Review

Cancer Research

Development of PARP and Immune-Checkpoint Inhibitor Combinations

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Abstract

PARP inhibitors drive increased DNA damage, particularly in tumors with existing defects in DNA repair. This damage not only promotes immune priming through a range of molecular mechanisms, but also leads to adaptive upregulation of programmed death ligand 1 (PD-L1) expression. In this context, PARP inhibition and programmed cell death 1 (PD-1)/PD-L1–targeting antibodies represent a rationale combination. In this review, we detail the basic and translational science underpinning this promising new combination, summarize available clinical data, and discuss the key questions that remain to be addressed during future development. *Cancer Res; 78(24); 6717–25. ©2018 AACR.*

Introduction

PARP inhibitors and antibodies that inhibit immune checkpoints, such as cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell-death 1 (PD-1), are two classes of drugs that have transformed the treatment of multiple cancers in recent years. Here, we detail the biology of DNA damage repair (DDR) and antitumor immunity that underpin these important anticancer therapies and review the intrinsic links between DNA damage, inflammation, and the immune response, which together support the rational combination of PARP inhibition and immune-checkpoint blockade (ICB). We also summarize the ongoing clinical efforts, potential challenges, and open questions that remain with respect to further developing this combination.

DNA Damage and PARP Inhibition

Both cells and DNA are exposed to continuous damage, which, if severe, can lead to cell death or, if accumulated over time, to the development of cancer. As such, the detection and repair of DNA damage is a critical process, managed by numerous semiredundant pathways (Fig. 1A; ref. 1). DNA single-strand break (SSB) damage is managed by three general pathways: (1) mismatch-mediated repair (MMR) mainly repairs errors that escape proofreading during replication; (2) base excision repair removes shorter stretches of damage that do not affect tertiary DNA structures; and (3) nucleotide excision repair removes longer stretches of damage, often resulting from UV light, which do affect tertiary structures. Potentially more serious, double-strand breaks (DSB) are repaired via two pathways: (1) homologous recombination (HR) is utilized when the sister copy of the damaged DNA is present as a template; (2) nonhomologous end joining (NHEJ) is utilized where no sister copy is available, and is more error-prone.

PARP1/2 are DNA-damage sensors, which bind to DNA lesions (2) and catalyze the generation of poly(ADP-ribose) chains. These negatively charged chains facilitate chromatin remodeling, the recruitment of protein complexes critical to DNA repair, and have also been shown to affect replication fork progression speed (3). In the absence of PARP, SSBs in DNA persist, eventually resulting in DSBs, and replication progression is accelerated, limiting the ability of cells to stall replication and repair DNA. In normal cells, accumulated DSBs are repaired by HR or NHEJ. However, in cells with mutations in breast cancer 1 (*BRCA1*) or *BRCA2*, HR is defective, and loss of PARP function results in the accumulation of DSBs and eventual cell death (4, 5). The discovery of this synthetic lethality between BRCA and PARP prompted the exploration of PARP inhibition as treatment for cancers with *BRCA1/2* defects, initially in ovarian and breast cancers, where defects in *BRCA1/2* occur in up to 20% of patients (6, 7). The FDA has now approved several PARP inhibitors for the treatment of recurrent platinum-sensitive ovarian cancer; olaparib, niraparib, and rucaparib as maintenance therapy following chemotherapy in unselected patients and olaparib and rucaparib for the treatment of patients with *BRCA1/2* mutations in later lines of therapy (8–10). More recently, olaparib received approval for the treatment of patients with *BRCA1/2*-mutant breast cancer, following progression on previous treatments (11), and talazoparib was granted priority review based on data in the same setting (12).

Although the greatest efficacy of PARP inhibitors has been observed in tumors with *BRCA1/2* mutations, patients without these mutations can also potentially benefit. In particular, patients harboring tumors with high levels of genomic scarring, such as LOH suggestive of a defect in DDR (9, 10), or whose tumors have mutations in other, non-BRCA1/2, DDR genes (13). Defects in DDR genes are present across a broad range of tumor types, including prostate, bladder (14), pancreatic (15), and non–small cell lung (16) cancers, and clinical trials of PARP inhibitors are ongoing in many of these settings.

