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Review Article

Therapeutic Targeting of DNA Damage Repair in the Era of Precision Oncology and Immune Checkpoint Inhibitors

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ABSTRACT

Cancer manifestation is a multistep process involving accumulation of various genetic and epigenetic changes that results in oncogenic "hallmarks of cancer" processes including genomic instability. Exploitation of aberrant DNA-damage response (DDR) mechanisms in cancer is in part a goal of many therapeutic strategies, and recent evidence supports the role of targeting DDR in modulating the tumor immune microenvironment to enhance immunotherapeutic response. Improved cancer profiling, including next-generation and whole-genome mutational sequencing of tumor tissue, as well as circulating nucleic acids, has enhanced our understanding of the genetic and epigenetic molecular mechanisms in tumorigenesis and will become fundamental to precisely target tumors and achieve cancer control. With the successes of poly(ADP-ribose) polymerase inhibitors (PARPi) and immunotherapies, the intersection of DDR molecular machinery and corresponding antitumor immune response has gained much interest with a focus on achieving therapeutic synergy using DNA damage-targeting agents and immunotherapy. In this review, we provide a bench-to-bedside overview of the fundamentals of DDR signaling and repair as they relate to cancer therapeutic strategies including novel DDR-targeting agents. We also discuss the underlying mechanisms that link DDR signaling to antitumor immunity and immunotherapy efficacy, and how this knowledge can be used to improve precision medicine approaches in the treatment of cancer.

Keywords: DNA damage repair, DDR, cancer immunology, PARP inhibition, synthetic lethality, precision oncology, immunotherapy

INTRODUCTION

Mechanisms of DNA damage detection, response, and repair are critical to preserving genomic integrity and preventing malignancy. Depending on the mechanism of DNA damage and lesion formation, the DNA-damage response (DDR) is achieved by various sensor, signaling, and effector proteins.[1,2] DNA single-strand break (SSB) damage is remedied by three main pathways: base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR). The more severe DNA double-strand breaks (DSBs) are resolved by two major DSB repair pathways: homologous recombination (HR) and nonhomologous end-joining (NHEJ).[1,2] Alterations of these the DDR and replication stress (RS) pathways result in unchecked replicative immortality, accumulation, and propagation of additional genetic abnormalities by bypassing physiologic checkpoints, which ultimately leads to cancer development. As our understanding of the complexity of DDR signaling as well as the interplay of these pathways with other cellular processes grows, so too does the list of potential therapeutic targets and strategies to exploit DDR vulnerabilities in tumor cells.

Whole-exome and transcriptome analysis has empowered the goal of precision medicine by enabling specific biomarker-driven treatment strategies based on a tumor's dependency, including DNA repair network deficiencies.[3] In the setting of DNA repair pathway defects, increased dependence on remaining intact repair pathways is necessary for cancer cell survival and proliferation, providing an avenue to therapeutically exploit

DNA repair deficiencies for cancer treatment. The most successful therapeutic example includes the use of poly (ADP-ribose) polymerase inhibitors (PARPi), which typify a synthetic lethal approach for the treatment of cancers with compromised ability to repair double-strand DNA breaks by HR, including those with defects in BRCA1/2.[4–6]

In response to DNA damage, DDR pathway mediators regulate immunoregulatory signaling,[7] potentially affecting the balance between tumor progression and immune surveillance, with potential implications for immunotherapy utility and outcomes. The interplay between defective DSB repair proteins or therapeutic use of DDR inhibitors and accumulation of chromosomal abnormalities, higher tumor mutational burden (TMB), oncogene activation, and tumorigenesis has also been shown to alter immunologic vulnerability. More specifically, dysfunctional DDR has the potential to augment immune recognition, activate immunostimulatory genes, increase tumor infiltrating lymphocytes (TILs), and antitumor immune production of interferon (IFN)-γ with resultant immunosuppressive tumor programmed death-ligand 1 (PD-L1) upregulation.[8–12] Similar effects can be observed as a result of genomic stress induced by DNA-damaging treatments, including radiation therapy (RT) and platinum-based chemotherapies. This may occur in part as the result of chromosomal fragments that stimulate the cytosolic sensing cGAS/STING pathway, promoting antitumor immunity through activation of T and natural killer (NK) cells and neoantigen recognition.[12–16]. These pathways will be discussed later in this review.

Going forward, understanding the specific mutational, transcriptional, and immunologic profiles of individual malignant processes is critical in rational use of therapeutic interventions that target susceptible components of DDR and antitumor immunity. Because precision medicine approaches are now an important arsenal in standard of care cancer treatment, we explore genomic and transcriptomic alterations in cancer, how these may be therapeutically exploitable, challenging mechanisms of resistance and the growing data on the relationship between DDR targeting and immunotherapy to inform novel combination treatment strategies.

Overview of DDR and Repair Signaling

Cells accumulate DNA damage as the result of stochastic mutational kinetics and cytotoxic stress, and DDR is central to the recognition and downstream repair of SSBs and DSBs. DDR accomplishes this by arresting proliferation and allowing for repair or facilitating removal of damaged cells through activation of senescence or apoptosis. Cancer cells often contain abnormal DDR signaling and RS machinery that contributes to oncogenesis by increasing DNA damage and genomic instability[17] and this often increases reliance on alternate error-prone repair pathways. This may present as an increased susceptibility to DNA-damaging therapies and DDR inhibition.

Progression of DDR signaling is dependent on the specific type of DNA damage, where numerous proteins are involved in interconnected repair pathways: BER, NER, and MMR pathways are responsible for repairing SSBs, and HR and NHEJ pathways participate in the more severe DSB repair. A multitude of DNA damage sensors, effectors, and transducers enact DDR mechanisms. Ataxia telangiectasia mutated (ATM), ATM- and RAD3-related (ATR), and DNA-dependent protein kinase (DNA-PK) act as core regulators of DDR signaling (Figure 1). Following DNA damage, sensor proteins and complexes directly recognize DNA structure and recruit ATM, ATR, and DNA-PK to strand breaks; examples of these include poly(ADP-ribose) polymerases-1 and -2 (PARP1/2), H2AX, Ku70/880, and MRN (MRE11/RAD50/NBS1). PARP1/2 are important DNA-damage sensors and regulators of BER-mediated SSB repair, as well as other DDR pathways including a prospective role in DSB repair.[18,19] The Ku complex, which is composed of Ku70 and Ku80 subunits, also mediates DSB repair albeit via more distinct and antagonistic mechanisms than that of PARPs. Binding of PARPs to DSBs promotes alt-EJ, whereas Ku complex binding recruits and activates the DNA-PK catalytic subunit, resulting in NHEJ. As such, competition between PARP1 and Ku complex binding at DSBs is an important biologic concept determining DDR with therapeutic implications. The MRN complex is a DNA sensor that can also bind DNA ends resulting in recruitment and activation of ATM. ATM and ATR protein kinases, operating together via downstream targets checkpoint kinase 1 (CHK1) and checkpoint kinase 2 (CHK2), respectively, play a vital role in DDR signaling by maintaining replication fork stability and the regulation of cell cycle control checkpoints.[20] ATM is the primary kinase accountable for phosphorylation of H2AX, an early step in recruitment of DDR mediators. DNA-PK activity is required for NHEJ, and the WEE1 nuclear kinase regulates mitotic entry and nucleotide reservoirs during DNA damage response.[20]

Loss of function mutations in crucial genes involved in DDR and cell cycle checkpoints, such as BRCA1/2, ATM, ATR, CHEK1/2, BRD4, PTEN, or TP53, can result in impaired removal of genome mutations, accumulation of DNA damage, and increases the risk of oncogenesis.[21] Mutational data analysis across major tumor types supports this; for example, TP53, ATM, and ATR are highly mutated in bladder cancer (50%, 11.2%, and 4.1%), lung adenocarcinoma (51.8%, 7.9%, and 5.7%), and colorectal adenocarcinoma (58.6%, 5.7%, and 2.1%, respectively).[3] In men who develop metastatic castration-resistant prostate cancer (mCRPC), approximately a quarter have a mutation in DNA repair genes, with the most common mutated genes being *BRCA2* (44%), *ATM* (13%), *CHEK2* (12%), and *BRCA1* (7%).[22] Tumor cells persist despite these barriers to genomic fidelity and cell proliferation by activating alternate repair pathways in

