Review Article

Clinical translation for targeting DNA damage repair in non-small cell lung cancer: a review

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Abstract: Despite significant advancements in screening, diagnosis, and treatment of non-small cell lung cancer (NSCLC), it remains the primary cause of cancer-related deaths globally. DNA damage is caused by the exposure to exogenous and endogenous factors and the correct functioning of DNA damage repair (DDR) is essential to maintain of normal cell circulation. The presence of genomic instability, which results from defective DDR, is a critical characteristic of cancer. The changes promote the accumulation of mutations, which are implicated in cancer cells, but these may be exploited for anti-cancer therapies. NSCLC has a distinct genomic profile compared to other tumors, making precision medicine essential for targeting actionable gene mutations. Although various treatment options for NSCLC exist including chemotherapy, targeted therapy, and immunotherapy, drug resistance inevitably arises. The identification of deleterious DDR mutations in 49.6% of NSCLC patients has led to the development of novel target therapies that have the potential to improve patient outcomes. Synthetic lethal treatment using poly (ADP-ribose) polymerase (PARP) inhibitors is a breakthrough in biomarker-driven therapy. Additionally, promising new compounds targeting DDR, such as ATR, CHK1, CHK2, DNA-PK, and WEE1, had demonstrated great potential for tumor selectivity. In this review, we provide an overview of DDR pathways and discuss the clinical translation of DDR inhibitors in NSCLC, including their application as single agents or in combination with chemotherapy, radiotherapy, and immunotherapy.

Keywords: DNA damage repair (DDR); non-small cell lung cancer (NSCLC); DNA damage repair inhibitor (DDR inhibitor)

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Introduction

DNA damage and genomic instability in non-small cell lung cancer (NSCLC)

In recent decades, lung cancer (LC) research has shown significant advancements in screening, diagnosis, and treatment, thanks to the rapid development of technologies such as low-dose computed tomography (LDCT) scan, minimal invasive techniques (1), stereotactic ablative radiotherapy (SABR), new targeted therapy, and new immunotherapy. These advancements have improved the survival rate of LC patients by 56% in men and 32% in women (2). Despite this progress, LC remains the leading cause of cancer death, with an estimated 2.2 million new cases and 1.8 million deaths recorded in 2020 (3).

LC has two major pathological subtypes: the predominant NSCLC (85%) and small cell lung cancer (SCLC; 15%). NSCLC can be further divided into lung adenocarcinoma (LUAD; 50%), squamous cell carcinoma (LUSC; 40–30%), and large cell carcinoma (LCC; 20–10%) respectively.

The stability of the genome is paramount to the survival and reproduction of all cells. Friedberg *et al.* reported that human body is subjected to between 10,000 and 1,000,000 instances of DNA damage per day (4). DNA damage caused by endogenous (for example free radicals) (5,6) or exogenous (for example ionizing radiation) factors (7-9) can lead to genome instability and diseases such as cancer. DNA double strand breaks (DSBs) are the most severe type of damage, as accumulation of incorrectly repaired or unrepaired DSBs can cause mutation, genomic instability, or induce cell death (10).

LC generally exhibits a distinct genomic profile compared with other tumors, with high somatic mutational burden (11). Smoking is the main cause of LC, accounting for 90% of cases, however, approximately 20% of newly-diagnosed LUAD cases are attributed to non- or light-smokers in developed countries now. Smokers have higher somatic mutational burden than non-smokers (12) and smokers carry additional genomic instability processes that are likely to contribute to tumor progression (13). NSCLC primary tumors exhibit high genomic diversity with heterogenous tumor driver mutations present that clones may not all carry the same mutation making it very difficult for the patient to benefit from targeted therapies.

DNA damage is repaired by specific cellular pathways during normal cell cycle. When DNA damage fails to be repaired or excised, the mutations will eventually trigger carcinogenesis. For instance, epidermal growth factor receptor (EGFR) exon 19 deletion corrected with decreased expression of ERCC1 impacts ERCC1 foci formation in response to DNA cross-link damage, contributing to DNA damage repair (DDR) deficiency (14). Germline variants of ataxia-telangiectasia mutated (ATM), tumor suppressor 53 protein (TP53), breast cancer 2 (BRCA2), EGFR, and Parkinson's Disease-Associated protein 2 (PARK2) had been linked to cancer risk in Mendelian disorders (15). Chromosomal instability may cause tumor heterogeneity and drug resistance, and epigenetic silencing of DNA repair genes may promote tumorigenesis. For instance, over 60% NSCLC cases present aneuploidy. Chromosomal instability elevates in the NSCLC patients with ROS1 fusion treated with crizotinib (16). In addition to mutations, epigenetic silencing of DNA repair genes may promote tumorigenesis. The Aurora kinase (AURK) family is involved in mitosis and chromosomal segregation. Abnormalities in AURK proteins can be associated with genomic instability. Overexpression of AURKA (17-22) or AURKB (23-25) was corrected with poor prognosis of overall survival (OS) in NSCLC. Some researches revealed that AURKA and AURAB was associated with resistance of EGFR-TKI (26-28), chemotherapy (29-31) and/or radiotherapy (17,32,33) in LC in pre-clinical models.

Target therapy and immune checkpoint inhibitors (ICIs)-based treatment with/without chemotherapy have been widely used in NSCLC. Despite a number of inhibitors had been developed for targeting EGFR, ALK, ROS1, KRAS, MET, NTRK, HER2 and RET, LUSC and LCC rarely present mutations in tyrosine kinase receptors compared with LUAD.

DNA repair in NSCLC

Various DNA repair pathways, including direct reversal repair (DRR), base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), non-homologous end joining (NHEJ), homologous recombination (HR), and interchain crosslinking repair, can circumvent DNA damage.

DNA damage caused by various agents such as alkylation, oxidation, ultra-violet (UV) radiation, and cross-linking requires different repair mechanisms. The mechanism of DRR is involved in reversing the *O*-alkylated DNA damage caused by methylguanine methyl transferase (MGMT) (34). DRR also removes photolesions caused by UV radiation with DNA-photolyase (35,36). The activity of the DNA repair enzyme 8-oxoguanine DNA N-glycosylase (OGG), is associated with LC (37). BER can repair small base

lesion damage such as the damage on 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-OHdG) by radicals with DNA glycosylase, apurinic/apyrimidinic (AP) endonuclease, DNA polymerase and DNA ligase (38,39). The BER pathway is one component of the larger DDR system that repairs and works with other pathways.

The NER mechanism is responsible for repairing Cyclobutane pyrimidine dimers (CPD) and pyrimidine-pyrimidone (6-4) photoproducts [(6-4)PP] caused by UV radiation (38). There is a group of proteins (XPA-XPG, RPA, CSA, CSB, ERCC6 and RAD23B, etc.) that are involved in NER process (40). In LC, Lys751Gln (41) and ERCC2-rs13181 (42) polymorphism pose significant risk in allele, heterozygote, and dominant comparisons.

MMR corrects base mismatch pairs and small loops. MMR does it with MSH2, MSH6, MLH1, PCNA and RPA proteins by identifying the site of the insertion-deletion loop, removing the lesion site and replacing it with newly synthesized DNA (43). These repair mechanisms have been associated with different cancers, including LC. MMR deficiency (dMMR) leads to multiple mutations at repetitive DNA sequence stretches known as microsatellite instability (MSI). MSI-high/dMMR varies widely among different cancer types. In LUAD, it accounted for 0.53–1% while 0.6% in LUSC respectively (44).

Currently, ICIs had been approved for MSI-high/dMMR in solid tumors. The deficiency expression of MSH2 or MLH1 in LUAD has been associated with resistance to immunotherapy (44). A study had reported MSI-high/dMMR group demonstrated greater survival and responded to ICIs in NSCLC (45). The high tumor mutation burden (TMB) corrected with DDR gene mutations and mutations of DNA methyltransferase 3a (DNMT3A) and DDR pathway-related genes increased tumor-infiltrating lymphocytes (46) and were important predictive markers for OS in NSCLC (47).