Despite these successes, significant potential to improve on the activity of PARP inhibitors remains. Active preclinical and clinical research is ongoing with respect to broadening responding patient

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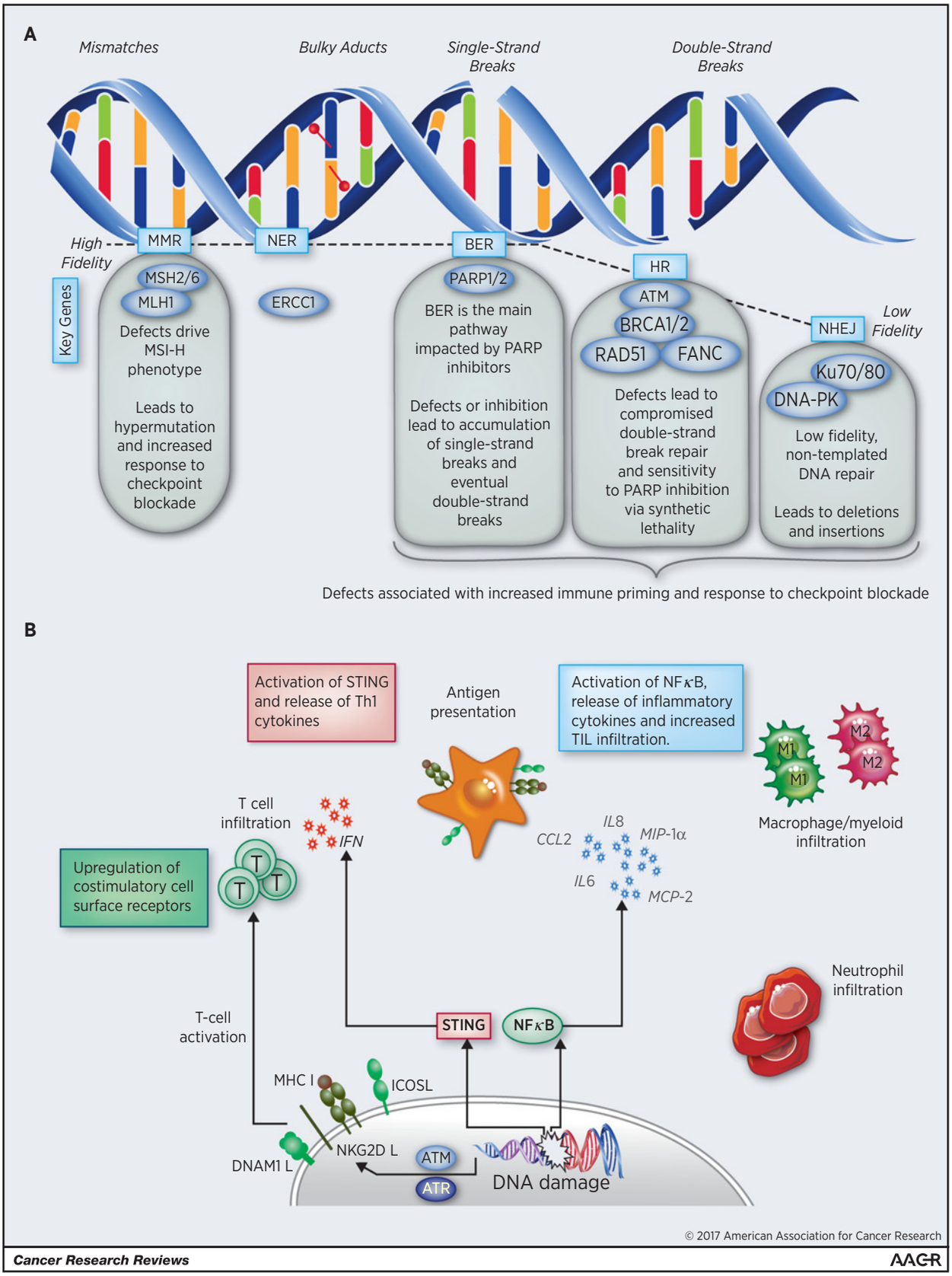

populations, overcoming emerging resistance, and improving the depth and duration of response and overall survival (OS). The development of different combination strategies encompassing PARP inhibitors is one potential way to address these opportunities and has been broadly reviewed previously (17). For the remainder of this review, we provide a deeper focus specifically on the rational combination with ICB.