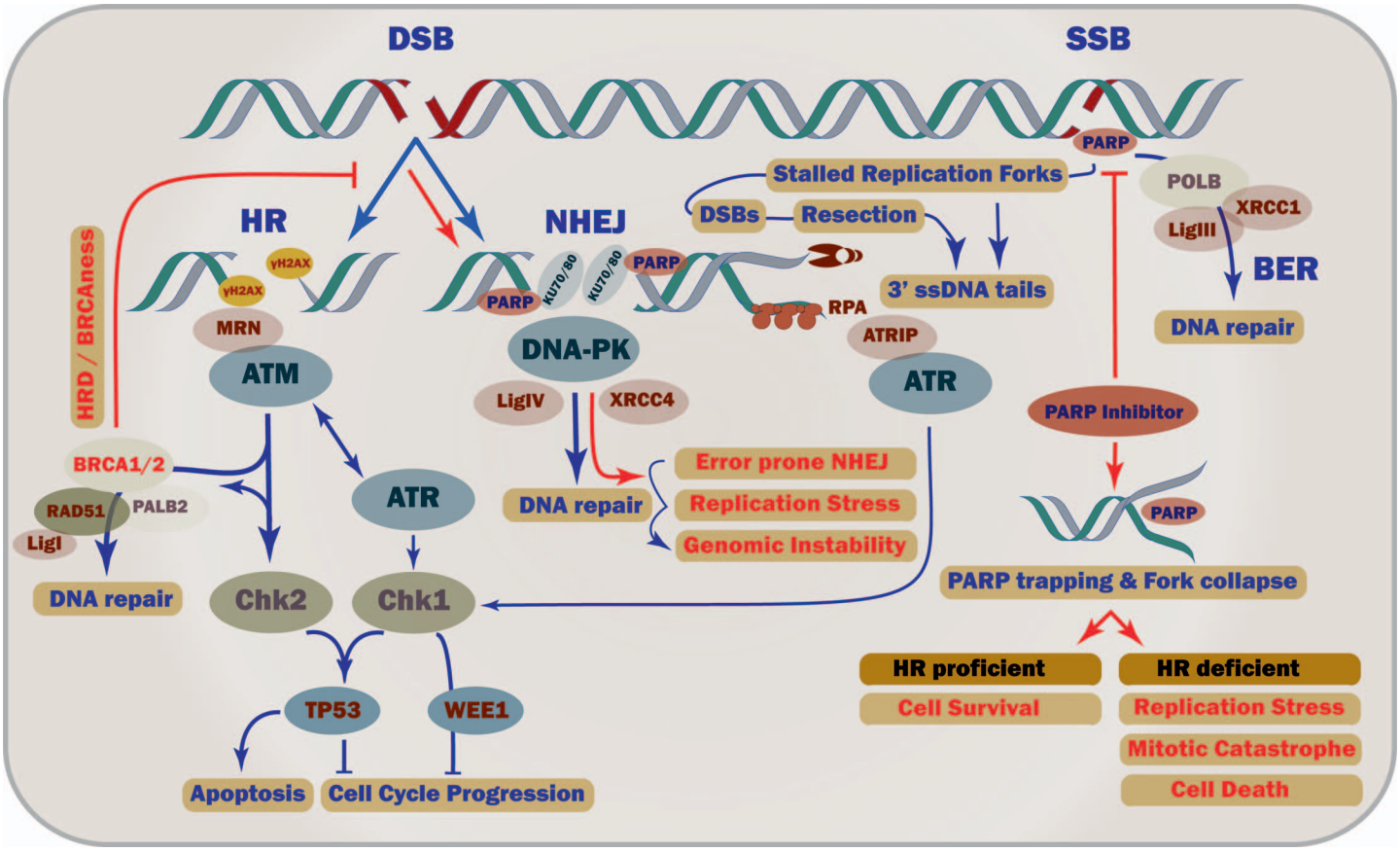

Figure 1. Overview of DDR, mechanisms of HRD, and PARPi-induced synthetic lethality. Single-stranded and double-stranded DNA breaks as a result of DNA-damaging therapies or endogenous replication dysfunction results in activation of DDR and repair signaling pathways. DDR signaling pathway initiation is mediated by three central DDR kinases: DNA-PK, ATM, and ATR, depending on the type of DNA damage. PARP enzymes facilitate SSB repair efficiency, as well as perform functions in DSB repair via HRR and NHEJ pathways. Significant cross talk between ATM and ATR pathways direct cell fate based on degree of DNA damage and associated DDR alterations. Classically, ATM/CHK2 signaling prevents tumor cell progression via cell cycle arrest, and ATR/CHK1/WEE1 signaling initiates DNA DSB repair by inducing checkpoints and activating key components of HRR, including BRCA1/2 activity. DSB repair occurs through NHEJ via DNA-PKcs recruitment. Synthetic lethality is a therapeutic outcome of PARP inhibition, particularly in tumor cells with HRR defects. This results in DSBs from unrepaired SSBs via PARP trapping and collapsed replication forks, resulting in genomic instability and cell cycle arrest in HR-deficient tumor cells. In HR-proficient tumor cells, loss of function or inhibitors for other key mediators of HR signaling can increase NHEJ dependence, whereby concomitant PARPi may also increase DSB and genomic instability.

ATM: ataxia telangiectasia mutated; ATR: ataxia telangiectasia and RAD3-related protein; ATRIP: ATR-interacting protein; CHK: checkpoint kinase; DDR: DNA damage response; DNA-PK: DNA-dependent protein kinase; DNA-PKcs: DNA-dependent protein kinase catalytic subunit; DSB: double-stranded breaks; HR: homologous recombination; HRD: HR deficiency; HRR: HR repair; MRN complex: MRE11/RAD50/NBS1; NHEJ: nonhomologous end-joining; PARP: poly(ADP-ribose) polymerase; PARPi: PARP inhibitors; RPA: replication protein A; SSB: single-strand breaks.

response to DDR deficiency, thereby counteracting sensitivity to lethal genomic insult by preventing cytotoxic stress and perpetuating oncogenesis. As a result of tumor cells often harboring oncogenic defects in DDR pathways and therefore having increased dependence on alternate DDR mechanisms to survive, there is an opportunity to exploit these dependencies by targeting the DNA repair pathways that lead to subsequent accumulation of lethal levels of DNA damage as compared with normal cells. For example, tumor cells with deficiencies in HRR pathways have reduced ability to repair DNA DSBs. Mutations in HRR components, such as BRCA1/2, PALB2, and ATM renders the repair pathway ineffective, resulting in homologous recombination-deficiency (HRD) and precise therapeutic exploitation (Figure 1). This creates a synthetic lethal interaction with inhibition of PARP1, which has been successful in the clinic.

DNA RS also closely interconnects with DDR signaling. Tumor cell hyperproliferation and associated oncogenic RS leads to replication fork stall and collapse with resultant accumulation of SSBs and DSBs, single-strand DNA (ssDNA), and ultimately multifaceted ATR-dependent response to maintain genomic stability. ATR is a key protein kinase involved in RS-response and plays important roles in cell cycle checkpoints and can mediate DNA DSB repair through HRR. ATR signaling activates an S/G2 cell cycle checkpoint, where unrepaired DNA damage can be resolved before entering mitosis through G2 cell cycle checkpoint activation. The

protein tyrosine kinase WEE1 plays dual roles in cell cycle progression involving both S-phase and G2/M checkpoints.[23] Defects in or inhibition of G2 checkpoint signaling permits cells with unrepaired DNA damage to enter mitosis prematurely, resulting in cell death. Many cancer cells exhibit an increased dependence on S and G2 DNA damage checkpoints as the result of irregular TP53 activity, which would otherwise stop G1 checkpoint signals. Ongoing DNA damage in cancer cells in the setting of DDR deficiencies therefore provides potential therapeutic opportunities that may overwhelm these correction mechanisms.

Therapeutically Targeting Tumor-associated DDR and Repair

Two well-studied HR repair pathway defects are mutations in BRCA1 and BRCA2, with germline variants initially discovered in patients with hereditary breast or ovarian cancer, which have provided the basis for HRD therapeutic targeting. However, somatic and germline BRCA1/2 mutations as well as alterations in other HR genes, such as ATM, ATR, CHK1, CHK2, PALB2, RAD51, BARD1, and FANC, are increasingly recognized by next-generation sequencing (NGS) techniques across tumor types.[24] These aberrations, which are not typically present in normal cells, may be therapeutically exploitable, particularly in combination with DNA damage-targeting therapies.[25] A preeminent goal of precision oncology is to identify these specific defects and dependencies and use targeted DDR inhibitors to selectively optimize cancer cell lethality.

PARP Inhibitors

One such important therapeutic approach that exploits DDR defects is the use of inhibitors of the (PARP) enzymes. These enzymes bind via zinc finger domains to SSBs via co-factor nicotinamide (β-NAD+) and catalyze the synthesis of PARP chains (auto-poly [ADP-ribosylation]), resulting in activation of intracellular signaling pathways that enable chromatin remodeling and recruitment of DDR-related protein machinery to prevent lethal accumulation of SSBs.[4,26] PARPi prevents DNA SSB repair and traps PARPs onto DNA. Normal cells with intact DDR signaling and salvage HR repair pathways demonstrate little or no toxicity to PARP inhibition.[4,6,27,28] However, in tumor cells with HRD, the combination of an endogenous genetic defect, such as HR deficiency, with PARP inhibition leads to unrepaired DSBs and collapsed replication forks and ultimately tumor cell death (Figure 1). This concept is termed *synthetic lethality*.[6]

Inhibition of PARP is a successful biomarker-driven therapeutic approach. Numerous PARPi have been developed, including olaparib, rucaparib, niraparib, talazoparib, and veliparib for patients with BRCA1/2 mutant or HR-deficient cancers.[5,28–30] Other strategies to exploit HR include inducing synthetic lethality by generating a BRCAness phenotype, including preclinical studies using combinations with inhibitors of epidermal growth factor receptor (EGFR), PI3K, BET, and others.[31–33] We recently reported promising results of a clinical trial with lapatinib and veliparib in non-BRCA1/2 mutated triple-negative breast cancer (TNBC) based on an induced DNA repair deficiency with EGFR inhibition (ClinicalTrials.gov Identifier: NCT02158507).[34]

Ovarian cancer

To date, three agents—olaparib, rucaparib, and niraparib—are currently approved in different therapeutic settings for ovarian cancer based on the results of multiple clinical trials demonstrating improved progression-free survival (PFS) (Table 1).[35,36] Although the most significant clinical benefit is seen in patients with germline *BRCA1/2* mutations, clinical trials have demonstrated intermediate and modest benefit in patients with *BRCA1/2*-wild-type HRD tumors and in patients without detectable HRD, respectively. Based on data from these trials, olaparib, niraparib, and rucaparib are US Food and Drug Administration (FDA) approved independent of *BRCA1/2* status in the maintenance setting for patients with ovarian cancer. Apart from *BRCA1/2* mutations, biomarkers that predict response to PARPi in ovarian cancer include RAD51C and RAD51D mutations, presence of HRD [as defined by high degree of locus-specific loss of heterozygosity (LOH)], and high-level BRCA1 promoter methylation.[37] PARPi monotherapy also has demonstrated clinical benefit for selected patients with ovarian cancer harboring deleterious or suspected deleterious germline and/or somatic *BRCA1/2* mutation with disease progression or relapse following prior chemotherapy.[35,36,38–40] Talazoparib and veliparib are currently in late-phase trials in patients with newly diagnosed ovarian cancer (Table 2).

