Editorial Commentary

PARP inhibition and immunotherapy: a promising duo in fighting cancer

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Yap and colleagues' (1) recent work reports the results of a large, phase 1b and 2 basket, nonrandomized trial exploring the combination of avelumab [anti-programmed death-ligand 1 (PD-L1)] and talazoparib [oral poly (adenosine diphosphate-ribose) polymerase inhibitor (PARPi)] in solid tumors. Their work builds on an ever-growing preclinical literature to examine patient-level, clinical viability of this combinatory approach in a range of solid tumors and molecular subtypes.

PARPis, such as talazoparib, target the DNA damage repair (DDR) pathway for double-stranded breaks. The DDR pathway is integral for genomic stability and includes canonical genes such as *BRCA1*, *BRCA2*, *ATM*, and *PALB2*. As a result, loss of DDR activity remains an important factor in genomic instability and secondary tumorigenesis (2). DDR for double-stranded DNA breaks involves homologous recombination (HR). PARPi targets HR repair (HRR) via the inhibition of poly (adenosine diphosphate-ribose) polymerase (PARP), leading to synthetic lethality and cellular death (3). Targeted susceptibility in cancers with DDR-HR deficiency (HRD) (e.g., breast, prostate, ovarian, and pancreatic cancers) has led to successful monotherapy (and combination therapy with other targeted therapies) with PARPi (4). However, management of resistance to PARPi remains an ongoing challenge with limited consensus on an approach (5,6).

Immunotherapy is an ever-expanding class of therapeutics that leverage and amplify antitumor host-response as a treatment modality across several cancers. After promising initial studies in melanoma, the selective targeting of immune checkpoint proteins, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and PD-L1, represents a key subclass of immunotherapies. Referred to as immune checkpoint inhibitors (ICIs), CTLA4 inhibitors (e.g., ipilimumab) and PD-L1 inhibitors (e.g., nivolumab and pembrolizumab) have been shown to have favorable responses in an ever-growing variety of solid tumors, including melanoma, lung cancers, gastroenterological cancers, and platinum-resistant ovarian cancers (OCs) (7).

Combining PARPi with anti-programmed cell death-1 (PD-1)/PD-L1 directed immunotherapy has emerged as a potential strategy to overcome the limitations of PARPi monotherapy. Preclinical studies have observed PARPi to increase neoantigen load and tumor mutational burden (TMB), both well-established biomarkers in responsiveness to ICI-like agents directed against PD-1/PD-L1 (8). Similarly, PARPis have been shown to upregulate PD-L1 expression, thereby suppressing T-cell activation and increasing immune-mediated tumor cytotoxicity (9). Preclinical studies have also observed combinatory PARP

inhibition and immunotherapy to have a synergistic effect in suppressing cancer cell growth and viability (1,10-13). Taken together, combinatory PARPi and PD-1/PD-L1 directed immunotherapy is a promising treatment strategy that capitalizes on complimentary antineoplastic pathways to potentially prolong treatment response and/or delay resistance.

Before Yap and colleagues' recent 2023 work, large-scale human trials examining the combination of PARPi and PD-1/PD-L1 directed immunotherapy were lacking. Yap and colleagues' study analyzed a total of 223 patients between 2017 and 2019 via the JAVELIN PARP medley trial (1). The goal of their study was to identify patient populations that would benefit most from the anti-PD-L1/PARP inhibitor study drug combination—avelumab and talazoparib. The authors assigned patients to 10 cohorts of advanced solid tumors, further stratified by molecular subtypes, including those with characteristics of known PARPi sensitivity [namely *BRCA1* and *BRCA2* mutations and DDR defects (DDR$^+$), the latter of which was defined using a 34-gene panel] or immunotherapy sensitivity (measured primarily via TMB status and PD-L1 expression). In particular, solid tumors examined included: non-small cell lung cancer (NSCLC) and DDR$^+$ NSCLC, triple-negative breast cancer (TNBC) and DDR$^+$ breast cancer (BC) [hormone-receptor positive, human epidermal growth factor receptor 2 (ERBB2) negative]; recurrent, platinum-sensitive OC and recurrent, platinum-sensitive, *BRCA1/BRCA2* altered OC; metastatic castration-resistant prostate cancer (mCRPC) and DDR$^+$ mCRPC; urothelial cancer; and *BRCA1/BRCA2* or *ATM*-altered solid tumors (1).

At its core, Yap and colleagues sought to identify synergistic activity as defined by improved response rate or duration of response (DOR) between PARPi and PD-1/PD-L1 directed immunotherapy, particularly in any of the tumor/molecular subtype combinations. Responses were most frequently observed, as expected, in BRCA-altered tumors: Response rates observed in the trial were favorable in certain subgroups when compared with prior studies using PARPi monotherapy in the same groups. Caveating cross-trial comparison, the present study observed a favorable comparison of combinatory treatment in BRCA-altered, platinum-sensitive OC compared with that of olaparib monotherapy in a similar population, evidenced by an increased progression-free survival (PFS) of 18 months when compared with other studies (14) (median PFS 12.7 months) and (15) (median PFS 13.2 months), suggesting better efficacy than olaparib monotherapy in this population. Similarly, in BC cohorts, the median DOR in patients with advanced TNBC (11.1 months) and DDR$^+$ BC (15.7 months) compared favorably with the median DOR in the EMBRACA study (5.4 months) that utilized talazoparib monotherapy (16), suggesting improved DOR with combinatory treatment in this population. Unfortunately, the response rate observed in the trial mirrored earlier reported responses with PARPi monotherapy in prostate cancers (17,18) and ICI monotherapy in NSCLC and urothelial cancers (19,20), suggesting that the addition of ICIs and *BRCA* alterations, respectively, may not provide uniform benefit in all subgroups of cancers. Ultimately, the authors concluded that no synergistic activity in combinatory avelumab and talazoparib treatment was observed in the JAVELIN PARP medley trial while appropriately acknowledging the limitations of cross-trial comparisons.