ICB and the Renaissance of Cancer Immunotherapy

Cancer immunotherapy has had a long and somewhat chequered history (18), but has witnessed significant successes in the last decade, driven mainly by ICB antibodies that promote T-cell activation. T cells are critical to adaptive immunity and contribute to improved outcomes in a range of cancers (19). Activation of T cells requires two signals: binding of the T-cell receptor (TCR) to cognate antigen, presented by MHC, and a costimulatory signal delivered by binding of CD28 on T cells to either CD80 or CD86 (20). These signals are complimented by a series of costimulatory and coinhibitory signals that spatially and temporally control T-cell function, preventing autoimmunity and inflammatory damage (21). T-cell activation can be seen as a balancing act between these stimulatory and inhibitory signals, and ICB represents an effective means of shifting that balance toward activation by diminishing inhibition.

After approximately 10 years in development, the anti–CTLA-4 inhibitor ipilimumab was the first ICB therapy to receive regulatory approval for the treatment of melanoma (22). Around the same time, early clinical trial data generated significant enthusiasm for targeting an alternative receptor, PD-1 (23). PD-1 is expressed on T cells following activation and delivers inhibitory signals through binding of two ligands, programmed death ligand 1 (PD-L1) or 2 (PD-L2). PD-1 is hypothesized to function later in T-cell activation than CTLA-4 (24), once effector T cells reach sites of inflammation.

In keeping with such a role, PD-L1 is found on a broad range of tissues, particularly under inflammatory conditions. PD-L1 is also expressed on the surface of tumors, prompting the hypothesis that the PD-1/PD-L1 pathway may be of critical relevance to cancer. This hypothesis has proved to be correct, as a number of antibodies targeting PD-1/PD-L1 have shown broad clinical activity, leading to regulatory approval for the treatment of multiple cancers (25), including melanoma (26, 27), squamous cell cancer of the head and neck (28, 29), Hodgkin lymphoma (30, 31), urothelial (32–36), Merckel cell (37), renal cell (38), non–small cell lung (39–43), gastric (44), and hepatocellular cancers (45); and for any MMR-deficient/microsatellite unstable tumor (46, 47).

As with PARP inhibitors, PD-1/L1 inhibition is only effective in a subset of patients, and a number of biomarkers have been explored that may identify patients likely to benefit (48). One such strategy of particular relevance to PARP inhibitor combinations is the exploitation of DDR defects. First highlighted in a study of the PD-1 inhibitor pembrolizumab in 28 patients with colorectal cancer, in which MMR-deficient patients demonstrated a response rate of 40%, as opposed to 0% in MMR-proficient tumors (49), this finding was further confirmed in 78 MMR-deficient patients, across 12 tumor types, who demonstrated a response rate of 53%, with 21% complete responses (46). The improved outcome in these patients is believed to be a result of increased mutational load, which is around 10 times higher in tumors with MMR deficiency (49) and those with POLE mutations (50), and is a known predictor for response to ICB (51–53), leading to greater immunogenicity and immune priming, as evidenced by increased immune infiltration and/or PD-L1 expression in breast (54), colorectal (55, 56), endometrial (57), and gastric (58) cancers.

