Combined PARP inhibitors and small molecular inhibitors in solid tumor treatment (Review)

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Abstract. With the development of precision medicine, targeted therapy has attracted extensive attention. Poly(ADP-ribose) polymerase inhibitors (PARPi) are critical clinical drugs designed to induce cell death and are major antitumor targeted agents. However, preclinical and clinical data have revealed the limitations of PARPi monotherapy. Therefore, their combination with other targeted drugs has become a research hotspot in tumor treatment. Recent studies have demonstrated the critical role of small molecular inhibitors in multiple haematological cancers and solid tumors via cellular signalling modulation, exhibiting potential as a combined pharmacotherapy. In the present review, studies focused on small molecular inhibitors targeting the homologous recombination pathway were summarized and clinical trials evaluating the safety and efficacy of combined treatment were discussed.

Contents

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Abbreviations: PARP, poly(ADP-ribose) polymerase; DDR, DNA damage response; SSB, single-strand break; DSB, double-strand break; ART, ADP ribosyltransferase; NHEJ, non-homologous end-joining; HRD, homologous recombination deficiency; RTK, receptor tyrosine kinase; EGFR, epidermal growth factor receptor; FMO, flavin-containing monooxygenase

Key words: PARP inhibitors, DNA damage response, small molecular inhibitors, combination therapy, clinical trials

1. Introduction

PARP inhibitors (PARPi) achieved a major breakthrough as targeted antitumor agents in the past decades; they are critical clinical drugs designed to cause cancer cell death by targeting PARP (1). An understanding of the roles of the PARP1 and PARP2 enzymes in the DNA damage response (DDR) led to long-term efforts to develop PARP1i/PARP2i (2-7). Cancer cells that suffer DNA damage caused by reactive oxygen species (ROS), chemotherapy, etc., are able to repair damage through single-strand break (SSB) repair. Due to the tumor-specific genetic defects, PARPi may induce the killing of cancer cells while sparing normal cells. The PARP family comprises a subset of nuclear proteins that detect SSBs and subsequently recruit DNA repair effectors, remodel chromatin and eventually repair DNA by PARylation of PARP substrate proteins. Based on the pivotal role of PARP in the DDR, PARPi were indicated to trap PARP at the site of damage by binding to the ADP ribosyltransferase catalytic domain, causing conversion to double-strand breaks (DSBs) and impairing the progression of replication forks. Two primary repair models, homologous recombination (HR) and nonhomologous end-joining (NHEJ), are involved in DSB responses in healthy and unmutated cells. However, in abnormal cells with BRCA1/2 deficiency or HR deficiency (HRD), the HR repair pathway may be inhibited and turn into error-prone NHEJ repair, eventually leading to cytotoxic DSBs. In addition, PARPi may suppress the classic NHEJ pathway (8,9). The above machanisms eventually lead to cell death (10-18). Based on this mechanism, four PARPi, olaparib, niraparib, rucaparib and talazoparib, have been approved by the FDA to be applied in human tumors with deleterious BRCA mutations or HRD in ovarian, breast, pancreatic and prostate cancer.

Although great successes have been achieved in the discovery and development of PARPi with satisfactory clinical benefits, new issues regarding PARPi are emerging during

clinical practice. Drug resistance is the first problem that affects the clinical response of patients receiving PARPi. The resistance to PARPi generated in BRCA1/2-deficient tumor cells mainly arises from five aspects: Somatic reversion or restoration of BRCA1/2 open reading frame (19), epigenetic reversion of BRCA1 promoter hypermethylation, hypomorphic BRAC1/2 allele (20), deficiency of PARP1 expression (21) and loss of end resection regulation (22,23). In addition, only patients harbouring BRCA mutations or HRD may benefit from PARPi therapy; however, these patients account for only a small proportion of the total cancer patient population. For instance, in ovarian cancer (OC), which benefits from PARPi the most, less than half of the patients with high-grade serous epithelial OC have alterations in HR repair genes (17). PAPRi resistance and the BRCA or HR status limit the clinical application of PAPRi. In these circumstances, combined therapy is a feasible strategy to improve the clinical benefit and expand the application of PARPi. Small molecular inhibitors are, in certain aspects, ideal candidates for combination treatment.

Small molecular inhibitors are agents with a molecular weight of 500-900 Da that target biomolecules. To date, various small molecular inhibitors have been approved by the food and drug administration (FDA) as targeted therapies and applied in multiple haematological cancers and solid tumors, such as epidermal growth factor receptor inhibitors (EGFRi), Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway inhibitors and phosphoinositide-3 kinase (PI3K)-AKT-mammalian target of rapamycin complex (mTORC) pathway inhibitors. As reported, the anti-tumor mechanisms of these inhibitors include increasing DNA damage, suppressing cellular DNA repair and affecting the expression of HRD factors (the major mechanisms are presented in Table I and Fig. 1). These mechanisms offer the possibility that small molecular inhibitors may have synergistic effects with PARPi and minimize PAPRi resistance. As mentioned above, biomolecules regulate processes including metabolism, transcription and transfer signalling within cells, and serve as components of cells (24). In addition, small molecular inhibitors have better oral bioavailability, higher tissue and tumor microenvironment penetration and higher selective toxicity profiles compared to therapeutic antibodies (25,26); tremendous research efforts have been made in this field.

In the present review, the roles of small molecular inhibitors in DNA damage were summarized, particularly those targeting biomolecules functions in HR. Based on these molecular mechanisms, the effects of the combination of PARPi and small molecular inhibitors were further demonstrated in cancer treatment studies and clinical trials. The present review aimed to promote the application of PARPi for treating cancer. It remains to be interpreted whether combined therapies may improve the prognosis of patients with BRCA1/2 deficiency and whether patients with HR repair defection may gain a clinical benefit compared to PARPi monotherapy.

2. Receptor tyrosine kinase inhibitors (RTKi) and PARPi

RTKs, which act as membrane receptor proteins and subsequently activate intracellular signalling, have been reported to participate in a variety of biological processes, such as growth, motility, differentiation and metabolism (27,28). The expression and activation of RTKs are of vital importance in tumor diagnosis and treatment; hence, the determination of the RTK concentration and phosphorylation degree is a focal spot in therapy development, particularly for metastatic breast cancer, gastrointestinal stromal tumor and non-small cell lung cancer (NSCLC) (29,30). Emerging evidence implies that disturbance of RTK signalling impacts DDR systems and subsequently exhibits a synergism with DNA-damaging agents in cancer treatment (31).