Breast cancer

For breast cancer, olaparib and talazoparib are FDA approved as single-agent regimens for previously chemotherapy-treated, HER2 negative, metastatic breast cancers with germline BRCA mutations based on clinical trials demonstrating increased median PFS (and less toxicity as compared with conventional chemotherapy) (Table 1). Maintenance olaparib for 1 year is now recommended following the completion of local treatment and (neo)adjuvant chemotherapy for patients with high-risk TNBC with germline BRCA1/2 mutations; pathogenic or likely pathogenic variants based on trials demonstrated significantly longer survival free of invasive or distant disease.[41] Trials of other PARPi in combination with alkylating agents are currently under way for advanced or metastatic TNBC[42,43] (Table 2). The phase 2 and 3 PARTNER trial of neoadjuvant olaparib in combination with carboplatin followed by the standard chemotherapy is under investigation in patients with TNBC and/or germline BRCA mutations (NCT03150576). Biomarker analyses from clinical trials have established a BRCA1ness gene signature as a significant predictive biomarker of

Table 1. Select clinical trials that resulted in clinical use of PARPi

Study ID	Conditions	Interventions	Outcome Measures	Phase
Ovarian Cancer				
NCT00753545	Platinum-sensitive relapsed serous ovarian cancer	Olaparib	PFS, 8.4 vs 4.8 mo (HR 0.35; $p < 0.00001$) OS, 29.8 vs 27.8 mo (HR 0.73; $p = 0.02$)	2
SOLO2/ENGOT-Ov21, NCT01874353	Platinum-sensitive relapsed *BRCA1/2*-mutant ovarian cancers	Olaparib	PFS, 19.1 vs 5.5 mo (HR 0.3; $p < 0.0001$) OS, 52.4 vs 37.4 mo (HR 0.71; $p = 0.03$)	3
NOVA, NCT01847274	Platinum-sensitive ovarian cancer, including *BRCA1/2* variants, as well as HRD tumors with similar molecular hallmarks, including LOH, large-scale translocations and telomeric allelic imbalance	Niraparib	PFS gBRCA, 21 vs 5.5 mo (HR .27; $p < 0.0001$) PFS non-gBRCA HRD, 12.9 vs 3.8 mo (HR 0.38; $p < 0.0001$) PFS non-gBRCA, non-HRD, 9.3 vs 3.9 mo (HR 0.45; $p < 0.0001$)	3
ARIEL3, NCT01968213	High-grade ovarian cancer, responded to platinum-based chemotherapy in the second-line or third-line settings	Rucaparib	PFS gBRCA 16.6 vs 5.4 mo (HR 0.23; $p > 0.0001$) PFS non-BRCA HRD, 13.6 vs 5.4 mo (HR 0.32; $p < 0.0001$) PFS non-HRD, 10.8 vs 5.4 mo (HR 0.36; $p < 0.0001$)	3
ARIEL4, NCT02855944	BRCA1- or BRCA2-mutated ovarian carcinoma	Rucaparib	PFS gBRCA, 7.4 vs 5.7 mo (HR 0.64; $p = 0.001$)PFS non-gBRCA (HR 0.67; $p = 0.002$)	3
Breast Cancer				
OlympiAD, NCT02000622	Metastatic breast cancers with gBRCA1/2 mutations	Olaparib	PFS, 7.0 vs 4.2 mo (HR 0.58; $p = 0.0009$) OS, 19.3 vs 19.6, n.s.	3
NCT02032823	High-risk, HER2-negative early breast cancer and germline BRCA1 or BRCA2 pathogenic or likely pathogenic variants	Olaparib	3-year invasive DFS, 85.9% vs 77.1% (HR 0.58; $p < 0.001$) 3-year distant DFS, 87.5% vs 80.4% (HR 0.57; $p < 0.001$)	
EMBRACA, NCT01945775	Advanced breast cancer and germline mutations in BRCA1 and BRCA2	Talazoparib vs standard of care chemotherapy	PFS, 8.6 vs 5.6 mo (HR 0.71; $p < 0.001$)	3
NCT03329937	HER2-negative gBRCAm, localized breast cancer	Niraparib	% response by MR, 90.5% % pCR, 38.1% SAE, 9.52%, all-cause mortality, 0%	1
Prostate Cancer				
PROfound, NCT02987543	mCRPC patients with alterations in at least 1 of 15 HRR-related genes who had progressed with prior treatment with a next-generation hormonal agent	Olaparib + abiraterone or enzalutamide	Radiologic PFS, 7.39 vs 3.55 mo (HR 0.34; $p < 0.0001$) ORR 28 vs 1% (OR 20.86; $p < 0.0001$)	3
TRITON2, NCT02952534	mCRPC and HRD	Rucaparib	ORR BRCAm 45.7% OS by gene BRCAm 17.2 mo ATM mutation 14.6 mo CDK12 mutation 13.9 mo CHEK2 mutation 11.1 mo Other gene mutation 11.6 mo	2
TALAPRO, NCT03148795	mCRPC with DDR defects	Talazoparib	ORR, 29.8%	2
POLO, NCT02184195	Metastatic pancreatic adenocarcinoma with gBRCAm	Olaparib	PFS, 7.4 vs 3.8 mo (HR 0.53; $p = 0.004$) OS, 19 vs 19.2 mo, n.s.	3
NCT01924533	Advanced gastric cancer	Olaparib + paclitaxel	PFS, 47 vs 39 mo (HR 0.84; $p = 0.06$) OS, 82 vs 62 mo (HR 0.79; $p = 0.03$)	3

Source: ClinicalTrials.gov; keywords included PARP inhibitor + disease site.
BRCAm: BRCA-mutated; DDR: DNA-damage response; DFS: disease-free survival; gBRCA: germline BRCA; HR: hazard ratio; HRD: homologous recombination-deficiency; HRR: homologous recombination response; LOH: loss of heterogeneity mCRPC: metastatic castration-resistant prostate cancer; MR: mismatch repair; OR: odds ratio; ORR: objective response rate; OS: overall survival; PARPi: poly(ADP-ribose) polymerase inhibitors; pCR: pathologic complete response; PFS: progression-free survival; SAE: serious adverse events.

Table 2. Active clinical trials (≥ phase 3) using PARPi

Study ID	Conditions	Interventions	Outcome Measures
EMBRACA, NCT01945775	Metastatic breast cancer with BRCA mutation	Talazoparib	PFS, OS
NCT05187208	Ovarian cancer	Niraparib	PFS, OS
NCT02163694	HER2-negative, BRCA-associated breast cancer	Veliparib + carboplatin + paclitaxel	PFS, OS, CBR, ORR
NCT02470585	Ovarian cancer	Maintenance veliparib + carboplatin and paclitaxel	PFS, OS
NCT02184195	gBRCA mutated pancreatic cancer	Olaparib	PFS, ORR, OS, DCR, QoL
NCT03534453	Relapsed ovarian cancer	Olaparib	TTF
NCT01905592	HER2 negative, gBRCA mutation-positive breast cancer	Niraparib	PFS, OS, gBRCA testing, TTF, ORR, DOR, QoL, biomarkers
NCT01874353	BRCA mutated ovarian cancer	Olaparib	PFS, OS, TTF, QoL
NCT03150576	TNBC and/or gBRCA positive breast cancer	Neoadjuvant olaparib + paclitaxel and carboplatin	pCR rate, RFS, BCSS, DMFS, LRFS, OS, QoL
NCT01847274	Ovarian cancer	Maintenance niraparib	PFS, TTF, OS
NCT02975934	mCRPC HRD	Rucaparib versus abiraterone acetate or enzalutamide or docetaxel	rPFS, ORR, DOR, PSA response, CBR, QoL
NCT04821622	DDR gene mutated mCRPC	Talazoparib + enzalutamide	rPFS, OS, ORR, DOR, PSA response, ctDNA burden and outcome, QoL
NCT01968213	Ovarian cancer	Maintenance rucaparib	PFS, OS
NCT01844986	BRCA mutated ovarian cancer	Maintenance olaparib	PFS, TTF, OS, QoL
NCT02000622	Metastatic breast cancer with gBRCA1/2 mutations	Olaparib	PFS, TTF, OS, ORR, QoL
ARIEL4; NCT02855944	BRCA mutant ovarian cancer	Rucaparib	PFS, ORR, DOR, QoL
NCT04729387	High-grade serous ovarian cancer, no gBRCA mutation	Olaparib + alpelisib	PFS, OS, ORR, CBR, TTR, DOR
NCT01082549	Squamous cell lung cancer	Gemcitabine and carboplatin with or without iniparib	PFS, OS

Source: ClinicalTrials.gov; keywords included PARP inhibitor + disease site.
BCSS: breast cancer specific survival; CBR: clinical benefit rate; ctDNA: circulating tumor DNA; DCR: disease control rate; DDR: DNA-damage response; DMFS: distant metastasis free survival; DOR: duration of response; gBRCA: germline BRCA; HRD: homologous recombination-deficiency; LRFS: locoregional relapse free survival; mCRPC: metastatic castration-resistant prostate cancer; ORR: objective response rate; OS: overall survival; PARPi: poly(ADP-ribose) polymerase inhibitors; pCR: pathologic complete response; PFS: progression-free survival; PSA: prostate-specific antigen; QoL: quality of life; RFS: recurrence free survival; rPFS: radiographic PFS; TTF: time to treatment failure.

response to neoadjuvant combination veliparib and carboplatin,[44] but additional trials are needed to better identify patients with PARPi-sensitive cancers.

Prostate cancer

On the heels of the PROfound trial, the FDA approved olaparib for the treatment of mCRPC with deleterious or suspected deleterious germline or somatic HRR gene mutations based on reduced risk of disease progression or death.[45] Interestingly, post hoc analysis examined the impact of prior chemotherapy and revealed a greater overall survival (OS) benefit among taxane-naïve patients with a BRCA1 or BRCA2 alteration, and conversely a greater OS benefit among taxane-experienced patients with ATM and cyclin dependent kinase 12 (CDK12) alterations. The phase 2 TOPARP-A and TOPARP-B trials reported that olaparib has activity against mCRPC with HRR defects, particularly BRCA2 homozygous deletions, biallelic loss of PALB2, and loss of ATM.[46–48]

The PARPi rucaparib is also approved for patients with mCRPC with germline or somatic BRCA mutations based on findings from the phase 2 TRITON2 trial, in which PARP inhibition improved objective response rate and a confirmed prostate-specific antigen (PSA) response.[49] Responses were also observed in patients with alterations in the DDR genes PALB2, FANCA, BRIP1, and RAD51B; interestingly, rucaparib has not shown responses in mCRPC with ATM, CDK12, or CHK2 alterations.[50,51] The TRITON3 randomized phase 3 confirmatory study has almost completed accrual (NCT02975934).

In preliminary results from the TALAPRO studies, the PARPi talazoparib has demonstrated favorable antitumor activity in heavily pretreated patients with mCRPC and HRR gene alterations, most commonly BRCA1/2 mutations.[52]

Loss of function of other tumor suppressor DDR proteins, which are involved in HR, such as RAD51, ATR, ATM, CHK1, CHK2, FANCA, BRIP1, and partner and localizer of BRCA2 (PALB2), also have been shown to permit sensitization to PARPi.[26,53] These findings support the potential that PARPi might be a useful therapeutic strategy not only for the treatment of BRCA-mutated tumors but also for the treatment of a wider range of non–BRCA-mutated tumors that are inherently HRD or "BRCAness/HRDness."[4,51,54]

Many active clinical trials are investigating PARPi in DDR-deficient malignancies, as well as in combination with radiotherapy, hormone therapy, chemotherapy, and immunotherapies (Tables 2–4).