Interestingly, a more recent study, in 60 patients with advanced urothelial carcinomas, has indicated that defects in DDR pathways beyond MMR may also enrich for antitumor responses to anti–PD-1/L1 (59). In this study, patients with a deleterious alteration in at least one of 34 DDR genes showed a response rate of 80% versus only 18.8% in patients lacking these alterations. Significant differences between the two populations were also seen in progression-free survival and OS. Although tumors with defects in these non-MMR DDR genes, such as *BRCA1/2* and other HR genes, also have increased mutational burden (50, 60–62), the magnitude is far smaller than that seen in MMR deficiency, and seems unlikely to fully explain increased response to ICB in these patients. Rather, these patients may have more fundamental differences in tumor immunogenicity, driven by intrinsic links between DNA damage and immunity (Fig. 1B).

Fundamental Links between DNA Damage, Inflammation, Cancer Progression, and Immunity

To detect pathogens, the immune system utilizes pattern recognition receptors (PRR) that recognize molecular motifs, termed pathogen-associated molecular patterns, conserved across multiple foreign organisms (63). PRRs also recognize similar motifs in endogenous cellular components, referred to as damage-associated molecular patterns (DAMP), generated following stress or damage. One such DAMP is cytosolic DNA, which is recognized by the DNA sensor cyclic GMP-AMP synthase (cGAS). Binding of DNA to cGAS leads to recruitment and activation of stimulator of interferon genes (STING), which promotes expression of IFN and other inflammatory cytokines via TANK-binding kinase 1 and interferon regulatory factor 3 (64). Recent studies have demonstrated that chromosomal instability (65) and deficiency in DDR genes, such as *ATM* (66) or *RAD51* (67), leads to accumulation of cytosolic DNA, triggering activation of STING and promoting type I immunity. In keeping with this biology, breast tumors positive for a gene signature of DDR deficiency, related predominantly to

Figure 1.

A, The main DDR pathways are indicated from left to right, as follows: MMR; nucleotide excision repair (NER); base excision repair (BER); HR; NHEJ. The form of DNA damage most relevant to each pathway is indicated along the top of the DNA strand. Relative fidelity of the repair systems is indicated by their position relative to each other on the vertical axis. Key genes in each pathway are indicated, together with highlighted roles in the response and activity of both PARP inhibition and checkpoint blockade. **B,** DNA damage promotes cell-extrinsic immunogenicity through activation of the STING and NF-κB transcription factors, which promote release of proinflammatory signals and increased infiltration of immune cells. Tumor cell–intrinsic immunogenicity is increased through the upregulation of MHC and costimulatory surface receptors, which increase the visibility of tumor cells to T cells.

HR-based repair, have increased STING activation and immune infiltrate compared with negative tumors (68). In addition to activation of STING, DNA damage has also been shown to lead to activation of the proinflammatory transcription factor NF-κB via PARP1 (69), and ATM-mediated SUMOylation (70) and phosphorylation of NF-κB essential modulator (NEMO).

The activation of STING and NF-κB following DNA damage would be expected to lead to increased inflammation and infiltration of tumors by immune cells, a phenomenon observed in patients with defects in multiple DDR pathways across multiple types of cancers. In breast cancer, low levels of BRCA1, ATM, and X-ray repair cross complementing 1 (XRCC1) expression associate with significantly higher levels of CD8 T-cell infiltration (71), as do mutation of *BRCA1* (72). In pancreatic cancer, signatures of DSB repair, as well as MMR deficiency, are associated with increased expression of genes related to T-cell infiltration and type I immunity (73). Similarly, in head and neck squamous cell cancer, methylation of HR genes, indicating reduced expression, correlates to increased expression of a type I immunity gene signature (74). Finally, defects in *BRCA1/2* are correlated to increased levels of PD-L1 expression (61, 75) and increased T-cell infiltration in ovarian cancers (61). This increased immune priming likely accounts for the improved response to ICB seen in tumors with DDR defects in pathways other than MMR, who do not present with such significant increased mutational burden.