EGFRi. EGFR is a transmembrane protein with cytoplasmic kinase activity that transduces growth signalling from the extracellular environment into the cell. The EGFR family has been verified to comprise four members: EGFR, human EGFR-related 2 (HER2; also known as neu/ERBB2), kinase-impaired HER3 and HER4 (32). These signalling pathways are involved in tumor growth and angiogenesis, as well as the activation of transcription factors related to cell growth and mitosis (33-35). Evidence has indicated that small molecular inhibitors, such as EGFRi, may act on healthy cells, which would cause specific toxicity. However, several small molecular inhibitors have been approved by the FDA as targeted therapies and applied in multiple haematological cancers and solid tumors, each of which has specific indications and individual toxicity profiles. The astonishing antitumor effect and adverse events underscore the importance of having a comprehensive reference to help guide clinical decisions when treating patients. With the desire for higher potency and overcoming drug resistance, EGFRi are constantly being developed and have been proven to suppress tumor growth *in vitro* and *in vivo*. However, single-agent EGFRi therapy is prone to adverse events, modest efficacy and drug resistance (36-38). EGFR amplification was indicated to be associated with DNA repair pathways and rendered glioma sphere-forming cells susceptible to PARPi (39,40). Further studies revealed that the intrinsic mechanism was Rad51 and Mre-11 upregulation mediated by EGFR, supporting the synergistic effect of EGFRi and PARPi (41,42). Certain EGFRi, such as gefitinib and cediranib, have undergone clinical trials in combination with PARPi.

The first generation of EGFRi

Gefitinib. Gefitinib, a classic agent of the first-generation EGFRi, is a synthetic low-molecular-weight anilinquinazoline compound that selectively targets HER1 or ErbB1 (43). In 2015, gefitinib was approved by the FDA for the treatment of patients with metastatic EGFR mutation-positive NSCLC.

In NSCLC, gefitinib treatment markedly reduced phosphorylated (p)-EGFR, p-AKT and p-MAPK levels, and increased cleaved PARP (44). In MDA-MB-468 and HCC1806 cells, pretreatment with gefitinib prevented the synthesis of IGFBP-3-NONO/SFPQ complexes, which comprise a multiprotein DNA repair complex and modulate DSB repair by NHEJ (45). In addition, in patients with EGFR-mutant NSCLC treated with gefitinib, the low mRNA levels of BRCA1 resulted in a relatively longer progression-free survival (PFS) and PARPi attenuated BRCA1 expression (46). In 2021, a case study reported that a 62-year-old patient with lung carcinoma with a BRCA2 germline mutation benefited from combination therapy (47). These studies on gefitinib and PARPi provide a basis for the combination of drugs in clinical trials.

Table I. Mechanisms of small molecular inhibitors modulating DNA damage repair.

A, EGFR inhibitors		
Type/name	Mechanism	(Refs.)
First-generation EGFR inhibitors		
Gefitinib	Prevents the synthesis of IGFBP-3-NONO/SFPQ complexes, which are comprised of a multi-protein DNA repair complex and modulate DSB repair by NHEJ	(45)
Lapatinib	Promotes pro-caspase-8 dimerization, which subsequently enhances the efficacy of DNA-damaging agents	(50)
Erlotinib	Inhibits cell growth and HR repair of chromosomal breaks and damages DNA double strands	(53)
Second-generation EGFR inhibitors		
Afatinib	Increases apoptosis and inhibits DNA damage repair	(53,60)
Vandetanib	Interferes with cellular DNA repair and enhances the activity of DNA damaging agents	(63)
Neratinib	BRCA2 mutations were correlated with the response to neratinib and high expression of ATM, BRCA2 and BRCA1 are associated with neratinib resistance	(65)
Third-generation EGFR inhibitors		
Osimertinib	Delays DNA damage repair	(68)

B, Multi-target RTK inhibitors		
Name	Mechanism	(Refs.)
Apatinib	Suppresses the repair of radiation-induced DSBs in hepatocellular carcinoma in a PI3K/AKT-dependent manner	(71)
Cediranib	Suppresses the expression of HRD factors BRCA1/2 and RAD51 recombinase	(73)
Imatinib	Reduces RAD51 protein levels and inhibits DNA damage checkpoint arrest in an ATM/ATR-dependent manner	(84,85)
Regorafenib	Induces DNA damage	(90,91)

C, Non-RTK inhibitors (JAK-STAT pathway)		
Name	Mechanism	(Refs.)
Ruxolitinib	Promotes DNA damage and genomic instability via ROS accumulation and decreases the molecules involved in DNA damage repair	(108-110)

D, PI3K-AKT-mTOR pathway inhibitors		
Name	Mechanism	(Refs.)
Copanlisib	Inhibits cell proliferation and cell cycle progression and BCR-independent activation of NF-κB and induces apoptosis	(123,124)
Buparlisib	Impairs the nonoxidative pentose phosphate pathway, contributes to nucleotide synthesis suppression and DNA damage and downregulates BRCA	(126-129)
Taselisib	Suppresses DNA damage repair and prolongs G2/M-phase arrest	(132)
Alpelisib	Decreases AKT and S6K1 phosphorylation, induces G0/G1 phase arrest and increases DNA damage	(137)
Ipatasertib	Increases intracellular ROS levels and subsequently increases DNA damage	(143)

Table I. Continued.

D, PI3K-AKT-mTOR pathway inhibitors

Name	Mechanism	(Refs.)
Perifosine	Induces RAD51 ubiquitination, blocks the RAD51-BRCA2 interaction and decreases HR-mediated DSB repair	(149)
MK-2206	Inhibits the activity of AKT and impacts DNA damage	(151)
Rapamycin	Decreases DNA damage and inhibits Rad51 focus formation	(156,157)
Everolimus	Inhibits the increase of p21 and the expression of DNA repair genes and mitotic checkpoint regulators	(159-161)

E, RAS/RAF/MEK/ERK pathway inhibitors

Name	Mechanism	(Refs.)
Dabrafenib	Alters the expression of the MUC gene, facilitates DNA damage and elevates ROS levels	(170,171)
Vemurafenib	Hampers the DNA damage repair	(173)
Selumetinib	Induces DNA damage and increases γH2A	(180)
Trametinib	Decreases DSB repair and facilitates repression on both HR and NHEJ by suppressing BRCA1, DNA-PK, RAD51, RPRM2 and Chk1	(182)
Dasatinib	Suppresses radiation-induced DNA damage repair in HN-5 cells and induces DNA damage	(186,187)

EGFR, epidermal growth factor receptor; IGFBP-3-NONO/SFPQ, insulin-like growth factor binding protein-3-NONO/SFPQ; DSB, DNA double-strand break; NHEJ, non-homologous end-joining; ATM, ataxia telangiectasia-mutated gene; BRCA, breast cancer associated gene; HRD, homologous recombination deficiency; RTK, receptor tyrosine kinase; ATR, ataxia-telangiectasia mutated and Rad 3 related protein; JAK, Janus kinase; STAT, signal transducer and activator of transcription; ROS, reactive oxygen species; PI3K, phosphoinositide-3 kinase; mTOR, mammalian target of rapamycin; BCR, B cell receptor; RAS, rat sarcoma; RAF, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase; ERK, extracellular signal-regulated protein kinase; MUC, mucoprotein; DNA-PK, DNA-dependent protein kinase; RRM2, ribonucleotide reductase regulatory subunit M2; Chk-1, checkpoint kinase 1.