While BER, NER and MMR fix single-strand break (SSB) repair, DSB repair requires HR, NHEJ and alternative end joining (alt-EJ) pathways. Homologous recombinant repair (HRR) is a complicated process pathway to repair DSB in S and G2 phases of the cell cycle. HRR faithfully duplicates the genome by providing the critical support for DNA replication and telomere maintenance due to its dependence on the existence of sister chromatids. For instance, in HRR, RAD51 is the core mechanism of RAD51 filament formation and DNA strand invasion. This repair also plays a role in the repair of DNA interstrand crosslinks (ICLs) with the collaboration of NER through involvement of ERCC1 endonuclease (48). The NHEJ pathway is essential for repairing DSBs throughout the cell cycle, while alt-EJ assists in repairing the residual DSBs when NHEJ and HR are unavailable. The tumor suppressor gene TP53 plays an important role in cell cycle regulation, and frequent TP53 mutations may cause DNA damage, leading to tumorigenesis and metastasis. The repair of interstrand crosslinking requires Fanconi anemia (FA) active proteins. It was reported that 49.6% NSCLC patients identified having deleterious DDR mutations and associated with improved clinical outcomes of ICIs (49). The understanding of these repair mechanisms can help in the development of more effective therapies for LC and other cancers.

Targeting DDR pathways can be exploited as a means of cancer therapy. In the following sections, we will discuss several DDR inhibitors including their application as monotherapy or in combination with chemotherapy, radiotherapy and immunotherapy and demonstrate their current landscape of research in NSCLC for clinical use. We also discuss potential predictive biomarkers of response in the pre-clinical or clinical trials. The list of DDR inhibitors is presented in *Table 1*.

Strategies for targeting the DDR in NSCLC

Single agent activity and determinants of sensitivity

Poly (ADP-ribose) polymerase (PARP) inhibitor

The PARP is a family of nuclear protein enzymes that are activated upon binding to damage DNA and involved in DDR. Inhibition of PARP impair repair of SSBs that leads to synthetic lethality in HR-deficient (such as deleterious of BRCA1/2) cells which unable accurately repair DSBs. Several PARP inhibitors have been approved by FDA against different cancers with or without HR-deficient such as olaparib, niraparib, rucaparib, talazoparib (50). The development of veliparib is not very successful, not very successful as it resulted in less PARP trapping and was inactive (51).

Studies on PARP1/2 inhibitor as a monotherapy had purported it as a novel therapeutic strategy for NSCLC cells with ERCC1-deficient (52), or deficiencies in HR genes [loss of function of BRCA1 and BRCA2, ATM and elevated RAD54L expression (53), or lysine methyl transferase 2C/D (KMT2C/D) mutation (54), or ELF3 expression (55), or AXL expression (56)]. PPP2R2A is commonly downregulated in NSCLC cells, and loss of PPP2R2A may serve as a marker to predict sensitivity to PARP inhibitor (57).

Table 1 List of DDR inhibitors in clinical trials

Type	Inhibitor	Selectivity/specificity	Status
PARP inhibitor	Niraparib	PARP1/2 (IC50 =3.8 nM/2.1 nM)	Approved in OC
	Olaparib	PARP1/2 (IC50 =5 nM/1 nM)	Approved in OC, BC, mCRPC and pancreatic cancer
	Talazoparib	PARP1/2 (Kis: 1.2/0.85 nM)	Approved in mCRPC and BC
	Rucaparib	PARP 1, 2 and 3 (IC50 =0.8, 0.5 and 28 nM)	Approved in mCRPC and OC
	Veliparib	PARP1/2 (Ki =5.2 nM/2.9 nM)	Phase 3 NSCLC
	RP12146	PARP1/2 (IC50 =0.62 nM/0.44 nM)	Phase 1 solid tumors
	AZD5305	PARP1/2 (IC50 =3 nM/1,400 nM)	Phase 1/2 solid tumors
	IMP4297	PARP1/2 (IC50 =6.27 nM/1.57 nM)	Phase 1 SCLC
	Parimparib	PARP1/2 (IC50 =0.83/0.11 nM)	Approved in OC in China
ATR inhibitor	Ceralasertib (AZD6738)	ATR (IC50 =1 nM)	Phase 3 NSCLC; phase 2 SCLC; phase 2 solid tumors; phase 2 ovarian cancer; phase 1 HNSCC
	M6620 (VX970, berzosertib, VE822)	ATR (IC50 =0.2 nM); >100-fold ATR *vs.* ATM/DNA-PK	Phase 2 SCLC; phase 1 solid tumors; phase 1 OC
	BAY1895344 (elimusertib, NSC#810486)	ATR (IC50 =7 nM); >60-fold selectivity to ATR compared to PI3K/AKT/mTOR pathway	Phase 1 solid tumors
	Gartisertib (M4344, YX-803)	ATR (IC50 <0.2 nM); >100-fold selectivity PI3K	Phase 1 solid tumors
	M1774 (tuvusertib)	ATR (IC50 =5 nM)	Phase 1/2 SCLC; phase 1 solid tumors
	ATRN-119	ATR (IC50 =4 nM), ATM (>600-fold), DNA-PK (>2,000-fold) and mTOR (>2,000-fold)	Phase 1 solid tumors
	RP-3500 (camonsertib)	ATR (IC50 =1 nM); 30-fold selectivity for ATR over mTOR (IC50 =120 nM) and >2,000-fold selectivity over ATM, DNA-PK, and PI3Kα kinases	Phase 1/2 solid tumors
	ART-0380	ATR	Phase 1/2 solid tumors
	ATG-018	ATR	Phase 1/2 solid tumors and hematologic malignancies
	IMP9064	ATR	Phase 1/2 solid tumors
AURKA inhibitor	AS703569 (R763)	ATR (IC50 =0.5 nM)	Phase 1 solid tumors
	Alisertib (MLN8237)	Aurora A (IC50 =1.2 nM), >200-fold higher selectivity for Aurora A than Aurora B	Phase 3 peripheral T-cell lymphoma; phase 2 SCLC; phase 2 OC; phase 2 AML; phase 2 DLBCL; phase 1/2 NSCLC
	ENMD2076	Aurora A (IC50 =14 nM), B (IC50 =290 nM); Flt3 (IC50 =3 nM); VEGFR2 (IC50 =36 nM); KIT (IC50 =120 nM); Abl (IC50 =295 nM); Abl (T315I) (IC50 =81 nm)	Phase 2 OC; phase 2 TNBC; phase 1 hepatocellular carcinoma; phase 1 multiple myeloma

Table 1 (*continued*)