In addition to altering the extrinsic immunogenicity of tumors at the level of the microenvironment, DNA damage can also alter the intrinsic immunogenicity of tumor cells through modulation of surface phenotype. For example, studies of aphidicolin and cytarabine have shown the ability of DNA-damaging agents to drive upregulation of natural-killer group 2, member D ligands, inducible T-cell costimulator (ICOS) ligand and MHC class I, in an ATM- or ATR-dependent manner (76, 77). These studies, though not directly related to PARP inhibition, suggest that increased DNA damage can make cells more visible to, and sensitive to killing by, T cells and natural killer (NK) cells, through modulation of surface phenotype. Although not clearly documented, it is also possible that the epigenetic changes that occur as a result of sustained DNA damage (78) could also affect the expression of key immunomodulatory proteins at the tumor cell surface.

Given this potential for DNA damage to promote inflammation and immune priming, patients deficient in key DDR pathways could be expected to demonstrate better prognosis. The data in this regard are mixed, with a number of large metaanlayses demonstrating improved prognosis for patients with ovarian cancer harboring mutations in *BRCA1/2* (79, 80), possibly due to the relationship between *BRCA1/2* mutations and platinum sensitivity. However, the data in patients with breast cancer are more mixed, with some studies indicating poorer prognosis in *BRCA1/2*-mutant patients (81, 82).

It is therefore clear that, despite the ability of DNA damage to promote immune priming, DDR-deficient tumors still ultimately escape immune control and grow unchecked. One explanation for this is that in the presence of DDR defects, DNA damage fails to resolve, but persists at a level that is nonlethal to the tumor. This low-level DNA damage continues to drive inflammatory signaling, stimulating continued infiltration by innate immune cells, like macrophages and neutrophils, which promote further DNA damage, via free radical release, and drive a switch in the immune milieu of the microenvironment from a Th1-skewed immunity, favoring cytotoxic T-cell function, to chronic inflammation and immunosuppression, both promoters of cancer progression and immune escape (83, 84). The result is a self-sustaining cycle of DNA damage and chronic inflammation, which is challenging to break through use of any single therapeutic approach, but which could potentially be addressed through the combination of PARP inhibitors and ICB.

Combining PARP Inhibition and Checkpoint Blockade

In the context of defective DDR, PARP inhibition can trigger catastrophic DNA damage and tumor cell death. This shift from chronic, low level, DNA damage, to more significant DNA damage has the potential to "reset" the inflammatory microenvironment of tumors, reinstating a productive Th1 immune response. Preclinical studies support this potential role for PARP inhibitors. The PARP inhibitor talazoparib has been shown to drive cytosolic DNA accumulation and STING activation in tumor cells *in vitro* (85) as well as STING activation *in vivo*, in mouse models of cancer, where it also leads to increased infiltration by immune cells and enhanced functionality of CD8 T cells and NK cells (85, 86). Similar immune priming, measured as a Th1 immunity gene signature, has been shown in several clinical studies to promote the response to ICB (87–89). At the same time, PARP inhibition has been shown to lead to upregulation of PD-L1 *in vivo* (90), likely as a result of the interferon expression described (91), but also *in vitro* and in xenografts. The latter finding suggests a parallel cell-intrinsic mechanism of PD-L1 regulation downstream of PARP, independent of external signaling. This adaptive and intrinsic upregulation of PD-L1 may function to inhibit immune responses downstream of PARP inhibitor–mediated priming, and could potentially be overcome through the combination of PARP inhibitor with an anti–PD-1/L1 antibody.

Initial preclinical studies, conducted in the *BRCA1*-deficient BR5 mouse ovarian cancer model (92), indicated that a combination of the PARP inhibitor veliparib with anti–CTLA-4 increases T-cell infiltration and IFNγ production, and improves survival. However, in the same study, combination with anti–PD-1/L1 led to less notable increases in T-cell activity and no improvement in survival. The increased activity for anti–CTLA-4 in this study is potentially explained by the generally greater activity observed for anti–CTLA-4 compared with anti–PD-1/L1 in preclinical mouse models. However, the lack of activity for the combination with anti–PD-1/L1 contrasts with more recent studies conducted in the *BRCA* wild-type EMT6 breast cancer, ID8 ovarian, and CT26 colorectal models (85, 90) and in the BRCA-deficient BrKras ovarian cancer model (93), in which the combination of anti–PD-L1 with the PARP inhibitors olaparib, talazoparib, and rucaparib, respectively, led to significantly improved antitumor activity. One explanation for these contrasting results is the use of different models, with differences in immune context. For example, the CT26 model, which demonstrated good activity for the combination, has been characterized as having high mutational burden and robust T-cell infiltration (94), factors that might lend themselves to predicting antitumor responses to immunotherapy. In contrast, the BR5 model, which demonstrated modest activity, is a genetically engineered mouse model (GEMM) developed by the targeted modification of a limited