A multicentre, randomized phase IB/IIB study, GOAL, recruited pathologically confirmed patients with stage IV NSCLC in Spain and Mexico. Eligible patients were randomly allocated (1:1) to receive gefitinib 250 mg daily or gefitinib 250 mg daily plus olaparib 200 mg three times daily in a 28-day cycle. However, comparing the PFS, overall survival, response rate, safety and tolerability, no significant differences were observed. The use of next-generation sequencing is supposed to identify PARP and BRCA1 expression in the subgroup of EGFR-mutant patients who may benefit from adjunctive therapy (46).

Lapatinib. Lapatinib interacts with the ATP-binding site of HER1 (EGFR1/ErbB1) and HER2/c-neu (ErbB2) and further inhibits downstream signalling cascades (48). Lapatinib reduced EGFR protein expression, increased the population of apoptotic cells and increased TP53 gene signals (49). To further investigate the association between lapatinib and DNA-damaging agents, a study in MCF-7 and MDA-MB-468 cells revealed that pretreatment with lapatinib or erlotinib promoted pro-caspase-8 dimerization, which subsequently enhanced the efficacy of DNA-damaging agents (50). Based on these results, a new treatment was proposed, namely the combination of lapatinib and PARPi, which was tested *in vivo* and *in vitro*. Under both circumstances, an anti-tumor effect was verified in triple-negative breast cancer (TNBC) and an increase in cytosolic BRCA1 and EGFR was found to be distant from their nuclear DNA repair substrates (51).

Erlotinib. Erlotinib is also a selective inhibitor of tyrosine kinase and functions in tumor cell division, cell cycle arrest and apoptosis (52). Although it has adverse effects, erlotinib has been approved by the FDA for the treatment of NSCLC and pancreatic cancer. It has been observed that in HER2 short hairpin RNA-transfected bladder cancer cells, cell growth was inhibited and more DNA was damaged after treatment with erlotinib (53). Similarly, in CRL-5876, human lung adenocarcinoma cells underwent DNA DSBs (54), and human breast cancer cells exhibited suppression of HR repair of chromosomal breaks (55). In an ovarian tumor xenograft model, treatment combining erlotinib and AZD2281 (olaparib, a potent inhibitor of PARP) exhibited a better ability to reduce tumor size compared to any monotherapy through downregulation of p-ERK1/2 and p-AKT (56). Furthermore, the gain-of-function mutation of EGFR was reported to induce PARPi resistance, thus supporting the combined therapy of PARPi (veliparib) and EGFRi (erlotinib) for lung cancer (57).

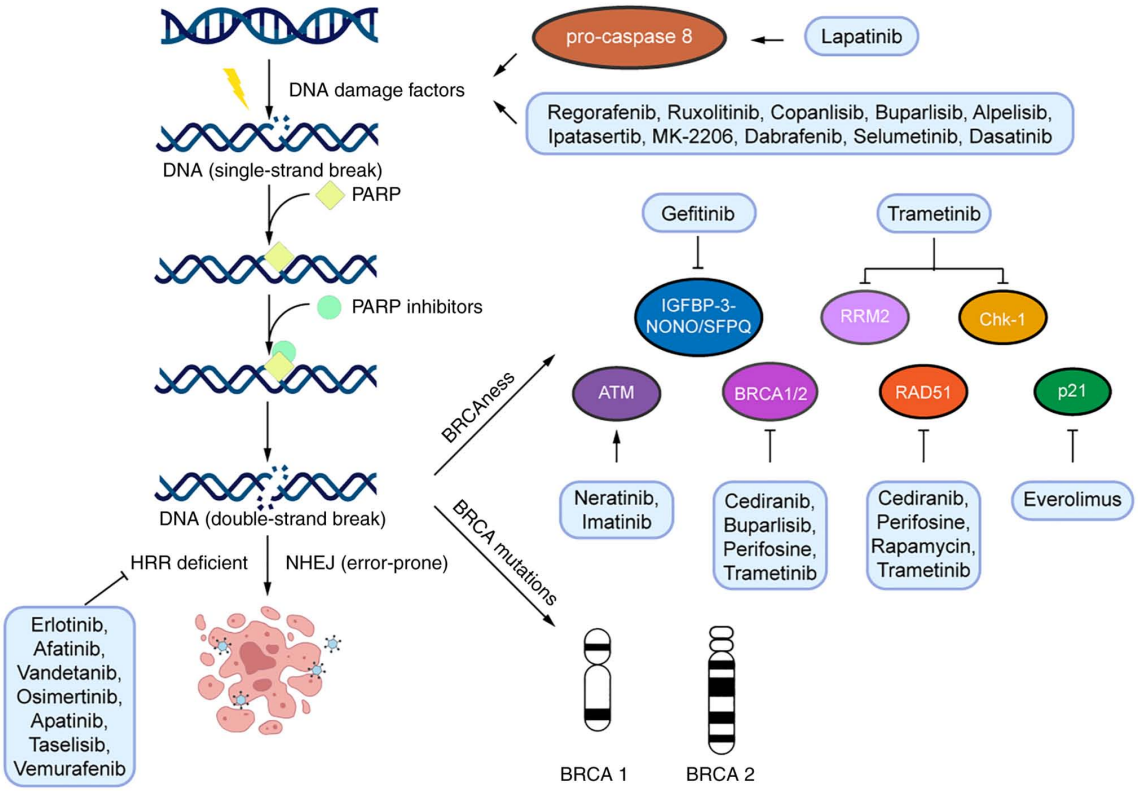

Figure 1. Small molecular inhibitors in DNA damage and DNA damage repair. Potential mechanisms of PARP inhibitor plus small molecular inhibitors combination treatment. PARP, poly(ADP ribose) polymerase; NHEJ, non-homologous end-joining; HRR, homologous recombination repair; ATM, ataxia telangiectasia-mutated gene; IGFBP-3-NONO/SFPQ, insulin-like growth factor binding protein-3-NONO/SFPQ; BRCA, breast cancer associated gene; RRM2, ribonucleotide reductase regulatory subunit M2; Chk-1, checkpoint kinase 1.

