotherapy displayed limited clinical activity in heavily pretreated patients with myeloid neoplasms despite robust target engagement, leading to study termination.[543] It also showed modest antitumor activity with hematopoietic dose-limiting toxicities as a single agent in a Phase IB trial (NCT02783300) in patients with solid tumors and NHL.[544] Another Phase II trial (NCT04676516) in HR+ breast cancer is complete, but results have not been reported. The lack of clinical activity and the dose-limiting toxicities of first-generation PRMT5i led to the development of the next-generation MTA-cooperative agents, which selectively bind the PRMT5-MTA complex elevated in *MTAP*-deleted cells, thereby sparing healthy tissues. BMS-986504 (MRTX1719) is one of these MTA-cooperative PRMT5i that is currently undergoing Phase II/III trials with pembrolizumab and CTx for first-line metastatic NSCLC with homozygous *MTAP* deletion (NCT07063745) and with paclitaxel/gemcitabine for untreated metastatic pancreatic ductal adenocarcinoma with homozygous *MTAP* deletion (NCT07076121), as well as other Phase I or II clinical trials (e.g., NCT06672523 and NCT06855771). In a Phase IB study (NCT05245500) in patients with *MTAP*-deleted advanced solid tumors, this compound showed durable antitumor activity,[545] including in those with heavily pretreated NSCLC with *EGFR* and *ALK* alterations.[546] Preliminary data of a Phase I/II trial (NCT05094336) with the PRMT5i AMG193 demonstrated a favorable safety profile and promising antitumor activity across a variety of *MTAP*-deleted solid tumors.[547] Several other next-generation MTA-cooperative PRMT5i are undergoing Phase I/II clinical trials in solid tumors with *MTAP* loss: BAY3713372 alone and in combination with other anticancer agents (NCT06914128); AZD3470 monotherapy (NCT06130553); and the compounds from Tango Therapeutics TNG908 as single agent (NCT05275478), TNG462 alone or with pembrolizumab (NCT05732831) and combined with RAS inhibitors (NCT06922591), and TNG456 alone or with abemaciclib (NCT06810544). AZD3470 is also being tested as a single agent and in combination with other anticancer agents in participants with hematologic malignancies (NCT06137144).

Concerning MAT2Ai, S095033 (AG-270) is a first-in-class oral small molecule MAT2Ai that demonstrated antiproliferative activity in *MTAP*-deleted cancer cells and CDX and PDX models, and these effects were synergistic with taxanes both in vitro and in vivo.[548] This resulted in an FIH trial (NCT03435250) as monotherapy in patients with advanced malignancies, which showed that this compound displays a manageable safety profile, although dose escalation was limited by off-target hepatobiliary

toxicities and preliminary evidence of clinical activity.[549] This off-target effect may be avoided by the development of a second-generation MAT2Ai, S095035, that is currently being analyzed in a Phase I/II trial (NCT06188702) as a single agent and in combination with the PRMT5i TNG462 in participants with advanced or metastatic solid tumors with deletion of *MTAP*. Two other MAT2Ai have progressed to Phase I clinical trials for advanced solid tumors with *MTAP* loss: IDE397 as a single agent and combined with taxanes (docetaxel or paclitaxel) or sacituzumab govitecan (NCT04794699) and ISM3412 as monotherapy (NCT06414460).

Epigenetic dysregulation, including alterations in chromatin remodelers, is considered a major driver of tumorigenesis. Mutations in genes encoding components of the SWI/SNF complex occur in approximately 20% of all human cancers, confirming their role as critical tumor suppressors.[550] This complex regulates chromatin remodeling for active transcription through the activity of two mutually exclusive ATPase catalytic subunits, SMARCA4 (BRG1) and SMARCA2 (BRM), which work together with other subunits, such as SMARCC1 and 2, SMARCB1 and ARIDs (e.g., ARID1A and B, ARID2).[551,552] Several co-dependencies have been identified in SWI/SNF-mutant cancers that can be targeted therapeutically, most notably the SMARCA4-SMARCA2 axis, where the loss of one paralog creates a dependency on the other. Other identified SWI/SNF-related SL pairs include: SMARCA4-ARID2, SMARCA4-ACTB, SMARCC1-SMARCC2 and ARID1A-ARID1B.[553–555] To exploit this specific vulnerability, Prelude Therapeutics developed two SMARCA2 degraders, PRT3789 and PRT7732, that are currently undergoing clinical trials for *SMARCA4*-mutant advanced or metastatic solid tumors. PRT3789, currently in a Phase II study in combination with pembrolizumab (NCT06682806), was well tolerated and showed encouraging signs of anti-tumor activity in a previous Phase I trial (NCT05639751[556]). Similarly, the SMARCA2 inhibitor LY4050784 (FHD-909) is being evaluated in Phase I studies in *SMARCA4*-mutated solid tumors alone or associated with several antitumoral agents (NCT06561685 and NCT06561685), based on preclinical data showing synergistic activity with pembrolizumab or KRAS inhibitors.[557] In contrast to these selective approaches, the orally bioavailable dual SMARCA4/SMARCA2 inhibitor FHD-286 with antitumor activity in mouse xenografts,[558] is being tested in another Phase I trial for advanced myeloid malignancies (NCT04891757). Recent data reported significant safety challenges, with approximately 10-15% of patients exhibiting the life-threatening differentiation syndrome despite some evidence of blast reductions.[559]