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Type	Inhibitor	Selectivity/specificity	Status
	MK5108	Aurora A (IC50 =0.084 nM), B (IC50 =27 nM), C (IC50 =19 nM)	Phase 1 solid tumors
	VIC-1911	Aurora A (IC50 =0.4 nm)	Phase 1 hepatocellular carcinoma; phase 1 NSCLC
	LY3295668	Aurora A (IC50 =0.8 nm), B (IC50 =1,038 nm)	Phase 1/2 NSCLC Phase 1 SCLC
	TAS-119	Aurora A (IC50 =1.0 nm), B (IC50 =95 nM)	Phase 1 solid tumors
AURKB inhibitor	Barasertib (AZD1152)	Aurora A (IC50 =1 nm), B (IC50 =1,100 nm)	Phase 2/3 AML
Pan-AURK inhibitor	Danusertib (PHA739358)	Aurora A (IC50 =13 nm), B (IC50 =79 nm), C (IC50 =61 nm); Abl (IC50 =25 nm); VEGFR3 (IC50 =161 nm)	Phase 2 multiple myeloma; phase 2 leukemia; phase 2 prostate cancer
	AMG900	Aurora A/B/C (IC50 =5 nM/4 nM/1 nM); >10-fold selective for Aurora kinases than p38α, Tyk2, JNK2, Met and Tie2	Phase 1 hematologic malignancies; phase 1 solid tumors
	AT9283	Aurora A, B (IC50 =3 nm); JAK2 (IC50 =1.2 nm); Abl (T315I) (IC50 =4 nm); Flt3 (IC50 =10 nm)	Phase 2 hematologic malignancies
APE1 inhibitor	Methoxyamine (TRC-102)	APE1 (IC50 =~50 mM)	Phase 2 NSCLC; phase 1/2 solid tumors
	Lucanthone	APE1 (IC50 =5 μM)	Phase 2 glioblastoma
	E3330 (APX3330)	APE1 (IC50 =5 μM)	Phase 1 solid tumors
	Gossypol (AT-101)	APE1 (IC50 =2.5 μM)	Phase 2 NSCLC; phase 2 hematologic malignancies; phase 2 glioblastoma; phase 2 prostate cancer
DNA-PK inhibitor	Nedisertib (peposertib, M3814, MSC2490484A)	DNA-PK (IC50 <3 nM)	Phase 1/2 rectal cancer; phase 1/2 SCLC
	VX-984 (M9831)	DNA-PK (IC50 =88±64 nM)	Phase 1 solid tumors
	CC-115	DNA-PK (IC50 =0.013 μM); mTOR (IC50 =0.021 μM)	Phase 1 solid tumors
	AZD7648	DNA-PK (IC50 =0.6 nM), >100-fold selective against 396 other kinases	Phase 1/2 solid tumors
	LY3023414 (samotolisib)	DNA-PK (IC50 =4.24 nM); mTOR (IC50 =165 nM); PI3Kα, PI3Kβ, PI3Kδ, PI3Kγ (IC50 =6.07 nM, 77.6 nM, 38 nM, 23.8 nM)	Phase 2 NSCLC; phase 2 solid tumors; phase 2 prostate cancer; phase 2 endometrial cancer; phase 2 PDAC; phase 2 TNBC
	Voxtalisib (XL765, SAR245409)	DNA-PK (IC50 =150 nM); mTOR (IC50 =157 nM); PI3K (IC_{50}s =39, 113, 9 and 43 nM for p110α, p110β, p110γ and p110δ)	Phase 2 OC; phase 1/2 BC; phase 2 lymphoma; phase 1 NSCLC; phase 1 glioblastoma
	XRD-0394	ATM and DNA-PK	Phase 1 solid tumors

Table 1 (*continued*)

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Type	Inhibitor	Selectivity/specificity	Status
WEE1 inhibitor	ZN-c3 (NCT04158336)	WEE1 (IC50 =3.9 nM)	Phase 2 pancreatic cancer; phase 2 OC; phase 2 uterine serous carcinoma; phase 1/2 AML
	Debio0123 (NCT03968653)	WEE1 (IC50 =0.8 nM)	Phase 1 solid tumors; phase 1 SCLC; phase 1/2 glioblastoma
	AZD1775 (adavosertib, MK1775)	WEE1 (IC50 =5.2 nM)	Phase 2 pancreatic cancer; phase 2 OC; phase 2 uterine serous carcinoma; phase 2 TNBC; phase 2 SCLC; phase 2 NSCLC
	IMP7068	WEE1	Phase 1 solid tumors
	SY-4835	WEE1	Phase 1 solid tumors
CHK1/CHK2 inhibitor	Prexasertib (LY2606368)	CHK1 (IC50 <1 nM); CHK2 (IC50 =8 nM); RSK1 (IC50 =9 nM)	Phase 2 OC; phase 2 SCLC
	MK8776 (SCH900776)	CHK1 (IC50 =3 nM), 500-fold selectivity against CHK2	Phase 2 hematologic malignancies
	GDC-0575 (ARRY-0575, RG774)	CHK1 (IC50 =1.2 nM)	Phase 1 solid tumors
	GDC-0425	CHK1 (IC50 =3 μM)	Phase 1 solid tumors
	PHI-101	CHK2	Phase 1 ovarian cancer
	BBI-355	CHK1	Phase 1/2 solid tumors
	PEP07	CHK1 (IC50 =1 nM); CHK2 (IC50 =1,630)	Phase 1 solid tumors
	SRA737	CHK1 (IC50 =1.4 nM), >1,000-fold selectivity against CHK2 and CDK1	Phase 1 solid tumors
	LY2603618 (rabusertib)	CHK1 (IC50 =7 nM); CHK2 (IC50 =12,000 nM)	Phase 1 NSCLC
	LY2880070	CHK1 (IC50 <0.001 μM)	Phase 1 solid tumors

DDR, DNA damage repair; PARP, poly (ADP-ribose) polymerase; OC, ovarian cancer; BC, breast cancer; mCRPC, metastatic castration-resistant prostate cancer; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ATR, ataxia telangiectasia and Rad3 related protein; HNSCC, head and neck squamous cell carcinoma; AML, acute myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; TNBC, triple negative breast cancer; AURK, Aurora kinase; DNA-PK, DNA-dependent protein kinase; PDAC, pancreatic ductal adenocarcinoma.

In advanced NSCLC, PARP inhibitor shows limited antitumor activity. Two trials tested olaparib maintenance in NSCLC patients with chemosensitivity; compared with placebo, a trend toward longer progression-free survival (PFS; 16.6 *vs.* 12.0 months) and OS (59.4 *vs.* 31.3 months) (58); compared with standard of care (SoC), no significant PFS (2.7 *vs.* 2.7 months) and OS (14.3 *vs.* 14.1 months) differences were observed (59). In the SAFIR02-lung trial, 2.1% (8/379) patients with pathogenic BRCA1/2 mutation indicated limited sensitivity to olaparib (60). Antitumor activity of niraparib single-agent was noted in NSCLC in the phase I dose-escalation trial; tumor shrinkage occurred in all two enrolled NSCLC patients, one BRCA2 mutation carrier had stable disease (SD) for 175 days, the other previous heavily treated patient maintained SD for 316 days (61). Talazoparib failed to show sufficient level of efficacy with 4% (1/24) overall response rate (ORR) and 54% (13/24) disease control rate (DCR) in LUSC with HRR deficiency [alteration in ATM, ataxia telangiectasia and Rad3 related protein (ATR), BRCA1, BRCA2, or PALB2] in a phase 2 Lung-MAP subgroup S1400G (62). In another subgroup S1900A of Lung-MAP, with rucaparib, the study chose stage IV NSCLC patients with high genomic loss of heterozygosity (LOH) and/or BRCA1/2 mutated and progression on or after platinum base chemotherapy and/or programmed death (ligand) 1 (PD1/PD-L1) antibody;

the study showed activity with 7% ORR (4 patients: 3 BRCA1/2-mutated and 1 LOH-high) and 7.8 months OS (63) respectively.

In these EGFR mutated LC patients, low BRCA1 mRNA levels were associated with longer PFS in erlotinib-treated patients and acquired resistance of EGFR-TKI treatment could promote the sensitivity of PARP inhibitors (64). A case report showed that olaparib with dacomitinib could prolong the survival of NSCLC patients with leptomeningeal metastasis (65). When compared combination of gefitinib and olaparib with solely gefitinib, the combination did not provide significant benefit (10.9 *vs.* 12.8 months) in a phase II trial (66); this could be attributed to high BRCA1 mRNA expression and low mRNA expression of CtIP (67). The phase I study of niraparib in combination with osimertinib in EGFR-mutated advanced LC is underway (NCT03891615) (*Table 2*).

AZD5305 is a second generation, highly selective PARP1 inhibitor. It is currently in phase I/II trial as monotherapy and in combination with other treatment in solid tumors which including NSCLC (*Table 2*).

ATR inhibitors

ATR and ATM are the members of the phosphatidylinositol 3-kinases-related kinases (PIKK) family of serine/threonine protein kinases. ATR is one of the two apical regulators in the DDR pathway of active cellular response includes cell cycle checkpoints and DNA repair. ATM share similar function and structure with ATR.