Table 1. Ongoing trials combining PARP inhibitors and checkpoint inhibitors

Combination	Trial	Description	References
Olaparib + Durvalumab	DORA[a] NCT03167619	Olaparib vs. olaparib + durvalumab in previously treated TNBC	N/A
	MEDIOLA NCT02734004	Basket study in gBRCA-mutant ovarian, or HER2$^-$ breast cancer, relapsed platinum-sensitive SCLC and gastric cancer	(99)
	BISCAY NCT02546661	Umbrella study in previously treated bladder cancer selected for defects in HR	N/A
	BAYOU NCT03459846	Study in cisplatin-ineligible bladder cancer	
	NCT02484404[a]	Basket study in previously treated ovarian cancer, gBRCA-mutant TNBC, NSCLC, SCLC, prostate cancer, microsatellite stable colorectal cancer	(109)
	HUDSON NCT03334617	Umbrella study in patients with NSCLC who have progressed on anti–PD-1/PD-L1	N/A
Olaparib + Pembrolizumab	KEYNOTE-365 NCT02861573	Umbrella study in previously treated mCRPC	N/A
Niraparib + Pembrolizumab	TOPACIO NCT02657889	Basket study in HER2$^-$ TNBC and ovarian cancer	(100, 101)
Rucaparib + Nivolumab	CheckMate 9KD NCT03338790	Umbrella study in mCRPC	N/A
	ATHENA NCT03522246	Phase III study in front line ovarian cancer	
	NCT03572478[a]	Phase I/IIa study in prostate/endometrial cancers	
Avelumab + Talazoparib	Javelin PARP Medley NCT03330405	Basket study in NSCLC, ovarian cancer, HER2$^-$ breast cancer, bladder cancer, and mCRPC	N/A
	Javelin BRCA/ATM NCT03565991	Tissue agnostic study in BRCA/ATM-mutant solid tumors	N/A
	NCT03637491	Triplet combination with binimetinib in Ras-mutant solid tumors	N/A
	Javelin Ovarian PARP 100 NCT03642132	Phase III study in front line ovarian cancer	
BGB-A317 + BGB-290	NCT02660034	Basket study in ovarian cancer, TNBC, mCRPC, bladder cancer, SCLC, HER2$^-$ gastric cancer, pancreatic cancer, and other solid tumors	(102)
Niraparib + PD-1 inhibitor	NCT03308942	Single-arm study in NSCLC	N/A
Niraparib + TSR-042	NCT03307785	Phase I/II in solid tumors	N/A
	FIRST NCT03602859	Phase III study in front-line ovarian cancer	
Veliparib + Atezolizumab	NCT02849496	HER2$^-$, BRCA-mutant TNBC	N/A
Rucaparib + Atezolizumab	NCT03101280	HER2$^-$, BRCA-mutant ovarian cancer and TNBC	N/A
Niraparib + Atezolizumab	ANITA NCT03598270[a]	Phase III study of maintenance treatment in recurrent ovarian cancer	

Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; TNBC, triple-negative breast cancer.
[a]Investigator-sponsored studies.

number of genes (95). Characterization of other GEMMs has indicated a low mutational burden, which may be associated with reduced responses to immunotherapy (96). Another potential explanation is the use of PARP inhibitors that differ with respect to catalytic inhibition and PARP trapping potencies (97), with veliparib being significantly less potent than olaparib, talazoparib, or rucaparib. It is possible that the use of more potent PARP inhibitors in the context of the BR5 model would yield a different result. In keeping with this theory, talazoparib, which has high catalytic and PARP trapping potency, demonstrated greater immune-modulatory and antitumor activity in the BR5 model (86) than was observed with veliparib (92).