Inhibition of the methyltransferase EZH2, the catalytic subunit of the other chromatin-remodeling factor with repressive functions PRC2, is SL with the inactivation of *ARID1A*, *PBRM1*, *SMARCA4, SMARCB1*.[560] Based on this, the FDA-approved EZH2 inhibitor tazemetostat (EPZ-6438) has progressed to several Phase I–II trials involving pediatric patients with *SMARCA4-/SMARCB1*-deficient advanced solid tumors, NHL, sarcomas and rhabdoid tumors, amongst others (e.g., NCT03155620, NCT02601937, NCT03213665, NCT05407441). In the Phase I study (NCT02601937) in *SMARCB1*-negative synovial sarcomas, tazemetostat showed promising antitumor activity.[561] In another trial (NCT03213665) in children with *SMARCB1* or *SMARCA4* loss, tazemetostat did not produce significant objective responses, but prolonged stable disease was observed in 33% of patients across different histologic diagnoses.[562] This drug is also being tested in Phase II studies in adult patients with *SMARCA4*, *SMARCB1* or *ARID1A* mutant advanced solid tumors (e.g., NCT05023655, NCT02601950, NCT03348631, NCT05151588). A Phase II study of tazemetostat in adults with soft tissue sarcomas (NCT02601950), resulted in long-term clinical activity in 2/13 patients with *SMARCB1*-negative sarcomas and 1/16 with a *SMARCB1*-negative solid tumor with generally mild to moderate adverse effects.[563] The other EZH2 inhibitor tulmimetostat showed efficacy in *ARID1A* mutant solid tumor models and improved cisplatin response in CTx-resistant models.[564] This compound is being studied in a Phase I/II clinical trial (NCT04104776), where it has shown preliminary signs of antitumor activity in *ARID1A*-mutated ovarian and endometrial cancers.[565]

ALC1 (CHD1L) is a nucleosome-remodeling enzyme that is recruited at DNA-damaged sites by PAR chains synthesized by PARP1/2 in order to facilitate chromatin relaxation.[566] *ALC1* depletion induces the accumulation of toxic BER intermediates resulting in ssDNA gaps and replication fork collapse. Moreover, *ALC1* loss is SL with HRD and, therefore, the inhibition of ALC1 could be employed to target HRD cancers. To this must be added that *ALC1* loss confers enhanced sensitization to PARPi by increasing PARP trapping on chromatin.[567] A brain-penetrant ALC1 inhibitor, EIS-12656, is being studied in a Phase I/II trial alone and in combination with olaparib or trastuzumab in patients with HRD solid tumors (NCT06525298).

DHX9 is a multifunctional ATP-dependent DExH-box RNA helicase with important roles in many processes, such as the regulation of DNA replication, transcription, translation and maintenance of genome stability.[568] The overexpression of DHX9 has been found in cancer and was correlated with poor prognosis.[569] In addition, the downregulation of DHX9 is SL in tumors with MSI-H or defective MMR[570] and with *BRCA1/2* LOF,[571] making DHX9 inhibitors (DHX9i) promising targets to treat these cancers. The oral DHX9i ATX-559 was being studied in a FIH trial for advanced or metastatic solid tumors, including *BRCA1/2*-/MMR-deficient and MSI-H tumors (NCT06625515), but has been recently terminated due to an adverse event profile.

Beyond the DDR, SL is being exploited through metabolic dependencies, such as targeting the MAT2A-PRMT5 axis in *MTAP*-deleted tumors, and epigenetic vulnerabilities, notably SMARCA2 in *SMARCA4*-mutant cancers. Emerging strategies also include inhibiting the methyltransferase EZH2 in *SMARCB1*-deficient cancers, the nucleosome remodeler ALC1 to enhance HRD sensitivity, and the RNA helicase DHX9 in MSI-H or *BRCA1/2*-deficient contexts. While early-generation agents often faced dose-limiting toxicities, the field is now shifting toward biomarker-dependent and isoform-selective molecules, such as the MTA-cooperative PRMT5i and the SMARCA2-specific degraders, in order to maximize the therapeutic index and minimize off-target effects.