Gastrointestinal cancers

In patients with BRCA1/2-mutated pancreatic cancer, olaparib monotherapy has demonstrated modest benefits in PFS[38,55] (Table 1); these benefits resulted in FDA approval in the maintenance treatment for germline BRCA-mutated advanced pancreatic adenocarcinoma that had not progressed on platinum-based chemotherapy. These results have opened opportunities to study combination strategies with PARPi.[56] In gastric cancers, *BRCA1/2* mutations are uncommon. However, more frequent loss of ATM expression as measured by immunohistochemistry has served as rationale for PARPi therapy.[24] Promising phase 2 clinical trial data reported that olaparib plus paclitaxel versus placebo plus paclitaxel resulted in longer OS durations, and patients with low baseline levels of tumor ATM protein expression had the greatest benefit. However, the phase 3 GOLD trial of the same regimen did not meet its primary end point of improved OS in the olaparib-treated group, in neither the overall population nor an ATM-low subpopulation,[57] suggesting that factors outside of ATM loss influence PARPi response in gastric cancer, highlighting that single-gene or single-protein biomarker approaches might be inadequate.[58] Use of PARPi in patients with other gastrointestinal malignancies or with other DDR defects such as ATM, PALB2, and CHEK2 are ongoing (Table 2). As our knowledge of other specific tumor cell DDR abnormalities and the interplay with other cellular processes increases, synthetic lethality approaches targeting DDR proteins, perhaps in multimodality combinations, will likely become more prevalent.

Resistance to PARP Inhibition

Despite biomarker-driven use of PARPi, limited response and durability suggests mechanisms of innate and/or acquired resistance to single-agent therapy. Patients with BRCA1/2-mutant cancers have experienced the most durable responses based on long-term clinical trial data, yet most even initially responsive patients develop resistance. Initial sensitivity and development of resistance likely is dependent on the restoration of HR repair capacity though activation of redundant DDR signaling activity, secondary mutations, or alterations in DDR mediators such as BRCA1/2, RAD51C, RAD51D, and PALB2. Furthermore, activation of oncogenic signaling pathways that slow cell cycle progression and subsequent , mitigation of RS via replication fork stabilization, as well as DDR pathway-independent mechanisms potentially contribute to therapeutic resistance.[24] Acquired resistance via BRCA reversion mutations must also be considered as a key resistance mechanism to both platinum-based chemotherapies and PARPi.[59] Many cancer cells also exhibit an increased dependence on S and G2 DNA damage checkpoints as the result of irregular p53 signaling that would otherwise stop G1 checkpoint signals. As such, therapeutic inhibition of S and G2 checkpoint components, including ATR, ATM, CHK1, CHK2, and WEE1, represent a hopeful anticancer strategy, and specific agents are actively being investigated. Studies so far have provided insight into mechanisms of resistance to PARPi; however, a better understanding of adaptive DDR responses and interconnectedness with other oncogenic pathways is required to overcome both innate and acquired resistance, and to expand therapeutic potential of DDR inhibitors.

Innate PARPi resistance may result from decreased inhibitor binding to PARP and DNA trapping as the result of mutations or loss of PARP1 expression.[46,60] Innate resistance may also be caused by increased PARP1 auto-PARylation, subsequent release of PARP from DNA and restoration of PARP signaling, and decreased PARPi-induced DNA damage as the result of endogenous deficiency in PAR glycohydrolase (PARG) activity.[61]

BRCA and RAD51c promoter methylation are positive predictive biomarkers for sensitivity to PARPi, whereas a single unmethylated gene copy is sufficient to confer resistance.[62,63] Exome analyses performed on primary tumor biopsy as well as on metastatic sites of disease revealed de novo TP53 mutations; analyses also showed increased frequencies of preexisting TP53 mutations compared with primary tumors, suggesting that TP53 status may be associated with PARPi resistance in the presence of BRCA mutations.[64] Genome-wide mutagenic screens also identified full-length and point mutations of PARP1 that cause in vitro and in vivo PARPi resistance.[60]

From these studies it is clear that current biomarkers of PARPi resistance are numerous and diverse, suggesting presence of tissue- and variant-dependent mechanisms of response and resistance that require further investigation. Precision approaches to combinatory strategies targeting molecular susceptibilities to thwart acquired resistance may also enhance and prolong DDR inhibitor response. In support of targeted combinatory strategies, NGS profiling of sensitive and resistant cell lines has revealed that oncogenic pathway activation (e.g., RAS, PI3K, or androgen receptor signaling) may promote HR repair activity and PARPi resistance in certain contexts.[65–67] Another study demonstrated that the ALK kinase inhibitor ceritinib synergizes with PARPi by attenuating complex I of the mitochondrial electron transport chain, which resulted in increased production of reactive oxygen species and subsequent induction of oxidative DNA damage that is repaired in a PARP-dependent manner. Combination of ceritinib and PARPi in this study was synergistic irrespective of HR status, and induced tumor regression more effectively than olaparib alone in high-grade serous ovarian carcinoma patient-derived xenografts.[68]

Table 3. Active clinical trials using other DDR inhibitors

Study ID	Conditions	Interventions	Outcome Measures	Phase
ATR inhibitors				
NCT03188965	Advanced solid tumors and lymphomas	BAY1895344	Safety and tolerability, CBR	1
NCT02487095	Small cell cancers	VX-970 (M6620) + Topotecan	Safety and tolerability, CBR, PFS, DOR OS, H2AX phosphorylation, PBMC FC	1, 2
NCT02595892	Ovarian cancer	Berzosertib + gemcitabine	PFS, ORR, CBR, CA125 levels, OS	2
NCT05338346	Advanced solid tumors and hematologic malignancies	ATG-018	Safety and tolerability, ORR, DOR	1
NCT04616534	Advanced pancreatic and ovarian cancer, and advanced solid tumors	Elimusertib + gemcitabine	Safety and tolerability, ORR, DOR, PFS, PK, OS, HRD, RS, DNA damage	1
NCT04972110	Advanced solid tumor	RP-3500	Safety and tolerability, PK, CBR	1, 2
NCT04802174	SCLC and high-grade neuroendocrine cancers	Berzosertib + lurbinectedin	Safety and tolerability, PK, PFS, DOR, OS	1, 2
NCT04535401	Advanced or metastatic cancers of the stomach and intestines	Elimusertib + chemotherapy	Safety and tolerability, PFS, OS, PBMC DDR signaling, ATM status	1
NCT03669601	Neoplasms	AZD6738 + gemcitabine	Safety and tolerability, efficacy	1
NCT05269316	Advanced solid tumors	IMP9064	Safety and tolerability, ORR DCR, PFS, OS	1
NCT04657068	Advanced solid tumors	ART0380 + chemotherapy	Safety and tolerability, PK, PFS, DOR, ATM IHC	1, 2
NCT04855656	Advanced solid tumors	RP-3500 + RP-6306 (PKMY1 inhibitor)	Safety and tolerability, PK, CDK1 IHC, CBR, gamma-H2AX IHC	1
NCT02595931	Advanced solid tumors	Berzosertib + irinotecan	Safety and tolerability, ORR, PFS, PK	1
PARPi + ATR inhibitors				
TRAP, NCT03787680	Prostate cancer	AZD6738 + olaparib	CBR, PFS, biomarker-based response	2
NCT04149145	Ovarian cancer recurrent	M4344 + niraparib	Safety and tolerability, ORR, PFS	1
NCT04065269	Gynecologic cancers	AZD6738 + olaparib	ORR, DCR, PFS, TTP, OS	2
NCT04497116	Advanced solid tumor	RP-3500 + talazoparib	Safety and tolerability, ORR, PK, PD biomarkers of DNA damage	1, 2
NCT04267939	Advanced solid tumors (excluding prostate cancer) or ovarian cancer	BAY1895344 + niraparib	Safety and tolerability, PK	1
NCT03682289	Solid tumors	AZD6738 + olaparib	ORR, DOR, PFS	2
DDRiver Solid Tumors 301, NCT04170153	Metastatic or locally advanced unresectable solid tumors	M1774 + niraparib	Safety and tolerability, PK	1
CAPRI, NCT03462342	High-grade serous carcinoma	AZD6738 + olaparib	AE rate, ORR, PFS	2
ATM inhibitors				
NCT04882917	Advanced solid tumors	M4076	Safety and tolerability, ORR, DOR, PFS, FC, and IHC	1
NCT03423628	Glioblastoma multiforme	AZD1390 + RT	Safety and tolerability, EFS, ORR, OS	1
CHK inhibitors				
CREATIVE; NCT04678102	Ovarian cancer	PHI-101	Safety and tolerability, ORR, DCR, DOR, PFS, OS, TTP, genetic variation	1
NCT02873975	Solid tumors with RS or HRD	LY2606368 (prexasertib)	ORR, OS	2
NCT04023669	Medulloblastoma	Prexasertib	Safety and tolerability, ORR, DOR, PFS	1
NCT05275426	Ewing sarcoma	LY2880070	ORR	2
DNA-PK inhibitors				
NCT04555577	MGMT unmethylated glioblastoma or gliosarcoma	Nedisertib + RT + surgery + temozolomide	Safety and tolerability, ORR, PFS, OS	1
NCT05002140	Advanced cancer	XRD-0394 + RT	Safety and tolerability, pharmacokinetics	1

Table 3 continues on next page

Table 3. Continued

Study ID	Conditions	Interventions	Outcome Measures	Phase
WEE1 inhibitors				
NCT02194829	Metastatic pancreatic adenocarcinoma	Adavosertib + gemcitabine	Safety and tolerability, PFS, OS, CBR	1, 2
NCT01164995	Ovarian cancer	Adavosertib + carboplatin	Safety and tolerability, PK, radiographic and laboratory response	2
NCT02101775	Ovarian cancer	Adavosertib + gemcitabine	PFS, ORR, CA125 response, OS, Aes, P53 mutations, p53 protein expression	2
NCT03345784	Cervical, upper vaginal and uterine cancers	Adavosertib + cisplatin + RT	Safety and tolerability, PK, PFS	1
NCT04768868	Advanced solid tumors	IMP7068	Safety and tolerability, PK, ORR	1
NCT03668340	Uterine cancer	AZD1775	ORR, PFS, CBR, DOR, Aes	2
NCT05291182	Advanced solid tumor	SY-4835	Safety and tolerability, PK, ORR, PFS, DCR, DOR	1
NCT03385655	Prostate cancer	Adavosertib	CBR, PSA response, ORR, AEs, PFS, OS	2
NCT03385655	Prostate cancer	Adavosertib	CBR, PSA response, ORR, AEs, PFS, OS	2

Source: ClinicalTrials.gov; keywords included PARP inhibitor or DDR target or DDR inhibitor + disease site.
AE: adverse event; CBR: clinical benefit rate; DCR: disease control rate; DDR: DNA-damage response; DOR: duration of response; EFS: event-free survival; FC: flow cytometry; HRD: homologous recombination-deficiency; IHC: immunohistochemistry; ORR: objective response rate; OS: overall survival; PBMC: peripheral blood mononuclear cell; PD: pharmacodynamics; PFS: progression-free survival; PK: pharmacokinetics; PSA: prostate-specific antigen; RS: replication stress; SCLC: small cell lung cancer; TTP: time to progression.