Second-generation EGFRis

Afatinib. Afatinib binds irreversibly to cysteine 797 of EGFR and cysteines 805 and 803 in HER2 and HER4. It also inhibits the transphosphorylation of HER3 protein. Phosphorylation within the ErbB dimer is blocked and downstream signalling pathways are disrupted when cells are treated with afatinib, leading to cell apoptosis both *in vitro* and *in vivo*. Afatinib was revealed to significantly increase PFS in patients with advanced NSCLC resistant to gefitinib or erlotinib (58,59). In a previous study, when cotreatment with radiotherapy was applied, afatinib possessed a better ability to kill cells, cause apoptosis and damage DNA than erlotinib (53). In addition, in a gefitinib-resistant cell subline of NSCLC (PC-9-GR), afatinib was indicated to increase apoptosis and inhibit the DDR (60).

Vandetanib. Vandetanib is approved by the FDA as a once-daily oral multikinase inhibitor targeting the rearranged during transfection (RET) tyrosine kinase, vascular endothelial growth factor receptor (VEGFR) and EGFR for the treatment of progressive medullary thyroid cancer, as well as NSCLC and breast cancer (61). In the CAL-27 oral squamous cell carcinoma cell line, vandetanib interfered with cellular DNA repair to enhance the efficacy of photodynamic therapy (PDT) (62). Apart from synergistic effects with PDT, vandetanib enhanced the activity of DNA-damaging agents as a result of G1 phase accumulation (63).

Neratinib. Neratinib is a pan-TKI targeting HER1, HER2 and HER4 that is primarily applied in HER2-positive breast cancer treatment and was approved in the USA in 2017. As monotherapy or a component of combination therapy, it is undergoing clinical trials in metastatic breast cancer, advanced breast cancer, NSCLC, colorectal cancer and glioblastoma (64). In a 115-cancer cell line panel, BRCA2 mutations were correlated with the response to neratinib and high expression of ATM, BRCA2 and BRCA1 was associated with neratinib resistance (65). Neratinib has also been indicated to cause DNA damage by γH2AX phosphorylation and ATM activation (66). This result offers support for further fundamental and clinical studies exploring the combination therapy effect of neratinib and PARPi.

Third generation of EGFRi

Osimertinib. Osimertinib is a third-generation EGFRi that inhibits cell proliferation by binding to cysteine-797 in the EGFR ATP-binding sites. Compared with other EGFRis, osimertinib is able to penetrate the blood-brain barrier to reach the central nervous system and attack brain metastasis (67). A study revealed that osimertinib functioned in a concentration-dependent and time-dependent manner by means of proliferation inhibition and DDR delay in EGFR T790M mutant NSCLC (68).

Multitarget RTKi

Apatinib. Apatinib is a highly selective inhibitor of VEGFR-2, which inhibits c-kit, c-src and RET tyrosine kinase (69). Apatinib is the second anti-angiogenetic drug approved in China for advanced metastatic gastric cancer (GC). However, it has limited efficacy for chemotherapy-experienced patients with other advanced cancers (70). Colony formation

assays revealed that apatinib suppressed the repair of radiation-induced DNA DSBs in hepatocellular carcinoma (HCC) in a PI3K/AKT-dependent manner (71).

Cediranib. Cediranib is a potent and selective inhibitor of VEGFR-1, -2 and -3 and is metabolized via flavin-containing monooxygenase (FMO)1, FMO3 and uridine 5'-diphospho-glucuronosyltransferase 1A4 (72). Previous studies have suggested that cediranib was able to induce hypoxia and thus suppress the expression of HRD factors BRCA1/2 and RAD51 recombinase (73). Based on these theories, a mouse model injected with epithelial ovarian cancer (EOC) cell lines was established and cediranib was verified to abrogate prosurvival signaling in the antiapoptotic AKT pathway and subsequently enhanced the efficacy of olaparib (74).

In a phase I formulation bridging trial (NCT01116648), the combination therapy of cediranib and PARPi was used to generate preliminary evidence of anticancer activity in high-grade serous ovarian cancer (HGSOC) (75). Furthermore, females with recurrent platinum-sensitive ovarian cancer were recruited in a phase II trial (NCT01116648) to compare the effects of cediranib and olaparib in combination with those of olaparib alone. Among the 90 subjects enrolled, 46 received olaparib monotherapy at 400 mg twice daily (bid) and 44 received combination therapy with cediranib 30 mg once daily (qd) and olaparib 200 mg BID. The median PFS increased from 9.0 to 17.7 months in the group cotreated with cediranib. In addition, in subjects with deleterious germline BRCA1/2 mutation (gBRCAm) status, the median PFS increased from 16.5 to 19.4 months (P=0.06), while in those with non-gBRCAm or unknown status, an increase from 5.7 to 16.5 months (P=0.008) was observed (76,77). Another phase I clinical trial (NCT02484404) recruited patients with advanced breast cancer or gynaecological malignancies with gBRCAm. The trial tested the 3-drug combination in a 3 + 3 dose escalation. Cediranib was taken discontinuously (5 days on/2 days off) at 15 or 20 mg with durvalumab 1,500 mg intravenously (iv) every 4 weeks, and olaparib tablets 300 mg bid. The primary end-point was the recommended phase 2 dose (RP2D), while secondary end-points were response rate, pharmacokinetics and correlative analyses. The recommended RP2D was cediranib 20 mg daily (5 days on/2 days off) with durvalumab 1,500 mg iv every 4 weeks and olaparib tablets 300 mg bid (78-80). Furthermore, two more vital phase III trials (NCT02446600 and NCT02502266) have been performed in ovarian cancer (81); both are three-armed studies and recruited patients with recurrent platinum-sensitive HGSOC and platinum-resistant HGSOC, respectively. PFS was the primary end-point in both trials. The ICON9 trial (NCT03278717), sponsored by Cancer Research UK, plans to investigate platinum-sensitive recurrent HGSOC, endometrial histology or clear-cell ovarian cancer. The EVOLVE trial (NCT02681237) recruited 34 heavily pretreated patients assigned to three cohorts: Platinum-sensitive after PARPi; platinum-resistant after PARPi; or progression on standard chemotherapy after progression on PARPi. Patients received olaparib 300 mg twice daily with cediranib 20 mg once daily until disease progression or unacceptable toxicity. The primary end-points were the objective response rate (RECIST v1.1) and PFS at 16 weeks (82). However, these clinical trials are currently in progress and no data have been published, yet.