ATR and ATM are prime targets of DDR inhibitors. ATR inhibitor has demonstrated therapeutic potential activity in cancer treatment.

Several compounds targeting ATR are moving to clinical trial stage. M6620 (VX970/Berzosertib/VE822) was well tolerated, with preliminary antitumor responses observed in a patient with metastasis colorectal cancer (mCRC) harboring ATM loss and AT-rich interactive domain-containing protein 1A (ARID1A) mutation reached complete response (CR) and 29 months PFS (68). Ceralasertib (AZD6738) monotherapy was well tolerated and resulted in confirmed partial response (PR) and a high proportion of prolonged SD in advanced tumors of PATRIOT trial (69). BAY1895344 (Elimusertib, NSC#810486) was tolerable and had antitumor activity in patients with various advanced solid tumors with certain DDR deficiency including ATM loss (70). M4344 (YX-803) is currently in phase I single-agent or in combination with carboplatin study to determine the safety and maximum tolerated dose (NCT02278250). The trial of M1774 as monotherapy and in combination with niraparib is recruiting the patients with metastatic or locally advanced unresectable solid tumors including a group to explore the biomarker of loss of function mutations in the genes for ARID1A, ATM, or alpha thalassemia/mental retardation syndrome X-linked (ATRX) and/or (death-domain-associated protein) DAXX (NCT04170153). There are no ongoing trials in NSCLC with ATR inhibitor monotherapy, but in combination with other anti-cancer treatments, M1774, M6620 and AZD6738 are currently on the development of phase II/III studies as listed in *Table 2*.

AURK inhibitor

AURK belongs to a family (known as AURKA, AURKB and AURKC) of highly conserved serine and threonine kinases that function as key regulators of the mitosis process. AURKA and AURKB constitutes potential targets in NSCLC. Several agents inhibited to AURK have been developed, AURKA inhibitors (TC-A2317, alisertib/MLN8237, ENMD2076, MK5108, VIC1911, LY3295668, TAS-119), AURKB inhibitors (Quercetin, GSK 1070916, barasertib/AZD1152) and pan-AURK inhibitors (danusertib/PHA739358, AMG900, AT9283).

MK-5108 had proven anticancer activity in NSCLC *in vitro* as monotherapy or in combination with chemotherapies (71). AT9283 is a multi-targeted kinase inhibitor of tyrosine and serine/threonine kinases including Aurora A and B, JAK2, and Abl. AT9283 alone indicated well tolerated, antiproliferative and apoptotic activity and demonstrated SD (≥6 months) in esophageal cancer (n=1), NSCLC (n=2) and colorectal cancer (CRC; n=1) in a phase I dose escalation study (72).

Danusertib (PHA-739358) is a small-molecule pan-aurora kinase inhibitor. A trial reported that danusertib single-agent reached marginal antitumor activity, the progression free rate at 4 months (PFR-4) was 10.4% (5/48) in NSCLC (all histotypes), 16.1% (5/31) in LUSC and 0% (0/14) in SCLC (73). Another phase II study evaluated the efficacy of danusertib alone in advanced treated NSCLC in a Simon two-stage design; 3/19 patients were PFR-4 in stage I, the antitumor activity was better in LUSC better than non-squamous NSCLC (nsqNSCLC) (PFS: 6.4 *vs.* 2.2 months, OS: 10.6 *vs.* 7.6 months); 5/31 evaluable squamous patients were PFR-4 in stage II (74).

Tanaka *et al.* (75) discovered AURKB inhibitors as potent enhancers of osimertinib-induced apoptosis and combined EGFR-TKI and AURKB inhibitor could overcome EGFR-

Table 2 Ongoing clinical trials of DDR inhibitor in NSCLC

Drug	Indication	Title of the study	Combination	Phase	Biomarker	Identifier
Olaparib	NSCLC	SAFIR02_Lung - Efficacy of Targeted Drugs Guided by Genomic Profiles in Metastatic NSCLC Patients	Monotherapy	2	BRCA	NCT02117167
AZD1775 (adavosertib, MK1775)	sqNSCLC	AZD1775 Plus Carboplatin-Paclitaxel in Squamous Cell Lung Cancer	Chemotherapy	2	NA	NCT02513563
Methoxyamine (TRC-102)	NSCLC	Methoxyamine Hydrochloride, Pemetrexed Disodium, Cisplatin, and Radiation Therapy in Treating Patients With Stage IIIA-IV Non-small Cell Lung Cancer	Chemoradiotherapy	1	NA	NCT02535325
Ceralasertib (AZD6738)	NSCLC	National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer	Durvalumab	2	NA	NCT02664935
Niraparib	Solid tumor; NSCLC	Study of Niraparib, TSR-022, Bevacizumab, and Platinum-Based Doublet Chemotherapy in Combination With TSR-042	TSR-042	1	NA	NCT03307785
Olaparib; ceralasertib (AZD6738)	NSCLC	Phase II Umbrella Study of Novel Anti-cancer Agents in Patients With NSCLC Who Progressed on an Anti-PD-1/PD-L1 Containing Therapy	Durvalumab + AZD6738; durvalumab + olaparib	2	NA	NCT03334617
Rucaparib	nsqNSCLC	Rucaparib and Pembrolizumab for Maintenance Therapy in Stage IV Non-Squamous Non-Small Cell Lung Cancer	Pembrolizumab	1/2	NA	NCT03559049
Olaparib	NSCLC	Study of Durvalumab+Olaparib or Durvalumab After Treatment With Durvalumab and Chemotherapy in Patients With Lung Cancer (ORION)	Durvalumab + chemotherapy	2	NA	NCT03775486
Ceralasertib (AZD6738)	NSCLC	Precision Immuno-Oncology for Advanced Non-small Cell Lung Cancer Patients With PD-1 ICI Resistance	Durvalumab	2	NA	NCT03833440
Niraparib	NSCLC	Niraparib in Combination With Osimertinib in EGFR-Mutated Advanced Lung Cancer	Osimertinib	1	EGFR-mutated	NCT03891615
Olaparib	nsqNSCLC	Study of Pembrolizumab With Maintenance Olaparib or Maintenance Pemetrexed in First-line (1L) Metastatic Nonsquamous Non-Small-Cell Lung Cancer (NSCLC) (MK-7339-006, KEYLYNK-006)	Pembrolizumab	3	NA	NCT03976323
Olaparib	sqNSCLC	A Study of Pembrolizumab (MK-3475) With or Without Maintenance Olaparib in First-line Metastatic Squamous Non-small Cell Lung Cancer (NSCLC, MK-7339-008/KEYLYNK-008)	Pembrolizumab	3	NA	NCT03976362
Alisertib (MLN8237)	NSCLC	Alisertib in Combination With Osimertinib in Metastatic EGFR-mutant Lung Cancer	Osimertinib	1	EGFR-mutated	NCT04085315

Table 2 (*continued*)

Table 2 (*continued*)