Taken together, the available preclinical and translational data strongly support combining PARP inhibition and ICB, and based on these data, a number of clinical trials are currently ongoing (Table 1). Up to now, data from three different PARP inhibitor/anti–PD-1/L1 combinations are available: olaparib/durvalumab (98, 99), niraparib/pembrolizumab (100, 101), and BGB-A317/BGB-290 (102). Both of the first combinations were well tolerated, with toxicities in line with those observed for the relevant agents in monotherapy settings. In contrast, the latter combination demonstrated an increased rate of hepatic toxicity, suggesting that tolerability of PARP inhibitor/anti–PD-1/L1 combinations may vary depending on the agents being utilized and/or the exact setting. All three combinations showed evidence of antitumor activity in a range of settings. In castration-resistant prostate cancer (98), the olaparib/durvalumab combination led to PSA responses ($\geq$50% reduction) in 47% of 17 patients. Patient benefit was greater in those with DDR defects (PFS 16.1 months) versus those with no defects, or unknown status (PFS 4.8 months). Accepting the limitations of cross-trial comparisons, these results compare favorably with monotherapy data in similar settings, where olaparib (13) demonstrated a 22% PSA response rate, with a PFS of 9.8 months in patients with DDR defects and 2.1 months in those without, whereas anti–PD-1 agents showed an 11% PSA response rate (103). In platinum-resistant ovarian cancer (101), the niraparib/pembrolizumab combination demonstrated an overall response rate (ORR) of 25%; this response rate is in line with that observed for PARP inhibitor monotherapy in *BRCA1/2*-mutant patients in this setting (104), but is

encouraging given activity for the combination was independent of DDR defect status. In relapsed platinum-sensitive, *BRCA1/2*-mutant ovarian cancer (99), the olaparib/durvalumab combination demonstrated an ORR of 63%, which is also in line with PARP inhibitor monotherapy activity in this setting (104). Finally, the niraparib/pembrolizumab combination has also shown preliminary activity in advanced triple-negative breast cancer (100), with an ORR of 28% (60% in *BRCA1/2*-mutant patients; again in line with PARP inhibitor monotherapy; ref. 105). These early breast and ovarian data are supportive of further exploration of the combination, as it is possible that the combination may bring benefit to a broader population, without DDR defects, as compared with monotherapy PARP inhibition, or in the form of longer-term benefit in all patients; the latter being likely given that the benefit of ICB is seen predominantly as improved survival (106).

Future Perspectives and Conclusions

Overall, clinical studies conducted to date suggest combinations of PARP inhibition and anti–PD-1/L1 agents are well tolerated and demonstrate antitumor activity in a range of tumor types. However, given the early nature of these data, several key questions remain unanswered. Most critically: what is the magnitude and nature of benefit from combination treatment versus monotherapy? Does benefit vary across different tumor types, lines of therapy, or biomarker-defined populations? Is there an optimal dose or schedule for treatment?

With respect to the nature of combination versus monotherapy benefit, the clinical studies described to date, and outlined above, have, by their nature, relied upon early endpoints, such as ORR. In patients with limited responsiveness to PARP inhibition, such as those lacking DDR defects, response rate may be an informative endpoint. However, in settings where response to PARP inhibition is already high, such as in *BRCA1/2*-mutant ovarian cancer, it may be more appropriate to assess combination benefit in terms of improved duration of response or improved survival, necessitating extended monitoring in such studies.