OTHER PROMISING DDR PATHWAY TARGETS

Ataxia telangiectasia mutated (ATM) and ATM- and RAD3-related (ATR)

ATR and ATM protein kinases, operating together via downstream targets CHK1 and CHK2, respectively, play vital roles in DDR signaling by maintaining replication fork stability and the regulation of cell cycle control checkpoints.[20] It is increasingly understood that functional crosstalk following DNA damage exists between ATM, ATR and the NHEJ-mediator DNA-PKs such that impaired function of these mediators represents a therapeutic opportunity for synthetic lethality. ATM is the key kinase involved in phosphorylation of histone H2AX on serine 139 (γH2AX), signifying DNA damage. Although hundreds of downstream substrates of ATM have been identified, fundamentally, activation of CHK2 is vitally involved in G1-S-phase checkpoint activation.[69] ATM also participates in stabilization of p53 through the phosphorylation and subsequent inhibition of proteasomal degradation by MDM2.[69] ATM and ATR both cooperate in the process of DSB repair during ionizing radiation (IR) or genotoxic stress. However, ATM is principally involved in response to DSBs, whereas ATR is primarily activated by SSBs; for example, ATM inhibition has been shown to hypersensitize tumor cells to IR and DNA DSB-inducing chemotherapeutics.[19] Emphasizing its role in DSBs repair and interconnectedness of DDR pathways, ATM, along with nuclease activity or Mre11, is required to generate the replication protein A–coated ssDNA needed for ATR recruitment and CHK1 activation during S and G2 cell cycle phases.[69] ATM deficiency in cancer is not uncommon, with mutations found in many solid tumors. ATR inhibitors are an emerging DDR-targeting strategy for cancers with HRDness, including deleterious *ATM* and *BRCA1/2* mutations, and have been shown in early-phase trials to confer sensitivity to ATR inhibitor regimens.[24] ATR and ATM are potential targets of DDR inhibitors under increasing preclinical and clinical investigation (Table 3).

ATM Deficiency and Enhanced Sensitivity to PARP Inhibition

ATM deficiency or inactivation has been shown to increase sensitivity to PARPi in preclinical models (Figure 1).[3] The rationale for PARPi use in HRD cancers historically extends from the high sensitivity and synthetic lethality observed in BRCA1/2-mutant tumors; however, ATM deficiency also results in HRDness and is thought to promote dependence on alternate DDR mechanisms.[19]

In support, favorable response rates to olaparib were observed in a phase 2 trial for patients with prostate cancer that had progressed on prior standard treatments and who had defects in DDR genes such as BRCA1/2, ATM, or CHEK2.[46–48] It remains unclear what contribution ATM deficiency plays to PARP sensitivity in this setting, especially in the context of BRCA1/2 or other HRD-related gene mutations. This notion is supported by findings from the TRITON2 trial, which suggests ATM and CDK12 mutations confer less benefit from rucaparib as compared with BRCA1/2 loss in patients with mCRPC.[51]

However, limited responses to single-agent PARPi even in BRCA1/2-mutant tumors and unexpected response in non-HRD tumors suggest that innate or acquired resis-

Table 4. Active clinical trials using PARPi + IO combinations

Study ID	Conditions	Interventions	Outcome Measures
PARPi + IO			
CT03951415	Metastatic or recurrent endometrial cancer	Olaparib + durvalumab (PD-L1)	PFS, ORR, OS, predictive biomarkers in tumor biopsy
ImmunoProst, NCT03040791	Prostate cancer + DDR defects	DDR defects + nivolumab	PSA response rate, rPFS, PFS, OS
NCT03404960	Pancreatic adenocarcinoma	Niraparib + nivolumab	PFS, proportion of tumors with HRD, correlation of HRDs with response, immune activation, ORR, DOR, OS
DORA, NCT03167619	Advanced TNBC	Olaparib + durvalumab (PD-L1)	PFS, OS, ORR
Javelin, NCT03330405	Locally advanced (primary or recurrent) or metastatic solid tumors	Talazoparib + avelumab	OR, PSA tumor marker, CA-125 tumor marker, or biomarker PD-L1, TTR, DOR, PFS, OS, biomarker TMB
NCT02953457	BRCA1/2 mutated ovarian cancer	Olarib + durvalumab + tremelimumab	PFS,OS
NCT04034927	Recurrent ovarian cancer	Olaparib + tremelimumab	PFS, OS
NCT02571725	BRCA-deficient ovarian cancer	Olaparib + tremelimumab	ORR, PFS
NCT05319249	AML	NK cells + talazoparib	CR, EFS, RFS, OS
NCT04779151	Bladder cancer, gastric adenocarcinoma, GE adenocarcinoma, H&N, biliary tract cancer, clear cell RCC	Niraparib + dostarlimab	ORR
NCT05201612	Metastatic HRD colorectal cancer	Olaparib + pembrolizumab	ORR, DCR, PFS, OS, DOR
NCT05366166	LA-HNSCC	Olaparib + pembrolizumab	PFS, OS, LRC DMFS, CPS
NCT04483544	Cervical carcinoma	Olaparib + pembrolizumab	Immune ORR, PFS, no. of patients with baseline tumor deficiencies, DOR
NCT03639935	Advanced or metastatic biliary tract cancer	Rucaparib + nivolumab	ORR, PFS, OS
NCT04276376	DDR-deficient or platinum-sensitive solid tumors	Rucaparib + atezolizumab	ORR
NCT04681469	HPV-negative HNSCC	Niraparib + IO	Rate of MPR, PFS, genomic expression
PRIO, NCT04728230	Extensive stage lung SCC	Olaparib + durvalumab with carboplatin, etoposide, and/or RT	PFS, ORR, OS
NCT04209686	Advanced gastric adenocarcinoma	Olaparib + pembrolizumab + paclitaxel	OS
NCT03025035	Advanced BRCA-mutated or HDR-defect breast cancer	Olaparib + pembrolizumab	PFS, ORR, OS, clinical benefit rate (CBR = CR + PR + SD), DOR
NCT04493060	Germline or somatic BRCA1/2 and PALB2 mutated metastatic pancreatic cancer	Niraparib + dostarlimab	DCR12, ORR, PFS, OS
MiST, NCT03654833	Mesothelioma, malignant	Bemcentinib + pembrolizumab or niraparib + dostarlimab or bevacizumab + atezolizumab	DCR12, DCR24, ORR
NCT04739800	Ovarian cancer	Olaparib + cediranib maleate + durvalumab	PFS, ORR, OS
NCT03830918	Advanced solid tumors and extensive-stage small cell lung cancer	Niraparib + atezolizumab	ORR, OS
NCT04336943	Biochemically recurrent prostate carcinoma + high predicted neoantigen load	Olaparib + durvalumab	PSA response, QoL
NCT02484404	Colorectal and breast neoplasms	Olaparib and/or cediranib + durvalumab	ORR, PFS, pretreatment tumor PD-L1 expression and clinical response, PSA response, peripheral immune subsets, plasma cytokines
NCT04633902	Advanced melanoma with HR mutation	Olaparib + pembrolizumab	ORR, PFS, OS
NCT04548752	Metastatic pancreatic adenocarcinoma with inherited BRCA mutations	Olaparib + pembrolizumab	ORR, PFS, DOR, OS
NCT05392686	Lung cancer	PARPi + PD-1 inhibitor	PFS
NCT04701307	Lung SCC and other high-grade neuroendocrine carcinomas	Niraparib + dostarlimab	PFS, ORR, DCR12, OS
NCT04985721	Advanced tumors with HRD	Pamiparib + tislelizumab	CBR, HRD phenotype as a predictor of response

Table 4 continues on next page

Table 4. Continued

Study ID	Conditions	Interventions	Outcome Measures
NCT04334941	Extensive stage lung SCC with SLFN11 positive biomarker	Talazoparib + atezolizumab	PFS, OS
NCT04592237	Aggressive variant prostate carcinoma	Niraparib + cetrelimab + cabazitaxel and carboplatin	PFS, OS, response rate by circulating tumor cells
NCT04978012	Nasopharyngeal carcinoma	Fluzoparib and camrelizumab	ORR, DCR, DOR, PFS, OS, ORR by PD-L1 TPS subgroups, ORR by HRR status
NCT03801369	Metastatic TNBC	Olaparib + durvalumab	ORR, CBR, PFS, OS, DOR
NCT04837209	TNBC	Niraparib + dostarlimab + RT	ORR, PFS, OS, QoL
NCT03522246	Ovarian cancer	Maintenance rucaparib + nivolumab	PFS, OS, ORR, DOR
NCT04592211	Gastric cancer stage with HRR mutation and MSS	Olaparib + pembrolizumab + paclitaxel	PFS, ORR
NCT05065021	Ovarian cancer	Niraparib + dostarlimab	Biomarker-guided treatment, ORR, PFS, CA125 response rate, DCR
NCT04713514	Ovarian cancer	OSE2101 + pembrolizumab	PFS, ORR, OS
NCT03651206	Ovarian or endometrial carcinosarcoma	Niraparib + dostarlimab	ORR, OS, PFS, QoL
NCT04508803	Breast cancer with germline mutations	Niraparib + HX008 (PD-1 mab)	ORR, OS, PFS, CBR, DOR
COMPRENDO, NCT05033756	HER2 negative breast cancer with a deleterious germline mutation or HRD	Olaparib + pembrolizumab	Safety and tolerability, ORR, DOR, PFS, OS
ATR inhibitors + IO			
DDRiver Solid Tumors 320; NCT05396833	Metastatic or locally advanced unresectable solid tumors	M1774 + ICI	Safety and tolerability, PK, PD biomarker, ORR
NCT04576091	Recurrent H&N cancer	Elimusertib + pembrolizumab + SBRT	Safety and tolerability, PFS, ORR, OS, QoL
ATM inhibitors + IO			
NCT02588105	Advanced solid tumors	AZD0156 + olaparib and chemotherapy	Safety and tolerability, tumor response, ATM-associated protein levels and activity, CTCs, ctDNA, OS
DNA-PK inhibitors + IO			
NCT03724890	Solid tumors	M3814 + avelumab	Safety and tolerability, ORR, DOR, PFS, tumor size, OS