Drug	Indication	Title of the study	Combination	Phase	Biomarker	Identifier
Talazoparib	sqNSCLC	Combination Treatment (Talazoparib Plus Avelumab) for Stage IV or Recurrent Non-Squamous Non-Small Cell Lung Cancer With STK11 Gene Mutation (A LUNG-MAP Treatment Trial)	Avelumab	2	STK11 gene mutation	NCT04173507
M6620 (VX970, berzosertib, VE822)	NSCLC	Testing the Addition of an Anti-cancer Drug, Berzosertib (M6620, VX-970), to the Usual Treatments (Carboplatin and Gemcitabine) and to Pembrolizumab for Patients With Advanced Squamous Cell Non-small Cell Lung Cancer	Pembrolizuma + chemotherapy	1/2	NA	NCT04216316
Olaparib	NSCLC	Study of Pembrolizumab With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib in Stage III Non-Small Cell Lung Cancer (NSCLC) (MK-7339-012/KEYLYNK-012)	Pembrolizumab + chemoradiotherapy	3	NA	NCT04380636
Niraparib	NSCLC	Placebo-controlled Study Comparing Niraparib Plus Pembrolizumab Versus Placebo Plus Pembrolizumab as Maintenance Therapy in Participants With Advanced/Metastatic Non-small Cell Lung Cancer	Pembrolizumab	3	NA	NCT04475939
Alisertib (MLN8237)	NSCLC	Osimertinib in Combination With Alisertib or Sapanisertib for the Treatment of Osimertinib-Resistant EGFR Mutant Stage IIIB or IV Non-Small Cell Lung Cancer	Osimertinib	1	EGFR-mutated	NCT04479306
BAY1895344	Solid tumor; NSCLC; SCLC	Testing the Addition of an Anti-cancer Drug, BAY 1895344, to the Usual Chemotherapy Treatment (Cisplatin, or Cisplatin and Gemcitabine) for Advanced Solid Tumors With Emphasis on Urothelial Cancer	Chemotherapy	1	NA	NCT04491942
Olaparib	NSCLC; SCLC	Olaparib (LYNPARZA) Plus Durvalumab (IMFINZI) in EGFR-Mutated Adenocarcinomas That Transform to Small Cell Lung Cancer (SCLC) and Other Neuroendocrine Tumors	Durvalumab	2	EGFR-mutated	NCT04538378
Olaparib	NSCLC	A Platform Study of Novel Agents in Combination With Radiotherapy in NSCLC	Radiotherapy	1	NA	NCT04550104
Talazoparib	Solid tumor; NSCLC	The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	Monotherapy	2	BRCA1/2, ATM, other HRD status	NCT04591431
AZD5305	Solid tumor; NSCLC; SCLC	Study of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies	AZD5305 monotherapy; AZD5305 + paclitaxel; AZD5305 + carboplatin with or without paclitaxel; AZD5305 + trastuzumab deruxtecan; AZD5305 + datopotamab deruxtecan; AZD5305 + camizestrant	1/2	NA	NCT04644068
Niraparib	MPM; NSCLC	UNITO-001- Study in HRR/PDL1 Positive MPM/NSCLC	Dostarlimab	2	HRR/PD-L1 positive	NCT04940637

Table 2 (*continued*)

Table 2 (*continued*)

Drug	Indication	Title of the study	Combination	Phase	Biomarker	Identifier
Niraparib	Solid tumor; LC	Niraparib in the Treatment of Patients With Advanced PALB2 Mutated Tumors	Monotherapy	2	PALB2 mutated	NCT05169437
Methoxyamine (TRC-102)	nsqNSCLC	Testing the Addition of an Anti-Cancer Drug, TRC102, to the Usual Chemotherapy Treatment (Pemetrexed, Cisplatin) During Radiation Therapy for Stage III Non-Squamous Non-Small Cell Lung Cancer	Durvalumab + chemoradiotherapy	2	NA	NCT05198830
Ceralasertib (AZD6738)	NSCLC	A Phase III Study of Ceralasertib Plus Durvalumab Versus Docetaxel in Patients With Non Small Cell Lung Cancer (NSCLC) Whose Disease Progressed On or After Prior Anti PD (L)1 Therapy And Platinum Based Chemotherapy	Durvalumab	3	NA	NCT05450692
Olaparib	NSCLC	Randomized Trial Comparing Standard of Care Versus Immune- Based Combination in Relapsed Stage III Non-small-cell Lung Cancer (NSCLC) Pretreated With Chemoradiotherapy and Durvalumab	Durvalumab + chemotherapy	2	NA	NCT05568212
Parimparib	NSCLC	Pamiparib (BGB-290) Was Used in EGFR-TkIs Resistant Non-small Cell Lung Cancer	Chemotherapy	1	EGFR-mutated	NCT05573373
AZD5305	Solid tumor; NSCLC	Phase I/IIa Study for AZD5335 as Monotherapy and in Combination With Anti-cancer Agents in Participants With Solid Tumors	AZD5335 monotherapy. AZD5335 + AZD5305	1/2	NA	NCT05797168
M1774	nsqNSCLC	M1774 in Combination With Cemiplimab in Participants With Non-Squamous NSCLC (DDRiver NSCLC 322)	Cemiplimab	1/2	NA	NCT05882734
Ceralasertib (AZD6738)	NSCLC	A Study to Investigate Efficacy and Safety of Ceralasertib Plus Durvalumab in Participants Aged ≥ 18 Years With Advanced or Metastatic Non-small Cell Lung Cancer Whose Disease Progressed on or After Prior Anti-PD-(L)1 Therapy and Platinum-based Chemotherapy	Durvalumab	2	NA	NCT05941897
VIC-1911	NSCLC	Phase I Clinical Study of VIC-1911 Combined With Osimertinib in the Treatment of Advanced Non-small Cell Lung Cancer With EGRF- Mutation	Osimertinib	1	EGFR-mutated	NCT05489731
VIC-1911	NSCLC	A Phase 1a/1b Study of Aurora Kinase A Inhibitor VIC-1911 Monotherapy and in Combination With Sotorasib for the Treatment of KRAS G12C-Mutant Non-Small Cell Lung Cancer	Sotorasib	1	KRAS G12C-mutant	NCT05374538
LY3295668	NSCLC	A Phase Ib/II Trial to Evaluate Safety, Tolerability and Efficacy of Aurora Kinase Inhibitor LY3295668 in Combination With Osimertinib for Patients With EGFR-Mutant Non-Small Cell Lung Cancer	Osimertinib	1	EGFR-mutated	NCT05017025

DDR, DNA damage repair; NSCLC, non-small cell lung cancer; *BRCA*, breast cancer gene; sqNSCLC, squamous non-small cell lung cancer; NA, not applicable; nsqNSCLC, non-squamous non-small cell lung cancer; SCLC, small cell lung cancer; MPM, malignant pleural mesothelioma; ATM, ataxia telangiectasia mutated; HRD, homologous recombination deficiency; HRR, homologous recombinant repair; LC, lung cancer.

TKI resistance. Alisertib (MLN8237) treatment restored the susceptibility of resistant cells to EGFR-TKIs and partially reversed the epithelial-mesenchymal transition (EMT) process (76). The phase II trial tested single agent alisertib in patients had undergone two or fewer previous cytotoxic regimens; it was noted that the objective response in ten of 48 participants with SCLC and one of 23 patients with NSCLC (77). In patients with recurrent or metastatic EGFR wild-type NSCLC, the combination of erlotinib and alisertib was tolerable and effective (with one patient was PR >10 cycles and 5 patients were SD) in a phase I/II study (78). The combination of alisertib and osimertinib was an acceptable safety profile and established 10% (1/10) ORR in patients with advanced EGFR mutated LUAD who experienced progression on osimertinib monotherapy (79). In a phase 1b study of osimertinib plus alisertib or sapanisertib for osimertinib-resistant EGFR-mutant (EGFRm) NSCLC, osimertinib plus alisertib (n=20) showed median PFS was 1.9 months, ORR (5%) and DCR (40%) (80). There are two ongoing clinical trials using AURKA inhibitors VIC-1911 or LY3295668 in combination with osimertinib in EGFR mutant NSCLC (NCT05489731) (NCT05017025).

AURKA amplification is reported in NSCLC, and AURKA signaling may mediate adaptive resistance to KRAS inhibition. A study to research VIC-1911 combine with sotorasib for treatment of KRAS mutant NSCLC is ongoing (NCT05374538).