When considering tumor type and line of therapy, it is of note that data published to date have been in tumor types that have shown historic activity for PARP inhibition, but limited activity for anti–PD-1/L1. In tumor types where anti–PD-1/L1 is an established standard of care, for example, non-small cell lung cancer (NSCLC), response rate may be a more relevant endpoint, particularly outside of PD-L1–positive patient groups. A critical question to address though will be whether the combination has activity only in anti–PD-1/L1-naïve patients or also in those who have progressed on anti–PD-1/L1monotherapy—a group that represents a critical unmet medical need.

Elucidating the role of and interplay between different biomarkers with respect to activity will be critical to the success and future development for this combination, and necessitates the integration of precision medicine during early clinical trials. In this regard, the definition of DDR deficiency will likely be a critical factor in optimal patient selection. Obtaining contemporaneous tumor tissue and matched blood samples is key to fully characterizing not only the presence of DDR defects, but also their nature. For example, how many and which genes are mutated? Are the mutations heterozygous or homozygous? Are they germline or somatic, and, if they are somatic, are they early, relatively clonal, or late, subclonal, events? Such in-depth analysis is important in all settings, but is likely to be particularly relevant in settings such as NSCLC, where, in contrast to ovarian cancer, most mutations are likely to be somatic in nature. It will also be important to understand the distinct effects that different forms of DDR defects may have on tumor immunogenicity, both at the level of neoantigen compliment and of immune signaling within the microenvironment. To this end, it will crucial to integrate genomic profiling with sequencing of the T-cell receptor repertoire, gene expression profiling and IHC/fluorescent assessments of PD-L1 expression, CD8 T-cell infiltration, and broad immune infiltrate, in order to define the overlap between DDR and immune-related biomarker groups and to build a deeper understanding of how DNA damage interfaces with antitumor immunity.

The question of optimal dose and schedule is a challenging one to address. Given the limitations of preclinical modeling for this combination, it will likely be necessary to empirically determine an optimal schedule and dose clinically. Here, correlative studies including sequential tumor biopsies and serial blood collection may be informative, alongside standard assessments of tolerability and activity. A comparison of changes in the tumor microenvironment or TCR repertoire between pre- and posttreatment samples may identify differences between alternative doses and schedules. Given the relatively reduced tolerability of sustained PARP inhibition as compared with anti–PD-1/L1, it may be desirable, in patients undergoing sustained treatment, to deliver PARP inhibition on a more pulsatile schedule. Longitudinal tracking of ctDNA during treatment could be one potential way to inform the duration of such PARP inhibitor pulses, both by using ctDNA as a surrogate for tumor burden, but potentially by tracking the dynamics of resistance mutations (107), using these as a trigger for cessation and reinstatement of PARP inhibition.

Greater clarity with respect to these key questions and others, such as the role of PARP inhibitor potency, will be important as clinical trials' read out, and as basic and translational science, continues to bring new insights with respect to the mechanism and activity of both PARP inhibition and ICB individually, and in combination. Finally, although we have focused here on PARP inhibitor and anti–PD-1/L1 combinations, other targeted agents against components of the DDR are being evaluated for combination with ICB, including ATR inhibitors (108), which were shown to combine safely with the anti–PD-L1 durvalumab, resulting in early signals of activity. There are also other promising immunotherapeutic agents in development, which should be considered for combination with DDR inhibitors.

Disclosure of Potential Conflicts of Interest

R.A. Stewart is a full time employee of Pfizer Inc. T.A. Yap is a Medical Director of the Institute for Applied Cancer Science at University of Texas MD Anderson Cancer Center and reports receiving commercial research support from AstraZeneca, Bayer, Pfizer, Tesaro, Jounce, Eli Lilly, Seattle Genetics, Kyowa, Constellation, and Vertex Pharmaceuticals; received honoraria from the speakers' bureau of AstraZeneca, Merck, and Pfizer; and is a consultant/advisory board member for Aduro, Almac, Ignyta, Jansen, Merck, Pfizer, Roche, Seattle Genetics, Vertex Pharmaceuticals, AstraZeneca, Atrin, Bayer, Bristol-Meyers Squibb, Calithera, Clovis, Cybrexa, and Serono. No potential conflicts of interest were disclosed by the other author.

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