CONCLUSION AND PERSPECTIVE

Targeting specific genetic vulnerabilities in tumors using the SL concept has redefined modern oncology and represents a cornerstone of precision cancer medicine. A prominent example is the success of PARPi, which exploit the existing SL interaction between PARP and a deficient HRR pathway, particularly due to *BRCA1/2* mutations. Since their approval, PARPi have transformed the prognosis for patients with previously limited therapeutic options and have generated billions in revenues for pharmaceutical companies. Global sales for olaparib alone are expected to exceed $4 billion (accounting for 68% of the PARPi market share) by 2027, boosted by new licenses for early-line MT and novel combinations.[572] In terms of clinical outcomes, the approval of olaparib for the treatment of *BRCA1/2*m ovarian cancer has significantly enhanced both survival rates and quality of life of these patients. The expansion of indications, the commercialization of subsequent PARPi and their strategic inclusion as MT have redefined the treatment paradigm for HRD ovarian, breast, prostate, and pancreatic cancers. While landmark clinical trials (e.g., SOLO1, PAOLA1, PRIMA, VELIA, BROCADE3) demonstrated significant improvements in PFS, translating this benefit into final OS remains a variable challenge across different cancer types and patient cohorts. Moreover, recent evidence suggests that defects in other specific genes involved in HRR and/or associated DNA repair pathways, especially *PALB2*, and to a lesser extent *ATM* or *CHK2*, may also confer sensitivity to PARPi. Indeed, favorable clinical responses to PARPi in cancers with alterations in these

genes have been found (e.g., NCT01682772, NCT01891344, etc.), but additional trials with bigger cohorts are needed to fully define the predictive value of PARPi response. Despite the huge impact of PARPi on cancer treatment, safety concerns, often linked to non-selective trapping of PARP1 and PARP2, and the emergence of resistance remain critical hurdles. While trapping is essential for anti-tumor activity, its lack of isoform selectivity is linked to hematopoietic and gastrointestinal toxicities. Based on these findings, next-generation PARPi are shifting toward high-potency, PARP1-selective inhibitors (e.g., saruparib and AZD9574), which aim to maximize the therapeutic index by sparing PARP2 and avoiding the off-target effects associated with pan-PARP inhibition. Furthermore, despite the good initial response to PARPi, patients frequently develop resistance through different mechanisms, resulting in cancer relapse. Amongst the potential strategies to overcome this, combinations of therapies have been proposed, with the goal of amplifying the antitumoral efficacy of PARPi and targeting the acquired resistance mechanisms. Apart from their combination with CTx, RT or ICIs, PARPi may be associated with inhibitors of key effector kinases of the RSR (e.g., ATR, CHK1 and WEE1), as PARPi-resistant tumors seem to accumulate high levels of replication stress.[210,573] Additionally, they could be combined with POLQi, as HRD cancer cells tend to overexpress this gene and seem to be hyper-dependent on its knockdown. Indeed, cancer cells with acquired resistance to PARPi through inactivation of the *53BP1-shieldin* pathway also show hypersensitivity to these drugs. This stems from the fact that POLQ provides a critical "gap-filling" activity that effectively compensates for the HRR deficit, allowing the tumor to maintain replication continuity. Consequently, combining PARPi with ATR or POLQ inhibitors holds the potential to "unmask" this latent vulnerability by simultaneously disrupting the RSR, exhausting cell cycle checkpoints, and forcing the re-accumulation of lethal ssDNA gaps. As novel PARPi with higher selectivity and lower toxicity enter the market, along with ongoing research into combination therapies involving PARPi and other drugs, such as ICIs or other targeted therapies, the impact on patients' prognosis may become even more significant.