Apurinic/apyrimidinic endonuclease 1 (APE1) inhibitor

Human APE1 is an essential BER protein that is known to be processing of potentially cytotoxic a basic DNA damage site. The overexpression of APE1 was associated with DNA repair capacity and poor survival in solid tumors (81). APE1 could serve as a potent target of antitumor drugs and several APE1 inhibitors have been developed. There are three types of APE1 inhibitors, including APE1 nuclease activity inhibitor (such as, methoxyamine/TRC-102, lucanthone), APE1 redox activity inhibitor (E3330/APX3330) and inhibitors of the APE1/nucleophosmin (gossypol/AT-101).

APE1 inhibitors induced DNA damage, apoptosis, pyroptosis, and necroptosis in NSCLC cell line A549 and NCI-H460 and impeded cancer progression in NCI-H460 mouse model (82). E3330 (APX3330) is highly selective inhibitor of apurinic/APE1/redox factor-1 (Ref-1). The anti-tumor effect of E3330 had been demonstrated in preclinical model in NSCLC (83). CRT0044876, a selective APE1 endonuclease inhibitor, inhibited the AP endonuclease, 3'-phosphodiesterase, and 3'-phosphatase activities of APE1. CRT0044876 showed no cytoxic effect in either NSCLC cell line A549 or NCI-H460 (82).

Overexpression APE1 promoted chemotherapy and EGFR-TKI resistance in NSCLC (84). Pre-clinical models suggested that AT-101 might serve a promise drug candidate for overcoming EGFR-TKIs resistance in H1975 cells harboring $EGFR^{L858R/T790M}$ (85). A phase II trial of erlotinib and AT-101 in advanced EGFR-mutated NSCLC patients found 1 PR, 1 minor response (MR) and 3 SD in the enrolled six patients (NCT00988169).

DNA-dependent protein kinase catalytic subunit (DNA-PKcs) inhibitor

DNA-PK is a member PIKK family, which consists of a DNA-PKcs and a regulatory heterodimer Ku (Ku70/Ku80). DNA-PK plays a key role in repair of DSBs via NHEJ and it also involves in many other cellular processes. Reduced DNA-PK repair was associated with the risk of LC.

AZD7648, a highly specific and potent DNA-PK inhibitor, had anti-tumor activity in A549 NSCLC cell lines and xenograft models derived from LCs (86). The best ORR of nedisertib (peposertib, M3814, MSC2490484A) was SD in a phase I trial including two NSCLC patients (87). XRD-0394 is a dual kinase inhibitor of both ATM gene and DNA-PK. CC-115, inhibition of mTOR kinase and DNA-PK, was tested *in vitro* across a panel of 123 cancer cell lines including 39 LC cell lines and it potently inhibits proliferation and induces apoptosis in many cancer cell lines (88). In phase I trial, CC-115 showed clinical activity in endometrial carcinoma (CR, n=1, >4 years), head and neck squamous cell carcinoma (HNSCC), Ewing sarcoma, glioblastoma multiforme, castration-resistant prostate cancer (CRPC), and chronic lymphocytic leukemia (CLL) (PR, n=2 and SD, n=4), but it was found to cause apoptosis in NSCLC (n=1) (89).

In addition, as PIKKs have similar sequence to phosphatidylinositol-3 kinases (PI3Ks), the development of these inhibitors can base on small molecule inhibitors of PI3K. LY3023414 (samotolisib), a dual PI3K/mammalian target of rapamycin (mTOR) inhibitor, displayed PR of a patient with endometrial cancer harboring PIK3R1 and Phosphatase and tensin homolog (PTEN) truncating mutations and 13 (28%) additional patients had a decrease in target lesions by up to 30%, but the all 3 patients of NSCLC were no response in the first-in human phase I trial (90). XL765 (voxtalisib, SAR245409) is a new chemical entity that inhibits the kinases PI3K and mTOR. No partial response reported with XL765 and erlotinib in NSCLC

patients treated with EGFR inhibitor previously in phase I trial (91).

WEE1 inhibitor

WEE1 inhibitor, is a selective inhibitor of the WEE1 kinase, a key regulator of the G2/M and S phase cell-cycle checkpoints.

AZD1775 (adavosertib) is a highly selective, small molecule inhibitor of protein kinase Wee1 which allows cells to with a deregulated G1 checkpoint to progress. AZD1775 single agent demonstrated efficacy and well tolerated in mouse xenograft model in TP53-mutated subgroup of KRAS-mutated NSCLC (92). There are 61 clinical trials registered in CTG (https://clinicaltrials.gov) about AZD1775 from 2008. AZD1775 showed its antitumor activities especially in these cancers harbor DNA damage, such as mCRC with RAS and TP53 mutated (93). However, in a biomarker-driven phase 2 umbrella trial for patients with recurrent SCLC, no patient had partial response for ADZ1775 alone in 47 patients with different biomarkers in 4 groups (94). The scientists have not found the effective strategy to launch this product whatever the predictive biomarkers for response or in combination with other anti-cancer agents.

Another four compounds ZN-c3 (NCT04158336), Debio0123 (NCT03968653), IMP7068 (NCT04768868) and SY-4835 (NCT05291182) are currently in phase I trial in solid tumors which including NSCLC (*Table 2*).

CHK1 and CHK2 inhibitor

The cell cycles regulatory kinase, CHK1 and CHK2, coordinate with DDR pathways and immediate targets of the kinases ATM/ATR. CHK1/2 inhibitors have development for a long time, numerous compounds step towards slowly because of the complexity of optimizing dose and schedule selection and major questions mark over the efficacy. The dual CHK1/CHK2 inhibitor XL-844 (EXEL-9844) was terminated trials in 2008. PF0047736 was terminated to develop in 2012 in advanced cancers. SNS-032 (BMS-387032), a potent inhibitor of cyclin-dependent kinases 2, 7 and 9, demonstrated limited clinical activity in solid tumors. Prexasertib (LY2606368) demonstrated activity in different cancers, including 2 (4.4%) patients with squamous cell cancers (SCCs) (95), 4 (20%) patients with SCCs (96), 3 (5.2%) patients with SCLC (97) and one (11.1%) BRCA wild type triple negative breast cancer (TNBC) (98), however, one NSCLC patient had no response (95).

Researchers consider how to combine CHK1 inhibitors with other compounds or to find proper biomarkers to get more encouraging data. In pre-clinical model, the low levels of POLA1, POLE, and POLE2 protein expression in NSCLC and CRC cells corrected with CHK1 inhibitor sensitivity (99). UCN-01 (7-hydroxystaurosporine), the first CHK1/CHK2 inhibitor, contributed the antitumor activity *in vitro* and *in vivo* using A549 human LUAD cell line (100) and enhance the effective of radiation in cells with diminished TP53 activity (101,102). CHK1 expression in LUADs corrected with poor tumor differentiation and worse patient level and could be a predictive marker for CHK1 inhibitor (MK-8776) sensitivity *in vitro* study (103). Two patients (6.7%) showed partial response (melanoma and cholangiocarcinoma) in MK8776 monotherapy or in combination with gemcitabine phase I trial, however, one LUAD only have 1.43 months PFS (104).

Combinations with chemotherapy agents

In chemotherapy, cytotoxic drugs distort the chemical structure of DNA leading to inhibition of normal DNA replication. It makes strong rationale to combine DDR inhibitors with chemotherapy to enhance the DNA-damaging effect in cancer cells.