Imatinib. Imatinib is a 2-phenylaminopyrimidine derivative primarily used in the treatment of myeloid leukaemia (83). Imatinib was indicated to be related to DNA damage by reducing RAD51 protein levels in various previous studies (84). To further determine the mechanism of the antileukaemic action of imatinib, the inhibition of DNA damage checkpoint arrest was demonstrated to have a pivotal role in an ATM/ATR-dependent manner (85), and the downregulation of key DNA repair genes was also observed after imatinib treatment (86). In addition, ATM kinase-dependent phosphorylation of Nbs1, a member of the Mre11-RAD50-Nbs1 complex, was enhanced to improve the efficacy of imatinib (87). A stepwise study used a primary culture of ovarian cancer cells in 96-well plate assays and revealed that imatinib had a synergistic effect with olaparib and protected against olaparib cytotoxicity (88).

Regorafenib. Regorafenib is a small molecular inhibitor of kinases and targets various pathologic processes, including oncogenesis, tumor angiogenesis and tumor microenvironment formation. It was approved by the FDA for metastatic colorectal cancer in 2012 and advanced HCC in 2017 (89). A preclinical study to determine the potential of regorafenib in solid paediatric malignancy treatment has been performed both *in vitro* and *in vivo*. The results suggested that DNA damaging agents, such as a topoisomerase I inhibitor and irradiation, had efficacy in platelet-derived growth factor receptor-amplified tumors (90). To further validate this phenomenon, another study was conducted in TNBC MDA-MB-231, SUM159PT and MCF10a cell lines. Angiogenesis was inhibited and γH2AX was assessed to confirm the existence of the DDR after regorafenib treatment (91).

3. Non-RTKi (JAK-STAT pathway) and PARPi

The TKIs introduced above are reciprocal receptors on the cell membrane for the interconnection of cytokines or growth factors. The JAK family has four primary members: JAK1, JAK2, JAK3 and Tyk2 (92). Of the four members, JAK1, JAK2 and Tyk2 are expressed ubiquitously, while JAK3 is expressed mainly in haematopoietic cells (93,94). The STAT family comprises seven members: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6, and is a downstream target of JAK that functions in signal activation as well as transduction (95,96). Among these members, research focuses on STAT3 and STAT5, which may have roles in disease treatment resistance and are associated with multiple cancer types, such as leukaemia and lymphoma (97). The JAK/STAT pathway, which is also known as the IL-6 signalling pathway, was discovered >20 years ago and has been further investigated recently (98). This signalling pathway is involved in multiple important cellular activities, such as cell proliferation, differentiation, apoptosis, immune regulation and haematopoiesis (99). In a case-control cohort study conducted in New Zealand, carrying a risk allele associated with the STAT-JAK pathway was indicated to predispose patients to DNA damage (100). In A549 cells, the mechanism of X-ray-induced DNA damage was found to be related to the activation of the JAK/STAT pathway (101).

JAK inhibitors. JAK inhibitors (jakinibs) have been recognized as safe and efficient therapies for diseases generated

by inflammation, which have been mentioned above (102). Type I and type II cytokine receptors are a family of receptors comprised of >50 cytokines, interleukins, interferons, colony-stimulating factors and hormones. These receptors activate or suppress downstream signalling pathways in a JAK-dependent manner. Thus, interfering with JAKs may result in an immunomodulatory therapy with several adverse effects, such as cytopenia and infection (103). JAKs were reported to activate ATM/checkpoint kinase 2 (Chk2)/H2AX and ATR/Chk1 DDR, implying that JAKi may enhance the efficacy of PARPi by disrupting the DDR (104-106).

Ruxolitinib. Ruxolitinib competes with the ATP binding domain in the catalytic site of JAK1/JAK2 tyrosine kinase and was approved by the FDA for the treatment of myelofibrosis in 2011 and by the European Medicines Agency (EMA) in 2012 (107). Previous studies revealed an increased tendency of DNA damage and genomic instability in JAK2V617F expression models. As the underlying mechanism remains unclear, numerous studies are attempting to establish *in vitro* and *in vivo* models to answer this question. First, JAK2V617F-overexpressing cells were indicated to promote DNA damage and genomic instability via ROS accumulation (108,109). Furthermore, preclinical data suggest that the molecules involved in the DDR were deficient in JAK2V617F-expressing cells. Similar results have been observed in patients (110). In addition, JAK2 mutation has been linked to deficiencies in various DDR pathways (111). Conversely, another study established JAK2V617F-positive myeloproliferative neoplasms (MPNs) and indicated that the patients remained clinically and cytogenetically stable for numerous years (104). Based on these findings, a study reported a synergistic inhibition of MPNs with the combination of ruxolitinib and PARPi both *in vitro* and *in vivo* (112).

STAT inhibitors. In a study investigating the role of innate immune regulators in human papillomavirus (HPV) pathogenesis, STAT5 was indicated to be activated in HPV-positive cells and regulate HPV genome amplification through activation of ATM in part via peroxisome proliferator-activated receptor-γ. In addition, STATs function as activators of DNA damage and ROS production in TNFα-mediated senescence (113), providing evidence of the feasibility of cotreatment with STATi and PARPi.

4. PI3K-AKT-mTORC pathway inhibitors and PARPi

The PI3K family of enzymes is recruited once growth factor receptors are activated and generates 3' phosphoinositide lipids as second messengers to induce various cellular targeting proteins (114). Among the various second messengers, the serine/threonine kinase AKT is of vital significance (115). When AKT is stimulated, the rapamycin-sensitive mTORC1 signalling pathway is triggered. In addition, rapamycin-sensitive mTORC2 contributes to AKT phosphorylation at critical sites (116). As crucial kinases during the cellular lifespan, the PI3K-AKT-mTOR pathway contributes to cell proliferation, transcription, translation, survival and growth (117). This pathway is also related to autophagy and apoptosis (118). Therefore, once disturbed, various human malignancies occur (119). Thus, this pathway may serve as a pivotal antitumor therapeutic target for further research. In an HCC cell line model, PKI-587 promoted oxaliplatin sensitivity by suppressing the DDR pathway in a PI3K-AKT-mTOR-dependent manner (120). Huang *et al* (121) summarized the studies related to the PI3K pathway and DDR in ovarian cancer, which represents a novel targeted treatment in cancer as well as a combined treatment with PARPi.