Beyond the *BRCA1/2* and PARP axis, other interesting DDR-related SL interactions are under clinical investigation, such as the targeting of the DDR-kinases ATR, ATM, CHK1/2, DNA-PK and WEE1, the POLQ polymerase, the USP1 deubiquitinating enzyme, the RAD51 recombinase and APE1. These molecules are key members of the cellular response to DNA damage, and their inhibition in cancers with specific SL interactions leads to tumor cell death. These drugs are also able to sensitize cancer cells to CTx, RT, immunotherapy and other targeted therapy. Notably, the ATRi ceralasertib has progressed to Phase III clinical trials in NSCLC associated with durvalumab plus docetaxel (NCT05450692) or only with durvalumab (NCT06732401), while alnodesertib has recently received FDA Fast Track Designation for *ATM*-negative mCRC. Preclinical evidence also suggests that simultaneous inhibition of the three PIKKs, ATM, ATR and DNA-PK, may cause severe synergistic SL compared to single or dual kinase inhibition,[574,575] though the systemic tolerability of such broad DDR disruption requires further elucidation. The identification of novel SL interactions through advanced screening methods, such as CRISPR-Cas9, remains also essential to enhance the therapeutic potential of these drugs. DDRi have also demonstrated significant potential to chemo- and radiosensitize resistant tumors by impairing the repair of therapy-induced DNA lesions. By blocking key DDR proteins, these agents can enhance the cytotoxic effects of CTx or RT, leading to increased tumor cell death and improved clinical efficacy. Synergistic effects between DDRi and PARPi were also reported, but clear knowledge of optimal treatment schedules and factors producing distinct responses to these combinations is still missing. The identification of predictive biomarkers of response to DDRi (or the development of companion diagnostics) is also necessary to enable the stratification of patients in responders or non-responders, or to select those who may benefit the most from combination therapies. Additionally, resistance to other DDRi apart from PARPi, through different mechanisms including reversion mutations, epigenetic modification, stabilization of the replication fork and increased drug efflux, has also been reported and needs further research. The emergence of such resistance is often driven by clonal heterogeneity, needing more dynamic monitoring strategies such as liquid biopsy to monitor real-time SL dependencies. The successful application of novel DDR-based SL therapies also requires considering factors such as the zygosity of the target genetic alteration, its prevalence and role in a particular cancer, the potential on-target and off-target side effects (acute and long-term) resulting from the inhibition, the effect size and the penetrance of the SL interaction. An in-depth analysis of the synergistic effects and overlapping and/or cumulative toxicities from combination treatments should also be performed, as some clinical trials were terminated due to dose-limiting toxicities. SL is expected to evolve beyond genetic interactions into a contextual paradigm that will address additional tumor-specific conditions, such as metabolic SL, shaping the future of more precise and adaptive cancer therapies. Finally, while the vast majority of oncologic clinical trials focusing on SL target DDR, an increasing number of drugs in the clinical or preclinical setting inhibit non-DDR pathways for their use in a SL approach. These include inhibitors of metabolic enzymes (e.g., MAT2A, PRMT5), chromatin regulators (e.g., SMARCA4, SMARCA2, ALC1) or RNA helicases (e.g., DHX9), which suffer from the same limitations in their development as DDRi, including the requisite for robust patient-selection biomarkers and the identification of optimal combinatorial regimens with other oncologic drugs to prevent the emergence of resistance.

In conclusion, the growing interest in drugs targeting SL represents a revolutionary advancement in personalized cancer therapy, with drugs already approved that have reached important milestones and multiple others in the pipeline. These ongoing clinical trials explore SL interactions at different levels, which may broaden the arsenal of available effective cancer drugs, potentially offering tailored and potent treatments for cancer based on genetic profiling. Apart from the genetic interactions, the SL approach is expected to evolve into a more contextual paradigm that considers additional tumor-specific conditions, such as metabolic SL. This strategy holds potential to make a great impact on cancer treatment by offering highly specific therapies that selectively target cancer cells minimizing their effects over normal tissues, consequently providing more effective and less toxic treatments. However, continued research is essential to fully understand the intricate complexity of SL in the DDR context, maximize the therapeutic potential of SL-based therapies and discover additional druggable SL interactions.

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AUTHOR CONTRIBUTIONS

Cristina Camps-Fajol participated in the acquisition, analysis, visualization and writing of the data of the review article. Jordi Minguillón and Jordi Surrallés made substantial contributions to the conceptualization, design and revision of the work. All authors

met authorship criteria, drafting the work or revising it critically for important intellectual content. All authors have read and approved the article.

ADDITIONAL INFORMATION

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Competing interests: Jordi Surrallés has signed agreements (advisory boards, service provision, research collaboration or material transfer) in the last 3 years with Boehringer Ingelheim, Glaxo Smith Kline, Moderna Therapeutics, Roche, Rocket Pharmaceuticals and Pfizer. Jordi Surrallés and Jordi Minguillón have a patent repurposing of afatinib issued to IR Sant Pau, UAB and CIBER. Cristina Camps-Fajol declares that she has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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