PARP inhibitor with chemotherapy

The combination of DDR inhibitors (such as PARP inhibitor) in selected HR-deficient tumors cause synthetic lethality, lead to genomic instability and cell death (105). Mechanistic studies indicated that PARP inhibitor plus cisplatin could lead to sustained DSBs, prolonged G2/M cell cycle arrest and more pronounced apoptosis preferentially in NSCLC cells with low ERCC1 expression (106), or PTEN deficient (107). Pre-clinical studies demonstrated antitumor efficacy of PARP inhibitor adding in different chemotherapy agents in NSCLC (108). In combination of veliparib and carboplatin/paclitaxel (CP) confirmed safety and preliminary efficacy with 55% (6/11) ORR in a phase I Japanese NSCLC cohort (109). In the following phase II trial of untreated advanced NSCLC, the veliparib-CP group showed favorable trend in ORR, PFS and OS *vs.* CP alone [PFS: 5.8 *vs.* 4.2 months, hazard ratio (HR) =0.72, P=0.17; OS: 11.7 *vs.* 9.1 months, HR =0.80, P=0.27] in all evaluable patients; patients with squamous histology had better outcomes (PFS: HR =0.54, P=0.098; OS: HR =0.73, P=0.24) (110). However, no therapeutic benefit of adding veliparib to first line chemotherapy in phase III

trial, but risk of death was decreased by 34% in the LP521 population (110), and history of recent smoking was most predictive factor for veliparib-CP (111). In another phase III trial, there was no significant improvement of OS with veliparib plus chemotherapy in patients with nsqNSCLC, but improved OS in the LP52+ subgroup (112).

ATR inhibitor with chemotherapy

ATM loss by immunohistochemistry with ab32420 antibody was found in 41% (61/147) cases in LUAD cells and suggested to be a predictive biomarker for ATR inhibitor with cisplatin (113). A phase I study, with AZD6738- carboplatin, observed two PRs with low ATM or SLFN11 protein expression and 53% (18/34) SD patients; unconfirmed PR was found in a local advanced LUAD with four cycles of prior treatment (114).

Four (8.3%) patients (non-previously received gemcitabine) achieved PR with berzosertib and gemcitabine including a patient present with LUAD with no response of prior multiple chemotherapies (115). In the following phase Ib trial, berzosertib with gemcitabine in advanced and pre-treated NSCLC, four patients reached PR (4/38, ORR: 10.5%) and 18 patients had SD; in the exploratory cohort, ORR was 30% (3/10) in high LOH and 11% in low LOH, 33% (2/6) in high TMB, 12.5% (2/16) in intermediated TMB and 0% (0/3) in low TMB (116).

Testing the addition of BAY1895344 to chemotherapy for advance solid tumors is ongoing (NCT04491942), which is listed in *Table 2*.

APE1 inhibitor with chemotherapy

The phase I study published that 15 out of 25 patients with TRC-102 and pemetrexed evaluate SD or better, including LUSC (n=3) and nsqNSCLC (n=1) (117). Two clinical trials indicated that TRC-102 with temozolomide had anti-tumor activities in advanced solid tumor, with PR in a pancreatic neuroendocrine tumor (PNET) and prolonged SD in a NSCLC patient (5.5 months) (118), and PR (n=4, 1 NSCLC, 2 OCs, 1 CRC) (119).

WEE1 inhibitor with chemotherapy

WEE1 inhibition with TP53 mutation can disrupt both G1/S and G2/M, resulting in synthetic lethality and enhancing chemotherapy cytotoxicity. A phase II study of AZD1775 and carboplatin/pemetrexed in 1st line metastatic nsqNSCLC presented 4 (29%) patients reached PR (one patient with AZD1775 alone for one year) and one patient had TP53 mutation. Another phase II study of AZD1775 plus docetaxel in recurrent NSCLC showed 3 (9%) patients evaluated PR (120).

Some clinical trials use WEE1 inhibitor, but its clinical development hampered higher grade 3 toxicities when added to standard treatments and no effective predictive biomarkers. There are ongoing trials conducting WEE1 inhibitors with other agents, such as chemotherapy, radiation, PARP/ATR inhibitor (NCT02513563, NCT0333084, NCT02511795), anti-PD-1/PD-L1 inhibitor, which are listed in *Table 2*.

CHK1/2 inhibitor with chemotherapy

Cells may remain viable as a result of upregulation of commentary mechanism with CHK1/2 inhibitor alone and make more susceptible to extrinsic DNA damage, which cause the interest of combination.

LY2603618 (rabusertib), a small molecule selective inhibitor CHK1 inhibitor, may enhance the effects of antimetabolites. LY2603618 with pemetrexed- cisplatin demonstrated that median PFS was significantly longer (4.7 *vs.* 1.5 months, P=0.022) in phase II study in patient with advanced cancers (121). With treatment GDC-0575 (ARRY-0575, RG774) and gemcitabine, four patients achieved confirmed partial responses with GDC-0575, including one NSCLC (593+ days on study), two sarcomas and TNBC with TP53 mutation (122).

Combinations with radiotherapy and/or chemoradiotherapy (CRT)

Radiotherapy can cause targeted DNA damage, which leads to the combination of DDR inhibitors and/or chemotherapy had been considered to ongoing clinical research. Most advanced NSCLC patients may have brain metastasis and radiation therapy has been an available tool in that kind of patients, which causes the strategy about the combination of DDR inhibitors and whole brain radiation therapy (WBRT).

The result of phase I study was encouraging safety and preliminary efficacy of veliparib plus WBRT in NSCLC with brain metastases (123), regrettably, no statistically significant differences in OS, intracranial response rate, and time to progression between the treatment arms were observed in the phase II randomization trial (124). Inhibition of AZD6738 could improve radiotherapy in preclinical models of NSCLC (125). A parallel dose-escalation study of AZD6738 combined with palliative radiotherapy in solid tumors is underway (NCT02223923). These data will provide the basis to leverage the potential

radio-sensitization properties of a DDR inhibitor in combination with radiation in a variety of therapeutic settings.

Two phase I studies evaluate PRAP inhibitors plus CRT in patients with stage III NSCLC; Veliparib-CRT demonstrated acceptable safety and antitumor activity with an PFS of 19.6 months (126). A dose-finding study followed by a phase II randomization trial of CRT with or without veliparib (SWOG 1206); PFS was not difference between the two arms, while the OS was improved at 1 year 89% and 54%, respectively (127). The combination strategy was proved well tolerated and encouraging response with 20% (3/15) CR, 80% (12/15) PR and 49% of 2-year PFS rate in stage III nsqNSCLC (128) in the following phase I trial.

Combinations with other molecular targeted agents

DDR inhibitor-DDR inhibitor combination

Targeting enzymes in the same pathway also appears to have a synthetically lethal effect. Combination with different DDR inhibitors can induce synthetic lethality and also overcome acquired resistance to single agent.

As these mutations (such as BRCA1, BRCA2, ATM) alter the HRR pathway, there is increased reliance on other DDR pathways. ATR inhibitors overcame the bypass of BRCA1/2 in fork protection and PARP inhibitor resistance of BRCA-deficient cancers cells (129). Studies disclosed that combination of PARP inhibitor and ATR inhibitor induced death for ATM-deficiency cells of LUAD (130). Tumor reduction was observed in breast, prostate, pancreatic and ampullary cancers in AZD6738-olaparib group in a phase I trial (131). The signal of activity was seen with ceralasertib plus olaparib in recurrent platinum-resistant OC with BRCA1 mutation (132). In the pre-clinical models, KRAS-mutated NSCLC caused the increased levels of DNA damage and replication stress, which provided that inhibition of DDR was a promising strategy for olaparib plus AZD1775 (133). AZD7648 potentiated the activity of olaparib in xenograft and PDX models in NSCLC (134).

Some studies demonstrated replication fork arrest, ssDNA accumulation, replication collapse and synthetic lethal interaction between ATR inhibitor and other target inhibitors. The potential benefit of combination ATR inhibitor (VE-821) and CHK1 inhibitor (AZD7762) was seen in H460 lung tumor xenografts (135). PPP2R2A deficiency provided a biomarker to treat NSCLC with ATR and CHK1 inhibitor in pre-clinical study (136). The study confirmed the dependency on p53 mutation and ATM function for sensitivity to ATR inhibition by treating p53-mutated NSCLC cells with ATR inhibitor (VE-821) and ATM inhibitor (KU55933) (137). The effect of WEE1 inhibitor and ATR inhibitor was observed in NSCLC cell line (138).

Combination of other target agents

Some actionable oncoproteins can directly or indirectly regulate DDR and cell cycle checkpoint pathways, raising possibility of combination strategy with DDR inhibitors and other target agents.