Source: ClinicalTrials.gov; keywords included PARP inhibitor or DDR inhibitor/target + immune checkpoint inhibitor or antibody name or immunotherapy.
AML: acute myeloid leukemia; CBR: clinical benefit rate; CPS: combined positive score (PD-L1 expression) CR: complete response; CTC: circulating tumor cells; ctDNA: circulating tumor DNA; DCR: disease control rate; DDR: DNA-damage response; DMFS: distant metastasis free survival; DOR: duration of response; EFS: event-free survival; GE: gastroesophageal; H&N; head and neck; HNSCC: head and neck squamous cell carcinoma; HPV: human papilloma virus; HRD: homologous recombination-deficiency; HRR: homologous recombination response; ICI: immune checkpoint inhibitor; IO: immunotherapy; LA: locally advanced; LRC: locoregional control; MPR: major pathological response; MSS: microsatellite stable; NK: natural killer; ORR: objective response rate; OS: overall survival; PARPi: poly(ADP-ribose) polymerase inhibitors; PD-L1: programmed death-ligand 1; PFS: progression-free survival; PR, partial response; PSA: prostate-specific antigen; QoL, quality of life; RCC: renal cell carcinoma; RFS: recurrence free survival; rPFS: radiographic PFS; RT, radiation therapy; SBRT: stereotactic body radiation therapy; SCC: small cell cancer; SD: stable disease; TMB: tumor mutational burden; TNBC: triple-negative breast cancer; TPS: tumor proportion score (PD-L1 expression); TTR: time to tumor response.

tance may potentially be overcome by pairing of PARPi with other DDR inhibitors, including ATR inhibitors.[3] For example, olaparib monotherapy has demonstrated limited clinical benefit (40% response rate, following first-line chemotherapy) in recurrent BRCA1/2-mutant high-grade serous ovarian carcinomas, despite relatively high frequency of HR repair gene defects.[3] The addition of ATR inhibitors to PARPi, however, has shown increased efficacy as compared with PARPi alone in early trials of BRCA-mutant ovarian cancer, suggesting that PARPi increases the dependence on ATR activity for fork stabilization.

DNA-dependent protein kinase (DNA-PK)

DNA-PK is a key enzyme involved in the NHEJ pathway of DNA repair.[19] As a member of the PI3K–mammalian target of rapamycin (mTOR) enzyme family, DNA-PK also plays a vast role in cell survival and proliferation and has emerged as an interesting therapeutic target in the treatment of a variety of cancers, especially when used along with genotoxic chemotherapy or IR where NHEJ is a fundamental repair mechanism.

The putative effects of DNA-PK inhibitors to sensitize tumor cells to chemotherapy and IR has also been pursued in clinical trials. M3814 (nedisertib) is being tested in multiple trials including along with IR therapy in advanced solid tumors (NCT02516813). The DNA-PK pathway modulator CC-122 is being tested in multiple myeloma, advanced solid tumors, and non-Hodgkin's lymphoma (NCT01421524). CC-115, a dual DNA-PK and mTOR inhibitor, is in phase 2 studies to determine its

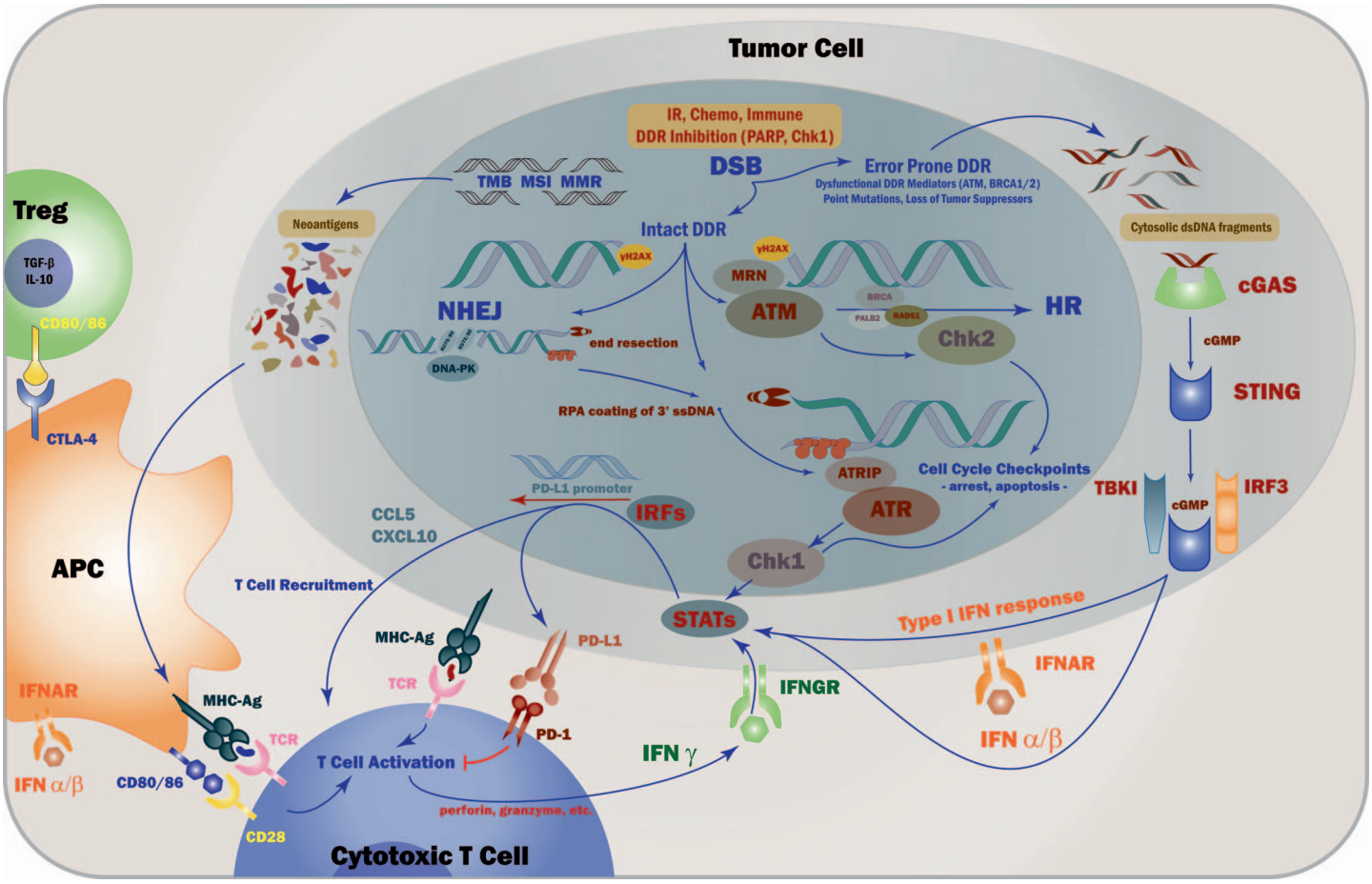

Figure 2. Interplay between DDR and immune surveillance in the therapeutic setting. Identifying mechanisms that link DNA damage-initiated tumor cell signaling and immune recognition may help identify potential precision targets driving tumor progression and immune escape. A combination of genomic stress induced by DNA-damaging treatments and DDR defects or MMR or MSI results in accumulation of chromosomal abnormalities, higher TMB, oncogene activation and tumorigenesis, as well as production of neoantigens resulting in enhanced immune recognition, activation of immunostimulatory genes, and increased TILs. Immune milieu in the tumor microenvironment may consist in part of cytotoxic antitumor immune cells ($CD8^+$ T cells), APCs, $CD4^+$ T cells, and NK cells, as well as immunosuppressive counterparts such as $CD4^+$ Tregs, myeloid-derived suppressor cells, and M2 macrophages. Therapeutic targeting of single- and double-stranded DNA breaks for repair with inhibitors of DDR, including PARPi, particularly in setting of DDR mutations or alterations that cause HR deficiency, can potentially increase generation of cytosolic DNA fragments, resulting in activation of the immunomodulatory cGAS/STING pathway that promotes antitumor immunity through activation of T and NK cells, neoantigen recognition, and increased PD-L1 expression via the JAK-STAT1/3-IRF1 pathway. IFN-induced tumor PD-L1 expression can suppress $PD\text{-}1^+$ cytotoxic antitumor immune cells via inhibitory binding. This DNA-damage induced antitumor immune response and subsequent tumor escape mechanisms presents a therapeutic opportunity to shift this balance by precisely targeting DDR defects as well as the subsequent tumor cell–initiated mechanisms of immunosuppression through use of ICIs such as anti-PD-1/PD-L1 and anti-CTLA-4 mAbs.

APC: antigen presenting cell; ATM: ataxia telangiectasia mutated; ATR: ataxia telangiectasia and RAD3-related protein; ATRIP: ATR-interacting protein; CD: cluster of differentiation CHK: checkpoint kinase; CTLA-4: cytotoxic T lymphocyte antigen-4; DDR: DNA damage response; DNA-PK: DNA-dependent protein kinase; DSB: double-stranded breaks; HR: homologous recombination; ICI: immune checkpoint inhibitor; IFN: interferon; IFNAR: IFN interferon; IFNGR: IFN gamma receptor; IL: interleukin; IR: ionizing radiation; IRF: interferon regulatory factor; mAbs: monoclonal antibodies; MHC: major histocompatibility complex; MMR: mismatch repair; MSI: microsatellite instability; NHEJ: nonhomologous end-joining; NK: natural killer; PARP: poly(ADP-ribose) polymerase; PARPi: PARP inhibitors; PD-L1: programmed death-ligand 1; RPA: replication protein A; TBKI: TANK binding kinase 1; ssDNA: single-stranded DNA; TGFβ: transforming growth factor beta; TIL: tumor infiltrating lymphocyte; TMB: tumor mutational burden; Treg: regulatory T cell.

efficacy in mCRPC and along with IR for glioblastoma (NCT02977780). M9831 is being tested in a phase 1 study with or without doxorubicin in patients with advanced-stage solid tumors (NCT02644278).