PI3K inhibitors. Emerging data suggest that the PI3K pathway has a role in DNA replication and genome stability, making DDR system inhibitors, such as PARPi, potential combination therapies for PI3K pathway pharmacologic inhibitors (121,122). For instance, copanlisib, buparlisib and alpelisib have been investigated in clinical trials combined with PARPi.

Copanlisib. Copanlisib is a panclass I PI3K inhibitor developed by Bayer that specifically targets the α and δ isoforms. In May 2017, copanlisib was approved by the FDA for the treatment of relapsed follicular lymphoma in adult patients with at least two prior therapies, which was further supported by the phase II study, CHRONOS-1. Copanlisib has been reported to inhibit the proliferation of various human cancer cell lines, inhibit cell cycle progression and induce apoptosis in multiple myeloma cells (123), inhibit BCR-independent activation of NF-κB in diffuse large B-cell lymphoma cell lines and inhibit growth in several lymphoma cell lines (124).

A phase Ib clinical trial (NCT03586661) sponsored by the M.D. Anderson Cancer Center is currently recruiting patients with recurrent endometrial and recurrent ovarian, primary peritoneal or fallopian tube cancer to study the effects of the synergy of niraparib with copanlisib. The included patients received oral niraparib qd on days 1-28 and copanlisib iv on days 1, 8 and 15 to determine the maximum tolerated dose (125).

Buparlisib. Buparlisib is an inhibitor targeting all isoforms of panclass I PI3K in a comparative ATP-binding manner. In a BRCA1-linked TNBC mouse model, carbon flux studies indicated an impaired nonoxidative pentose phosphate pathway and subsequent contribution to nucleotide synthesis suppression and DNA damage (126). In another study performed in Ishikawa, AN3CA and Nou-1 cells, DNA damage was observed with γ-H2AX accumulation after buparlisib treatment, while in Hec-108 cells, the HR repair system was interfered with (127). These results enhance the understanding of the effect of buparlisib on DNA damage (128). Due to the interaction between buparlisib and DNA damage, the synergy of buparlisib with PARPi was superior to either agent alone in *in vitro* and *in vivo* models (126-129). In addition to breast and prostate cancers, similar results have been observed in ovarian cancer cells, particularly with PIK3CA mutation. BRCA was downregulated after the cotreatment and may serve as a biomarker to recognize the response to PARPi (130).

Based on preclinical studies, a phase Ib trial was carried out among 24 patients with high-grade ovarian carcinoma and 46 patients with TNBC. The purpose was to investigate the maximum tolerated dose, toxicities, pharmacokinetics and biomarkers of the responses of combination treatment of PI3K inhibitors and PARPi. The recommended dose is 50 mg BKM120 qd with 300 mg olaparib bid. A synergistic effect was proven in phase I clinical trials regardless of the status of gBRCA; therefore, further clinical studies should be performed (131).

Taselisib. Taselisib is an inhibitor of p110α, p110δ and p110γ (132) and has demonstrated a clinical benefit in tumors with PIK3CA mutations in early clinical trials (133). In 26 head and neck squamous cell carcinoma (HNSCC) cell lines, pretreatment with taselisib enhanced radiation-induced apoptosis, as assessed via flow cytometry and clonogenic survival assays. Furthermore, the DDR was suppressed and G2/M-phase arrest was prolonged. This strategy provided a basis for further investigations regarding combined therapy (132).

Alpelisib. Alpelisib targets PI3Kα and its application in breast cancer is currently under investigation. Mutation or amplification of the PIK3CA gene that encodes the p110α subunit of PI3K (134) occurs frequently in solid tumors and therefore provides a new therapeutic target for tumors (135). Cotreatment of alpelisib with fulvestrant has been approved for application in postmenopausal females with hormone receptor-positive, HER-2-negative, PIK3CA-mutated, advanced or metastatic breast cancer (136). Kim *et al* (137) performed an *in vitro* study using eight GC cell lines, three of which were PIK3CA mutants. However, regardless of the PIK3CA mutation status, all eight cell lines exhibited decreased AKT and S6K1 phosphorylation levels and induced G0/G1-phase arrest when treated with alpelisib. Furthermore, the combination of alpelisib and paclitaxel produced a synergistic anti-tumor effect via increased DNA damage and apoptosis (137). Based on these preclinical works, it is presumed that the combination of PARPi with alpelisib may contribute to tumor therapies. To assess the safety and recommended dose of olaparib combined with alpelisib, a multicentre, open-label, phase Ib trial enrolling 34 patients was established following a 3+3 dose-escalation design (NCT01623349). Of the 28 patients in the dose-escalation cohort, 10 (36%) achieved a partial response and 14 (50%) had stable disease, which suggested that synergy of olaparib and alpelisib offers a feasible strategy for tumor treatment without insufferable adverse effects (138).

AKT inhibitors. AKT was reported to inhibit TOPBP1, a DNA repair/replication fork origin firing regulator, implying impacts on DNA damage and synergistic effects with PARPi (139). Based on this molecular mechanism, capivasertib has been studied in clinical trials to investigate its efficacy and safety when combined with PARPi.

Ipatasertib. Ipatasertib is a potent inhibitor targeting the ATP-binding domain of all three isoforms of AKT kinase (140). Strong antitumor activity of ipatasertib has been indicated in various cancer types, including breast, prostate, lung and colon cancer (141). Studies have revealed that AKT kinase contributes to DDR, DSB repair and apoptosis; however, the mechanisms have remained to be fully elucidated. Two activated mutations in AKT1-TDSD and AKT1-E17K have been demonstrated to accelerate DSB repair through a genetic approach (142). In an *in vitro* study, Yu *et al* (143) observed increased intracellular ROS levels and subsequently increased DNA damage after treatment with ipatasertib.

Capivasertib. Capivasertib is a potent selective pan-Akt kinase inhibitor. The efficacy of capivasertib monotherapy has been verified in various preclinical studies (144,145). This may be associated with signalling crosstalk as well as feedback loop disruption. A phase I trial enrolled 64 patients with advanced solid tumors to assess the efficacy of capivasertib with olaparib. In the first trial to combine PARPi and AKT inhibitor, 24 (44.6%) of 56 evaluable patients achieved a clinical benefit, including patients with gBRCA1/2m or BRCA1/2 wild-type (146). This observation suggests the requirement for further cotreatment therapy. Currently, an active but not recruiting nonrandomized open-label phase Ib study (NCT02208375) aims to investigate the oral PARPi olaparib with the oral AKT inhibitor capivasertib among patients with recurrent endometrial cancer, TNBC or ovarian, primary peritoneal or fallopian tube cancer. However, the maximum tolerated dose, toxicity profiles, response rate and PFS remain to be fully determined.