PARP inhibitors have a strong synergistic interaction with type I protein arginine methyltransferase (PRMT) inhibition. Methylated p53 re-activation and induction of massive apoptosis (PRIMA-1Met) (APR-246) strongly synergized with olaparib in NSCLC cell lines (139) and Methylthioadenosine phosphorylase (MTAP)-negative NSCLC and certain cancer cells were resistant to PARP inhibitors (140). DNA methyltransferase inhibitors (DNMTi) created a BRCAness phenotype through downregulating expression of HRR and NHEJ genes, leaded to combinatorial PARP inhibitor and DNMTi therapy robustly sensitize NSCLC cells to ionizing radiation *in vitro* and *in vivo* (141). Bloom syndrome protein (BLM) helicase inhibitor (ML216) with PARP inhibitor improved the radiosensitivity of olaparib resistant NSCLC cell (142).

A phase 1b study, the Notch inhibitor Crenigacestat (LY3039478) in combination with LY3023414 in patients with advanced solid tumors, demonstrated poorly tolerated and response (0% ORR and 18.8% DCR) (143). In metastatic LUSC, LY3023414 *vs.* necitumumab *vs.* LY3023414 plus necitumumab exhibited significant benefit with event-free survival (EFS; 14.2 and 32.4 *vs.* 38.9 days) (144). LY3214996 (ERK1/2 inhibitor) plus LY3023414 and additive abemaciclib (CDK4/6 inhibitor) resulted in synergistic inhibition of tumor growth in PDX models of RAS-mutant LC (145).

However, these combination of doublet inhibitors are still in early exploratory status, the overlapping toxicity creates a whole new challenges of dose selection.

Combinations with immunotherapy

ICIs which target PD-1 and PD-L1 can enable the immune system to recognize and target cancer cells. Over recent decade, ICIs with single agent or combination of other therapy has dramatically expanded for the treatment of LC from neoadjuvant to last line. However, ICIs vary

in their activity across different cancer types. Several biomarkers are associated with increase ICI response are PD-L1 expression, TMB, MSI or MMR-deficient. It is also explored that alteration of DDR genes related to high TMB and response of ICIs improvement. Unlike targeting genes mutation in cancer cells, the immune environment is complex, which lead future research shift to immune response effectiveness of combination therapy rather than identification biomarkers. Cancer causing genomic instability induce changes in the tumor environment and stimulate the generation of neoantigens on cancer cells, increasing the tumor response to immunotherapy and suggesting an effective therapeutic strategy to combine DDR inhibitors and immunotherapy.

Pre-clinical trial demonstrated PARP inhibitor potentiated IFN-γ-induced PD-L1 expression in NSCLC cell lines, enhanced in ERCC1-deficient contexts, promoted cellular immune response (146). Veliparib combined with nivolumab and platinum doublet CT was tolerated and had promising antitumor activity (confirmed objective response rate was 40%, and best ORR was 64%) in patients with advanced NSCLC in phase I dose escalation study (147). Olaparib-durvalumab indicated an acceptance toxicity and response in breast cancers (148) and mCRPC in the two phase II trials (149). Olaparib plus PD-1/PD-L1 inhibitor demonstrated response in two NSCLC patients with germline BRCA2 S497* (150) or BRCA2 G25085 (151). In the phase 2 JASPER trial, Niraparib-pembrolizumab as first line therapy showed clinical activity; 56.3% (9/16) ORR and 8.4 months PFS was found in cohort 1 [tumor proportion score (TPS) ≥50%]; 20% (4/20) ORR and 4.2 months PFS was discovered in cohort 2 (TPS 1–49%) in advanced NSCLC (152).

As PARP inhibitor plus immunotherapy shows promising therapeutic strategy in NSCLC, ongoing investigations are underway to evaluate the efficacy and safety. A phase I/II trial test rucaparib-pembrolizumab as maintenance therapy in stage IV nsqNSCLC after treatment of carboplatin, pemetrexed, and pembrolizumab (NCT03559049). A phase III trial treat pembrolizumab with concurrent chemoradiation therapy followed by pembrolizumab with or without olaparib in stage III NSCLC (NCT04380636) and a phase II trial compare SoC *vs.* olaparib-durvalumab in relapsed stage III NSCLC pretreated with CRT and durvalumab (NCT05568212). The phase III ZEAL-1L study is to compare the efficacy and safety of niraparib-pembrolizumab as maintenance therapy *vs.* placebo-pembrolizumab in patients who had SD or response to pembrolizumab plus platinum-based first-line induction chemotherapy for advanced NSCLC without known driver mutation (NCT04475939). A phase II study take talazoparib-avelumab in stage IV or recurrent nsqNSCLC with pathogenic STK11 mutation (LUNG-MAP Sub-Study) (NCT04173507). Please refer *Table 2* for ongoing trial in LC.

Besides PARP inhibitors, the ATR inhibitors in combination with ICIs have been in clinical development. In a phase 2 trial, AZD6738-durvalumab had promising antitumor activity among patients with metastatic melanoma who had failed ICIs therapy (153). Beyond melanoma, AZD6738-durvalumab in advanced NSCLC of D5330C00004 trial also published encouraging date; 1 CR and 3 PRs (2 confirmed and 1 unconfirmed) out of 21 patients were found in advanced NSCLC (n=3) and HNSCC (n=1) irrespective of PD-L1 expression (131). In HUDSON umbrella trial, AZD6738-durvalumab provided effective activity compared with durvalumab alone in ATM mutation tumors (n=18) with median ORR at 13.3% and a median PFS of 7.43 months and 100% of patients were followed through after 6 months (154).

Based on the previously studies result, more trials start to investigate the efficacy and safety of the combination of ATR inhibitors and immunotherapy (*Table 2*); a phase III study to evaluate AZD6738-durvalumab *vs.* docetaxel in advanced NSCLC progressed prior treatment (NCT05450692); AZD6738-durvalumab for advanced NSCLC patients with ICI resistance (NCT03833440); M1774 in combination with cemiplimab in nsqNSCLC (NCT05882734); testing the addition of berzosertib to carboplatin and gemcitabine and to pembrolizumab for advanced LUSC (NCT04216316).

It is also interesting to combine WEE1 inhibitor with immunotherapy. Antitumor activity was observed with a DCR for the overall cohort of 36% in a phase I study to investigate preliminary activity of AZD1775-durvalumab in patients with advanced solid tumors (155).

A phase II trial of TRC102 in combination of pemetrexed, cisplatin and radiation therapy followed by durvalumab in patients with stage III nsqNSCLC is underway (NCT05198830).

Conclusions

Genomic profiling helps identify promising DDR targets of NSCLC, such as PARP, ATR, CHK1, CHK2, WEE1, AURK, DNA-PK, APE1. Medicine targeting these proteins

are in various phase of preclinical or clinical development within different cancer types. The first approved DDR inhibitor, PARP inhibitors, have been used in certain patients with BRCA mutated. However, few DDR inhibitors run into phase 3 trial in NSCLC. Single agents of some DDR inhibitors show antitumor activity in NSCLC but limited. To improve the outcome, predictive biomarkers should be developed to optimize the response and an improve understanding of primary and acquired resistance mechanisms. The combination strategy of DDR inhibitors is usually chemotherapy and/or radiotherapy, which can enhance the effects. Combination of other target agents have demonstrated clinical potential and some of them step into clinical trials. Genomic instability of NSCLC influences innate and acquired immunity. Combination of DDR inhibitor and immunotherapy would be one of the most attractive future areas of research in NSCLC. While combine DDR inhibitor with different agents, their interactions should be considered. The appropriate dosing and scheduling of each agent to minimize toxicity adverse events and maximize benefits is critical factor for optimizing outcomes. In conclusion, we believe that comprehensive preclinical research into biology of DDR and clinical study progress in the DDR target agents, will lead great advances in the near future.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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