Checkpoint Kinase 1 and 2

The downstream substrates of ATR and ATM, CHK1 and CHK2, respectively, are central cell cycle checkpoint kinases that coordinate with interconnected DDR pathways. Many early investigatory CHK1 and CHK2 inhibitors were not developed further in large part given associated toxicities particularly in combination with chemotherapy.[70–72] Although selectivity, poor efficacy, and toxicity have hindered advancement of many of these inhibitors in early-phase clinical trials, efficacy has been promising in specific settings. For

instance, a patient with ATM-deficient small cell lung cancer (SCLC) and a RAD50-mutation experienced a complete response to the combination of irinotecan and AZD7762.[73]

The second-generation CHK1-selective inhibitor prexasertib (LY2606368) induced a 29% response rate with acceptable tolerability in women with measurable, recurrent high-grade serous or high-grade endometrioid ovarian carcinoma. Prexasertib-induced radiosensitization was tested in a phase 1b trial of patients with locally advanced head and neck squamous cell carcinoma (SCC) in combination with cetuximab-radiotherapy.; This study showed this regimen to be safe and resulted in 83.3% overall response rates with several complete responses.[74] Prior concern regarding toxicity, particularly in the combination therapy setting, as well as appropriate patient selection, remain challenges for CHK1/2 inhibitors.[75] These studies highlight the need for combination strategies with nonoverlapping toxicity profiles to foster hope for CHK1/2 inhibitor efficacy. Ongoing clinical trials of selective CHK1/2 inhibitors are ongoing, including prexasertib (LY2606368), GDC-575 (ARRY-575; RG7741), and CCT245737 (SRA737). Prexasertib is currently being tested in clinical trials for metastatic TNBC (NCT04032080), small round cell tumors, and rhabdomyosarcoma (NCT04095221), in combination with cyclophosphamide or gemcitabine in medulloblastoma (NCT04023669). GDC-575 (NCT01564251) and CCT245737 (NCT02797964 and NCT02797977) are in phase 1 testing as single agents or in combination with gemcitabine-based chemotherapy.

WEE1 Nuclear Kinase

WEE1, which is overexpressed and associated with outcomes across tumor types including glioblastoma and ovarian and breast cancer, activates G2/M cell cycle checkpoint by inhibiting CDK1/2, resulting in cell cycle arrest and procession of DNA damage repair. Avoidance of G2 checkpoint initiation by WEE1 inhibition results in premature mitotic entry, increased RS, and potentially lethal genomic instability. WEE1 inhibition can impair HR via CDK1-mediated phosphorylation of *BRCA1* and *BRCA2*.[76] It follows then that tumor cells with increased reliance on G2 checkpoints may be more susceptible to WEE1 inhibitor-induced G2 arrest and synthetic lethality by causing cells with unrepaired DNA damage to enter into mitosis and undergo mitotic catastrophe.[77]

Use of the WEE1 inhibitor, adavosertib (AZD1775; MK-1775), selectively inhibits the G2 checkpoint and lowers the threshold for mitotic lethality by sensitizing p53-deficient cells to genotoxic stressors such as chemotherapy and IR.[78,79] Adavosertib is currently in clinical development for patients with tumors harboring p53 mutations, specifically as a part of combinatory strategies with DNA-damaging treatments such as PARPi, chemotherapy, and IR.[80] Ongoing clinical studies evaluating WEE1 inhibitors in combination with other DDR inhibitors, chemotherapy, and/or IR in for multiple cancer types are ongoing[80] (Tables 3 and 4).

DDR Signaling as a Mediator of Antitumor Immunity and Immunotherapy Response

Immune evasion is a hallmark of cancer that is the result of complex tumor-host immunological interactions, in part directed by aberrant tumor immunologic signaling and adaptive mechanisms that avoid immune surveillance and elimination.[17] Co-inhibitory cell surface receptors that regulate T-cell function, such as CTLA-4 and PD-1, are expressed in the tumor environment in response to T-cell activation. The balance between co-stimulatory and co-inhibitory signals is crucial for cytotoxic T-cell activation and immunologic tolerance.[81] Tumors can exploit this balance through co-inhibitory receptor engagement, for example via tumor PD-L1 expression and/or upregulation, to escape T-cell–mediated tumor rejection. Immune checkpoint inhibitors (ICIs) are used to therapeutically target these co-inhibitor signals and are capable of unleashing antitumor activity.[82] ICIs, including monoclonal antibodies against PD-1 (pembrolizumab, nivolumab), PD-L1 (atezolizumab, durvalumab, avelumab), and CTLA-4 (ipilimumab), have generated durable responses across many tumor types.

Although tumor cell PD-L1 expression is the best predictor of response to anti-PD-1/PD-L1 therapies, it is increasingly clear that many other factors, including intact IFN-γ signaling, TMB, MMR deficiency, and even DDR alterations can play significant roles in patient response to ICIs.[8,12,83–86] Indeed, numerous studies have shown crosstalk between DDR and many immune-related outcomes, including PD-L1 expression (Figure 2).[87–89] By extension, clinical use of anti-PD-1/anti-PD-L1 monoclonal antibodies in mismatch repair-deficient tumors, for example, supports the notion that increasing tumor mutational load with DDR inhibitors may result in enhanced tumor cell immunogenicity and ICI response.[85]

Intact DDR signaling is important for innate immunity, activation of inflammatory cytokines, and expression of immune-receptor ligands on damaged tumor cells; in some instances the signaling can be used to predict ICI response.[90] Dysfunctional DDR signaling can elicit antitumor immune activation, supporting use of DDR biomarkers for ICI response and combinatory treatment strategies with DDR inhibitors and ICIs.[90] Highly mutated tumors often exhibit one or several mutations in key components of DDR or replicative pathways, including MSH2 for MMR/MSI, BRCA1/2 for HR, and polymerase epsilon (POLE) for DNA replication. Furthermore, targeting of DSB repair proteins with DDR inhibitors has also been shown to increase the TMB.[91] DDR-defect-dependent genomic instability, chromosomal fragmentation, and increased TMB can result in immune recognition, activation of immunostimulatory genes, increased TIL, and antitumor im-

mune production of IFN-γ.[9–12] Generation of chromosomal fragments stimulates the cytosolic sensing cGAS/STING pathway that promotes antitumor immunity through activation of T and NK cells, neoantigen recognition, and increased PD-L1 expression; this immune system stimulation is enhanced in the background of BRCAness/HRDness.[12–14,16,89]

There is also compelling evidence that mechanisms of resistance to DNA-damaging agents may also play a meaningful role in immunotherapy outcomes.[84,85] For example, defects in BRCA1/2 correlates to higher levels of PD-L1 expression,[12] and deleterious DDR mutations are frequent in non–small-cell lung cancer (NSCLC), which are associated with improved clinical outcomes in patients treated with PD-(L)1 blockade.[83] Conversely, it has been shown that tumor-intrinsic PD-L1 can regulate IFN-γ–induced apoptosis, DDR, RT, and chemotherapy resistance, and effects on Ras/Mek/ERK, PI3K/AKT, JAK/STAT,[92–97] which, altogether suggests a predictive role of DDR pathways in ICI response and creates treatment-exploitable immune signaling effects particularly regarding DDR inhibitor-ICI combinations.

DDR-Targeting and Immunotherapy Combinations

The effects of dysfunctional DDR signaling on the immune environment and consequential sensitization to ICIs serves as rationale for combining these with DDR-targeting therapies.[98] Mechanisms of synergy are based on preclinical data demonstrating that DDR deficiency results in accumulation of unrepaired DNA damage and resultant neoantigens capable of inducing $CD8^+$ T-cell infiltration and activation.[86] Innate immune response and $CD8^+$ T-cell activation are strongly correlated with favorable clinical response to ICIs, suggesting these DDR-dependent effects may further sensitize clinical response (Figure 2).

Immunotherapy and PARPi

Therapeutic targeting of genomic instability through the use of DDR inhibitors, including PARPi, have been shown to not only induce synthetic lethality in DDR-deficient tumor cells, but also to augment the tumor immune microenvironment through increased TMB and activation of immunostimulatory genes.[10,18] Multiple combination studies have used ICIs and DDR inhibitors, and preliminary efficacy data demonstrate that the combination of DDR-targeting agents with ICIs is a promising cancer treatment strategy[18,19] (Table 4). Combinations of ICIs with DDR-targeted inhibitors, especially those of PARP, have received extensive attention given high rates of intrinsic and acquired resistance, and immune-stimulating properties as the result of DNA repair inhibition. PARPi also upregulates PD-L1 expression,[88,97] likely as the result of DNA-damage–induced IFN-dependent immune activation, thus serving as rationale for combinations with anti-PD-L1 therapies to impinge on the competing immune consequences of PARPi monotherapy.

Breast and ovarian cancer

BRCA1/2 mutations have demonstrated as a predictive biomarker for response to PARPi and ICI therapies, and these are enriched in breast and ovarian carcinoma populations.[37,40] Specifically, BRCA1/2 mutations potentially result in increased immunogenic phenotypes,[87] suggesting that dual targeting of both DDR and CTLA-4- and/or PD-(L)1–mediated immunosuppression may be an effective strategy for some patients. In BRCA-mutated ovarian cancer, CTLA-4 antibody blockade synergized therapeutically with PARPi, which resulted in immune-mediated tumor clearance and increased long-term survival.[99] Combination durvalumab and olaparib has demonstrated clinical activity in previously treated, platinum-resistant recurrent ovarian cancer. KEYNOTE-162, investigating the combination of niraparib with pembrolizumab in patients with recurrent ovarian cancer, demonstrated an ORR of 25% and disease control rate (DCR) of 68%; however, subgroup analysis of patients with BRCA mutation revealed an ORR of 45% and DCR of 73%,[100,101] indicating BRCA mutation status might be predictive of positive clinical response to PARPi combined with ICIs.

The phase 2 MEDIOLA basket trial assessed the efficacy and safety of combination olaparib and durvalumab in patients with solid tumors, including ovarian cancer, breast cancer, and gastric cancer (NCT02734004). In germline BRCA-mutated (gBRCAm) platinum-sensitive relapsed ovarian cancer, this combination demonstrated an overall response rate (ORR) of 71.9% with a total of 7 out of 32 complete responses, and a DCR of 65.6% at 28 weeks[54] In gBRCAm HER2-negative metastatic breast cancer, the DCR was 80% at 12 weeks and 50% at 28 weeks, with ORR of 63%. Median PFS (mPFS) was 9.2 months and median overall survival (mOS) was 21.5 months. Moreover, patients with no prior line of chemotherapy had higher ORR and longer OS than those with two prior lines (respectively 78% vs 50% for ORR and 21.3 vs 16.9 months for OS).[54] In the phase 2 TOPACIO trial (NCT02657889), niraparib and pembrolizumab combination therapy has demonstrated clinical benefit in platinum-resistant TNBC, with numerically higher response rates in those with BRCA-mutated TNBC tumors (ORR of BRCAm vs BRCA wild-type, 47% vs 11%).[100,101]

Combination treatments with ICIs and PARPi are currently under intense exploration (Table 4), with encouraging preliminary results. Although the relationship between endogenous or PARPi-induced BRCAness and immunotherapy response is still being investigated, these ongoing clinical trials will help establish the effect of HR deficiency and DDR-targeting therapies on ICI outcomes in BRCA1/2-associated phenotypes.