Perifosine. Perifosine is an oral alkylphospholipid that inhibits AKT kinase activity by interfering with the pleckstrin homology domain and impairing its membrane localization and phosphorylation (147). Flow cytometry suggested arrested cell cycle progression at the G2 phase and western blot analysis indicated PARP activation upon perifosine treatment (148). In TNBC cells, perifosine was observed to induce RAD51 ubiquitination, block the RAD51-BRCA2 interaction and decrease HR-mediated DNA DSB repair. Based on this mechanism, research has explored the efficacy of the combination of perifosine and olaparib and revealed a synergistic antitumor activity *in vivo* (149).

MK-2206. MK-2206 is an orally active allosteric inhibitor targeting AKT1 and AKT2 enzymes and is under investigation for the treatment of solid tumors (150). In EOC cells, higher AKT activity was reported to impact DNA damage, which implied a synergism between MK-2206 and cisplatin or olaparib (151).

MTORC inhibitors. The mTORC1 signalling pathway has a critical role in the DDR to DNA damage (152,153). Everolimus has been applied in clinical trials to determine the synergism in concurrent treatment with PARPi.

Rapamycin. Rapamycin has acute activity on mTORC1 but chronic activity on mTORC2, the balance of which may be of vital importance in ageing research (154). Studies have revealed its capacities, such as cancer cell proliferation inhibition and lifespan promotion (155).

In a study including 35 patients with kidney transplant, DNA damage was analysed in peripheral blood lymphocytes. The decrease in DNA damage in lymphocytes after rapamycin treatment offered a new strategy for antitumor therapies (156). In addition to the DNA damage in lymphocytes, sperm DNA damage has also been measured among infertile patients with and without varicocele, which indicated a positive correlation with mTOR gene expression (157). Furthermore, in *in vivo* and *in vitro* TNBC models, rapamycin inhibited Rad51 focus formation induced by olaparib, suggesting the synergistic effect of cotreatment via DNA DSB or SSB repair (157).

Everolimus. Everolimus is a selective oral inhibitor of the mTORC1 complex, which is frequently activated in human malignancies. As a result, everolimus is supposed to slow tumor growth instead of inducing cell death (158).

Treatment with everolimus inhibited the increase in p21 and the expression of DNA repair genes and mitotic checkpoint regulators, which has been observed in multiple myeloma cells (159), hepatocytes with chronic liver injury (160) and

isogenic tumor cell lines (161). Studies have further suggested that the combination of everolimus and olaparib inhibited the growth of tumors, and were performed in clone A, U87-MG xenografts and BRCA2-mutated patient-derived xenografts of breast cancer (162,163).

A phase I open-label clinical study (NCT03154281) is recruiting 24 patients to investigate the safety and tolerability of niraparib in combination with everolimus in advanced gynaecological malignancies and breast cancer. The outcome of this study may offer fundamental support for the next phase of clinical studies.

5. Rat sarcoma (RAS)/rapidly accelerated fibrosarcoma (RAF)/mitogen-activated proteinkinase kinase (MEK)/ERK pathway inhibitors and PARPi

RAS was first identified as a downstream signalling molecule of EGF in 1984. EGF activates EGFR on the membrane and subsequently initiates guanine exchange factor to load RAS with GTP (164). The RAS-GTP dimer recruits RAF or RAF/MEK heterodimers to the plasma membrane and contributes to RAF activation via back-to-back dimerization, while a face-to-face homodimer facilitates the activation of MEK (165). An early study explored the downstream activity of MEK and revealed that MEK1/2 was able to regulate ERK1/2 by phosphorylating the conserved Thr/Tyr in the activation loop (166). This pathway has been confirmed to be related to DNA damage *in vitro* and *in vivo* and its inhibition promotes DNA damage (167).

RAF inhibitors. The active site of RAF is located at the interface of the N-terminal lobe and C-terminal lobe. RAF inhibitors form imperfect dimers in various positions of the αC-helix within each promoter. Unlike most small molecular inhibitors targeting all cells, RAF inhibitors selectively suppress RAF activity and downstream signalling pathways in BRAF-mutant cells (168).

Dabrafenib. Dabrafenib is an oral drug approved by the FDA and EMA alone or in combination with trametinib for the treatment of BRAF-mutant unresectable or metastatic melanoma and advanced NSCLC (169). Based on The Cancer Genome Atlas and GTEx databases, Jiang *et al* (170) determined that the expression of the MUC gene was altered by dabrafenib treatment, which facilitates DNA damage. Another study investigated the ROS levels in melanoma models and indicated elevated ROS levels, as well as increased DNA damage both *in vivo* and *in vitro* (171).

Vemurafenib. Vemurafenib is a selective BRAF V600E kinase inhibitor that binds to its ATP-binding sites and therefore inhibits cell proliferation in cells with BRAF V600E mutations (172). It is known that nonmelanoma skin cancer exhibits an ultraviolet radiation-induced DDR. Using south-western blotting, DNA damage and repair capacity were analysed and the results revealed that vemurafenib hampered the DDR (173). This finding is consistent with the previous study exploring the relationship between vemurafenib treatment and the DDR (174).

MEK inhibitors. MEK, encoded by 7 genes, is a downstream protein of RAF. Instead of targeting the ATP binding sites directly, MEK inhibitors bind to the pocket adjacent to them. This subset of therapies has been under investigation in phase I-III clinical trials in patients with various cancer types, such as advanced NSCLC, melanoma, colon cancer, ovarian cancer and papillary thyroid cancer (175-178).

Selumetinib. As a potent ATP-noncompetitive MEK1/2 inhibitor, selumetinib suppresses ERK phosphorylation and has been approved as an adjuvant treatment for thyroid cancer and as monotherapy in neurofibromatosis type 1 (179). To identify cofactors that may enhance the antitumor capacity of selumetinib, human tumor xenograft models were utilized. Research has indicated an improved antitumor effect compared to monotherapy and an increased level of γH2AX compared to temozolomide, a DNA-alkylating agent, when applied as a cotreatment of selumetinib and temozolomide. The data suggested a potential mechanism of the combination of selumetinib with PARPi, which may suppress tumor growth and proliferation in a DDR-inhibitory manner (180). Encouraged by these findings, a nonrandomized clinical trial is recruiting patients with endometrial, ovarian and other solid tumors with RAS pathway alterations and ovarian tumors with PARPi resistance.