Yap and colleagues' study highlighted *BRCA1* and *BRCA2*'s central role as biomarkers for response to PARPi. However, just as not all *BRCA1/BRCA2* alterations are pathogenic, not all *BRCA1/BRCA2* alterations confer PARPi sensitivity (6,21). This highlights the importance of next-generation sequencing—PARPi-sensitivity is not *BRCA* exclusive, with several other alternations known to confer PARPi sensitivity. This includes but is not limited to, DDR gene alterations, such as *ATM*, *RAD51B/C*, *CHK2*, and *PALB2*, and composite measures of HRD which combine loss of heterozygosity (LOH), telomeric-allelic imbalance (TAI), and large-scale state transition (LST) scores—collectively all markers of genomic and chromosomal instability (21). However, the lack of a consensus definition for HRD score and associated cut-points combined with mixed success predicting PARPi response to date warrants ongoing investigation (21). Predictive biomarkers for immunotherapy response are more established in the literature: PD-L1 expression, TMB, and combined positive score (CPS; a biomarker related to the proportion of tumor cells expressing PD-L1) (22). Genetic variations in DDR pathways, such as microsatellite instability (MSI), have also been shown to predict response to immunotherapy, and DDR-deficient tumors have been shown to have a higher TMB, thus sensitizing these tumors to both PARP inhibition and immunotherapy (22). This can result in specifying further subsets of non-*BRCA* tumor patient populations, such as NSCLC, that could similarly benefit from PARP inhibition. However, this relationship is not straightforward, as evidenced by Yap *et al.*'s study in which three-fourths of responses in NSCLC tumors were in

patients with high PD-L1 expression, and the only response (one out of five) in patients with NSCLC-DDR$^+$ cancers was in a patient with high PD-L1 positivity (1). This warrants more research into the potential benefits of DDR-targeted therapies in immunotherapy-sensitized tumors.

Yap and colleagues should be commended for their systematic accounting of possible confounds, including detailed molecular subtyping in this large cohort with PD-L1 expression, TMB status, CD8$^+$ count, and DDR$^+$ status. Yet this initially more agnostic approach ultimately gave way to a primary focus on DDR status where small subgroup sizes belie the author's primary aim of examining common responses across a large clinical cohort. Further limitations include the unclear contribution of prior chemotherapy regimens. Representing over 50% of the cohort, exposure to platinum-based treatments is known to confer resistance to DDR$^+$ tumors via cross-resistance mechanisms, such as restoration of HRR in tumor cells (23). Yet despite the limitations, the results of the study hold promise, particularly for BRCA-altered tumors. Favorable responses compared with PARPi monotherapy in certain cancer subgroups suggest the merit of this combination approach. Therefore, even if the optimal responders in a more general sense remain to be identified, consideration is warranted when designing furthermore focused trials.

The interplay between different resistance pathways with combination therapy also remains unclear. Resistance to PARP inhibition develops primarily through four main mechanisms: (I) drug availability (influenced by regulations in drug efflux); (II) mutations affecting PARP or PARP-related proteins (thereby decreasing efficacy of PARPi binding and/or retaining endogenous PARP function); (III) restoration of HR (largely attributed to restoration mutations in *BRCA1* and *BRCA2* function); and (IV) restoration of replication fork stability (5,6). Additionally, resistance to platinum-based chemotherapies has been identified as a strong predictor for PARPi resistance, thus necessitating an accounting of prior chemotherapy regimens, along with additional molecular subtyping before initiating PARP inhibition (23). Resistance to immunotherapy emerges from alterations in tumor antigens, namely through abnormal expression or antigen presentation, arising through *de novo* or acquired mechanisms (22). Ultimately, understanding potential downstream overlap in resistance pathways or synthetic delayed drug resistance (if no such overlap exists) would permit the identification of patients with specific tumor molecular (sub-)types that benefit most from combinatory PARP inhibition and immunotherapy. Here, in particular, next-generation targeted therapies may have a pivotal role in delaying the onset of resistance while complementarily exerting directed effects on key cellular pathways. Agents such as tyrosine kinase inhibitors (TKIs) (e.g., sorafenib, pazopanib) and more selective anti-angiogenesis approaches have already demonstrated promise in several solid tumors, including ovarian, endometrial, and bladder cancers (24). Overall, small molecule therapy is promising but more, larger-scale, studies are warranted to evaluate the pros and cons of this treatment and the prospect of combinatory therapy with other emerging therapies.

Conclusions

While accurately predicting response remains challenging, tumor molecular subtyping and genetically profiling are essential tools in transitioning to a tailored patient-specific treatment paradigm. Yap and colleagues' JAVELIN PARP medley trial highlights this by demonstrating that combinatory avelumab and talazoparib (and broadly, PARPi/immunotherapy broadly) can excel in a certain subgroup of patients defined using tumor molecular subtyping (namely those harboring *BRCA* alterations). Further research into the underlying biological mechanisms and deeper characterization in select patient groups are needed to understand the perceived lack of clinical benefit in non-*BRCA* tumors, and compared with monotherapy alone in BRCA-altered cancers. Yap *et al.*'s large-scale study will be both a template for future combination drug trials and the basis of future prospective, randomized trials in those specific populations to further the underlying goal—optimizing patient selection for management.

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