Prostate cancer

Prostate cancer is inherently sensitive to hormonal therapies; however, approximately 10% to 20% of

patients with advanced prostate cancer will develop castration-resistant prostate cancer within 5 years from diagnosis. Primary prostate cancers generally do not harbor targetable genomic alterations; however, approximately 20–25% of metastatic castration-resistant prostate cancer (mCRPC) is associated with DDR signaling defects, including 12.7% with pathogenic BRCA2 germline mutations, as well as other potentially targetable alterations, such as ATM, BRCA1, CDK12, FANCA, RAD51B, and RAD51C. However, response rates to PARPi vary widely and development of resistance remains problematic. The use of ICIs in mCRPC has also shown mixed efficacy; however, defects in mismatch repair, mutations in the exonuclease domain of the DNA POLE, high TMB, and the presence of biallelic loss of CDK12 among others have shown to be predictive biomarkers of response to immunotherapy in prostate cancer.[102] A subset of patients with mCRPC have a high mutation load because of alterations in mismatch repair genes, *MLH1* and *MSH2*. Thus, patients with mCRPC with a high mutational burden, particularly as a result from DNA repair defects, may benefit greatly from DDRtargeting agents and ICI combinations. A combination of PARPi and ICIs is actively being investigated in multiple clinical trials (Table 4). Trials such as Keynote-365 have evaluated ICIs plus PARPi in heavily treated patients with mCRCP, and have demonstrated improved PSA response rates, radiologic ORR, DCR, and PFS.

Lung cancer

The PACIFIC trial set the new standard of care for advanced NSCLC with the addition of maintenance durvalumab following chemoradiotherapy[103]; however, combination with PARPi is being evaluated to increase efficacy both in the first-line and maintenance therapeutic settings, and evaluate therapies to reverse ICI resistance. The KEYLYNK-012 study (NCT04380636) is a phase 3 trial evaluating pembrolizumab alone or in combination with olaparib post-chemoradiotherapy in patients with unresectable, locally advanced stage 3 NSCLC. This combination is also being studied in KEYLYNK-006 (nonsquamous; NCT03976323) and KEYLYNK-008 (squamous; NCT03976362) as first-line treatment for metastatic NSCLC. The phase 2, biomarker-directed HUDSON study is evaluating the combination of durvalumab in combination with olaparib in patients with NSCLC with HRR defects, and the combination of durvalumab and AZD6738 (ATR inhibitor) in those with ATM deficiency.

In the case of SCLC, most patients respond suboptimally to ICIs despite a relatively high TMB.[90] Recent studies have shown that targeting DDR promotes T-cell–mediated antitumor immunity in a STING-dependent manner,[14] setting the stage for potentially increased efficacy of PD-(L)1 inhibitors in patients with lung cancer. Early-phase, small cohort trials support this hypothesis that tumors with inflamed phenotypes as measured by tumor infiltrating $CD8^+$ T cells respond to the combination of durvalumab and olaparib, whereas the ORR for all patients irrespective of inflammatory phenotype is 10.5%; this difference highlights the need for large-scale prospective investigations of predictive biomarkers and therapeutic strategies to address ICI resistance in SCLC.[104]

Immunotherapy and Other DDR-Targeted Strategies

Targeting of other mediators of DNA damage response and repair pathways is actively being pursued as a strategy to enhance cancer immunotherapies. A preclinical study demonstrated that DNA-damage induced PD-L1 expression by IR or chemotherapy is attenuated by ATR inhibition, suggesting crosstalk between DDR and immune checkpoints, and providing rationale for combination therapy with ATR inhibitors and ICIs.[105] The ATR inhibitor ceralasertib (AZD6738) was studied in combination with durvalumab in patients with advanced or metastatic melanoma who had previously failed anti-PD-1 therapy, with an ORR of 31.0% and a DCR of 63.3%.[106] The median duration of response was 8.8 months (range, 3.8–11.7 months). Other clinical trials investigating the combination of ATR inhibitors and ICIs in various cancer types are ongoing (Table 4).

Adavosertib (AZD1775), a highly selective inhibitor of WEE1, was studied in combination with durvalumab in a phase 1 study (NCT02617277) in patients with advanced solid tumors, with preliminary evidence of antitumor activity and DCR for the total cohort of 36%[107]; a phase 2 study is ongoing based on these promising data. The phase 1b BISCAY trial is a biomarker-directed study in patients with metastatic muscle-invasive bladder cancer; patients with any HR deficiency will receive durvalumab with or without olaparib, and patients with CDKN2A or RB1 deficiency and/or amplifications of CCNE1, MYC, MYCL, or MYCN will receive durvalumab with or with adavosertib.[108]

In addition to inducing cell cycle arrest, CDK4/6 inhibitors have been found to enhance tumor immunogenicity through increased tumor antigen presentation, enhance T-cell activation, increase tumor PD-L1 expression, and suppress regulatory T-cell proliferation, providing rationale for combinatory regimens of CDK4/6 inhibitors and immunotherapy.[109] Furthermore, the SCP3-cyclin D1-CDK4/6 axis is activated by the antitumor immune response and facilitates tumor cell resistance to immunotherapy, suggesting that CDK4/6 inhibition may reverse immune escape and promote durable responses to ICIs. Preclinical studies have demonstrated that combination CDK4/6 inhibitors with ICIs and PI3Kα resulted in complete and durable regression in established xenograft mouse models of human TNBC.[110] CDK4/6 inhibitors in combination with ICIs are being investigated in clinical trials for various cancers, including breast cancer, head and neck squamous cell carcinoma (HNSCC), NSCLC, and hepatic cancers.

ATM inhibition has be shown to increase IFN signaling and sensitize pancreatic cancer to ICI therapy,[111] and ATM pathway inhibition has been reported to activate

innate immunity in ARID1A-deficient cancers and enhance immune activation following PD-L1 blockade.[112] ATM inhibitors (M3541 and AZD0156) are currently in early-phase clinical trials for treatment of solid tumors.

DNA-PK has been reported to activate STING-independent DNA sensing resulting in robust and broad Th1 immune activation[113]; this result suggests that targeted DDR inhibition may synergistically increase immunotherapy efficacy though DNA-PK–dependent immune augmentation. The DNA-PK inhibitor nedisertib is being studied in combination with avelumab with or without RT in patients with advanced solid tumors (NCT03724890).

CHK1 inhibition has been found to activate the cGAS/STING pathway and increase tumor PD-L1 expression in SCLC, which significantly enhances the efficacy of ICIs.[14] This study also identified MYC as a biomarker of CHK1 response, suggesting that combination strategies involving CHK1 inhibitors might be effective in cancers with MYC amplification or overexpression. These preclinical studies indicate the need to explore this combination in clinical trials.

Overall, for combinations of DDR-targeting therapy and immunotherapy, biomarker-directed preclinical and clinical studies to identify mechanisms of response and resistance is imperative. Most early-phase and ongoing clinical trials have been performed with unselected patients; however, more recent trials have focused on predictive DDR markers. For example, ARID1A, ATM, ATRX BRCA1/2, CDK12, CH1, CHK2, CCNE1, MYC, MRE11, MSH2, PARP1, PI3CA, POLD1, PPP2P2A, PTEN, RAD51B, XRCC2, and MMR status are a focus of ongoing clinical trials assessing predictive markers for DDR and immunotherapy combinations (NCT03842228, NCT02546661). These studies will help decipher clinical utility of current DDR and ICI combinations, and perhaps identify novel indications of lesser explored DDR targets for precise, patient-, tissue-, and cancer-specific therapeutic targets.

DISCUSSION AND FUTURE CONSIDERATIONS

Studies of the molecular underpinnings of DDR signaling and the interconnectivity with various cellular processes that alter oncogenesis and anticancer immunity have revealed a complex landscape of DDR pathways, uncovering new ways to personalize cancer therapy for each individual patient based on specific tumor cell genetic and immunologic signatures. Targeting DDR pathways is an effective method of treating certain cancers, for instance with the use of PARPi in HR-deficient (i.e., BRCA1/2 mutated) cancers. Increasing responsiveness and direction of response to current PARP and other DDR inhibitors is now a major focus. Pharmacologic induction of HRD phenotypes in otherwise HR-proficient tumors is also an area of recent exploration. For example, molecularly targeted agents such as mTOR or PI3K inhibitors may be able to create BRCAness or HRDness, and this area requires further exploration and clinical development. To build on the success of DDR-targeted monotherapies and overcome the clinical conundrum of eventual drug resistance, it is important to recognize opportunities to incorporate biomarker-directed treatment decision making and the use of combination strategies.

There is preclinical and mechanistic rationale for combining DDR-targeting agents with immunotherapy, with early-phase clinical trials demonstrating very promising antitumor effects. For example, the combination of olaparib and durvalumab in BRCA1/2-mutated ovarian cancer, niraparib and pembrolizumab in platinum-resistant ovarian cancer, and PD-(L)1 blockade for cancers with MMR deficiency may represent significant advances in cancer treatment paradigms. The combination of PARPi with ICIs is also being explored in HNSCC, soft tissue sarcoma, renal cancer, gastric cancer, and lymphoma, among others. However, many questions remain regarding optimal use in the first-line and maintenance settings, potential overlapping toxicities, the relationship between DDR gene alterations and known biomarkers of ICIs, and lack of bonified biomarkers to guide targeted agent selection and immunotherapy combinations.

More understanding of DDR activity in mitigating genomic instability and associated effects on innate and adaptive antitumor immunity is required to maximize clinical benefit of targeted therapies. Given the diversity of immunologic actions of DDR signaling, it will also be important to carefully select and develop DDR-immunotherapy combinations to avoid deleterious DDR signaling inhibition and attenuation of antitumor immunity. Recent preclinical and biomarker-directed clinical studies have made substantial advances in these areas; however, as our understanding of the relationship between tumor-intrinsic gene alterations and antitumor immunity develops, additional basic and translational investigations will be required to identify mechanisms of resistance and advance novel clinical strategies for DDR and immunotherapy approaches.

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