Trametinib. Trametinib is a second-generation small molecular inhibitor of MEK kinase, which is an ATP noncompetitive inhibitor against both MEK1 and MEK2 with a longer half-life and small peak-to-trough ratios. An *in vitro* study indicated that trametinib contributed to cell proliferation deceleration, cell cycle arrest in G1 phase and apoptosis (181).

As validated by Estrada-Bernal *et al* (182), mutant KRAS is frequent in almost 90% of pancreatic adenocarcinoma, which offers the potential to gain resistance to radiation and chemotherapy through RAF-MER-MAPK pathway activation. Clonogenic assays, comet assays and nuclear foci formation indicated a decrease in DNA DSB repair in multiple cell lines treated with trametinib, providing evidence of facilitated repression of both HR and NHEJ (182). The expression and activation of DNA repair proteins was determined by immunoblotting and suppression of BRCA1, DNA-PK, RAD51, RPM2 and Chk-1 was observed.

6. Src inhibitors and PARPi

As a nonreceptor protein tyrosine kinase related to malignancy formation, Src has been under investigation for three decades. Src is a nonprimary protein that contributes to tumor generation but rather participates in numerous signalling pathways associated with cell division and survival. Therefore, Src inhibitor monotherapy is not sufficient for tumor suppression (183). In BRCA2-null prostate cancer cell lines, upregulation of Src phosphorylation and a synergistic effect of Src inhibitors with PARPis were observed (184).

Dasatinib. Dasatinib is a potent multikinase inhibitor that targets Src family kinase and therefore blocks cell duplication, migration and invasion. In addition, it promotes apoptosis of tumor cells, suppresses metastatic spread of tumor cells and sensitizes or resensitizes tumor cells to multiple therapies (185). Among studies performed in 6 HNSCC cell lines as well as NSCLC cell lines with kinase-inactivating BRAF mutation (KIBRAF), dasatinib suppressed the radiation-induced DDR in HN-5 cells and induced DNA damage to senescence

Table II. Clinical trials of poly(ADP ribose) polymerase inhibitor and small molecule inhibitor cotreatment.

Trial (phase)	Author, year	Setting	Treatment	Efficacy	(Refs.)
GOAL (phase IIB/II)	Garcia-Campelo, 2020	Stage IV NSCLC	Gefitinib + Olaparib vs. Gefitinib	mPFS (mos): 10.9 vs. 12.8	(46)
NCT01116648 (phase I)	Liu, 2013	HGSOC	Cediranib + Olaparib vs. Olaparib	mPFS (mos): 16.5 vs. 8.2	(75)
NCT01116648 (phase I/II)	Liu, 2014	Platinum-sensitive, relapsed, high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer, or those with gBRCAm	Cediranib + Olaparib vs. Olaparib	mPFS (mos): 17.7 vs. 9.0	(76)
NCT01116648 (phase I/II)	Liu, 2019	Relapsed platinum-sensitive ovarian cancer of high-grade serous or endometrioid histology or had gBRCAm	Cediranib + Olaparib vs. Olaparib	mPFS (mos): 16.5 vs. 19.4 (gBRCAm); mPFS (mos): 16.5 vs. 5.7 (non-gBRCAm)	(77)
NCT02446600 (phase III)	Tattersall, 2022	Platinum-sensitive ovarian, fallopian tube or primary peritoneal cancer	Cediranib + Olaparib vs. Olaparib	mPFS (mos): 10.4 vs. 8.2	(81)
NCT03586661 (phase Ib)	Sun, 2020	Recurrent endometrial and recurrent ovarian, primary peritoneal or fallopian tube cancer	Copanlisib + Niraparib vs. Niraparib	Not specified	(125)
NCT01623349 (phase I)	Matulonis, 2017	High-grade ovarian carcinoma and triple-negative breast cancer	BKM120 + Olaparib vs. Olaparib	mPFS (mos): 6.9 vs. 4.8	(131)
NCT01623349 (phase Ib)	Konstantinopoulos, 2019	Recurrent EOC of high-grade serous histology or any histology but with known gBRCAmut or recurrent triple-negative breast cancer or any histology with known gBRCAmut	Alpelisib + Olaparib vs. Olaparib	10 (36%) achieved a partial response and 14 (50%) had stable disease	(138)
NCT03660826 (phase I)	Yap, 2020	Advanced solid tumors	Capivasertib + Olaparib vs. Olaparib	24 (44.6%) of 56 evaluable patients achieved clinical benefit, including patients with gBRCAm or BRCA1/2 wild-type	(146)

mPFS, median progression-free survival; mos, months; gBRCAm, deleterious germline BRCA1/2 mutation; NSCLC, non-small cell lung cancer; HGSOC, high-grade serous ovarian cancer; EOC, epithelial ovarian cancer.

dependent on Chk1 and p21 in KIBRAF (186,187). Based on the crosstalk associated with DNA damage, the effect of the combination therapy of dasatinib with olaparib has been evaluated in 18 cell lines representative of the most frequent solid tumors, which exhibited synergism in treatment (188).

7. Conclusion and future perspectives

The DNA damage repair system provides a genome-wide surveillance mechanism to preserve chromosome integrity by recognizing and repairing both exogenous and endogenous DNA defects. Impairment of these systems results in mutations and subsequently leads to tumorigenesis. However, no significant clinical responses were observed among patients with BRCA mutations or HRD. Limited monotherapy efficacy and drug resistance have become major concerns in certain targeted therapies, such as PARPi. There may be a risk of secondary tumors and therefore, the clinical management and efficacy of PARPi require to be further investigated in the future. Based on these aspects, combination therapies are currently under urgent investigation. Small molecular inhibitors have been approved by the FDA as targeted therapies. Their roles in the DDR were described above and are summarized in Table I, Fig. 1; cotreatment with PARPi and small molecular inhibitors may be performed to improve the limited efficacy of monotherapy. In Table II, the phase I/II clinical trials were summarized. The safety and efficacy have been confirmed and the tolerable doses have been determined through these trials. In the future, it is pivotal to identify patients who will benefit the most from the synergistic treatments. Furthermore, indicators to determine the likelihood of a clinical benefit may be obtained from matched tissue and blood samples. In addition to targeted therapies, immune therapies have become hot research topics and a prominent synergism has been confirmed in the cotreatment of anti-programmed death ligand 1 and PARPi. It remains to be determined whether small molecular inhibitors are able to sensitize cancers to immune therapy.

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Competing interests

The authors declare that they have no competing interests.

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