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Exceptional synergistic response of PARP inhibitor and immune checkpoint inhibitor in esophageal adenocarcinoma with a germline BRCA2 mutation: a case report

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***Abstract*:** Immune checkpoint inhibitors (ICIs) and poly (ADP-ribose) polymerase (PARP) inhibitors have shown efficacy in various tumors. A significant therapeutic challenge with either ICIs or PARP inhibitors as monotherapy is treatment failure from intrinsic primary resistance or the development of secondarily acquired resistance after a period of responsiveness. The combination of PARP inhibitors and ICIs could mitigate this by potentiating treatment response. We describe an 83-year-old male patient who initially presented with abdominal pain, and weight loss along with alternating constipation and diarrhea. Imaging and biopsy revealed metastatic esophageal adenocarcinoma. Genomic testing revealed germline BRCA2 mutation. The patient initially underwent a few cycles of chemoimmunotherapy. However, due to intolerance to chemotherapy, the patient's case was discussed at a multidisciplinary molecular tumor board. He was switched to PARP inhibitor olaparib and ICI nivolumab. This combination led to a durable complete response. A combination of poly-ADP ribose polymerase inhibitor (PARPi) plus ICI may work in synergy through various mechanisms including enhanced neoantigen expression, release of immune-activating cytokines, and increased programmed death-ligand 1 expression. This may culminate in accentuated efficacy outcomes with a manageable safety profile. This exceptional response with ICI and PARPi in our case is consistent with the synergistic value of this combination, and prospective studies are warranted to definitively characterize clinical utility.

Keywords: BRCA, combination therapy, DNA repair, esophageal cancer, homologous recombination, immune checkpoint inhibitor, PARP

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Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of multiple cancers.[1–3] Pembrolizumab and nivolumab have exhibited improved survival when combined with systemic chemotherapy in the first-line treatment for unresectable esophageal cancer.[4–6] More recently, poly (ADP-ribose) polymerase (PARP) inhibitors have also demonstrated significant activity in several cancer types, such as breast, ovarian, pancreatic, and prostate cancer with homologous recombination deficiency (HRD), such as those with BRCA1 or BRCA2 mutations.[7–10] Several ongoing clinical trials are investigating the benefit of PARP inhibitors in this clinical setting.[11,12] Despite these successes, many patients do not show long-term responses to PARP inhibitor monotherapy or in combination with chemotherapy. Most patients who initially responded to single-agent PARP inhibitor or ICI therapy eventually develop resistance and experience clinical progression.[13,14]

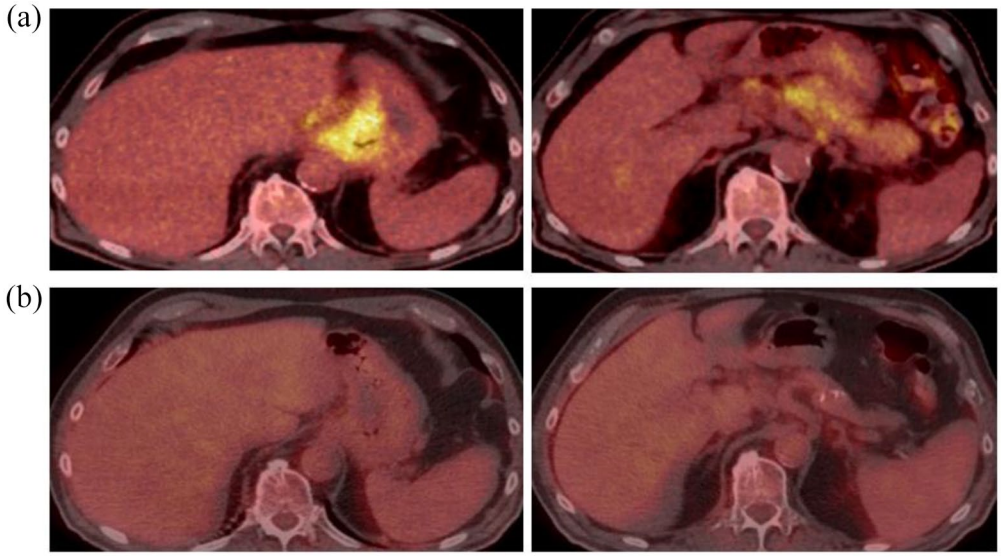

Figure 1. PET scans at diagnosis and 4 months after PARP inhibitor and ICI therapy. (a) Axial fused images from PET/CT prior to treatment show hypermetabolic primary mass at GEJ (left), hypermetabolic metastatic upper abdominal lymphadenopathy, and right hepatic lesion (right). (b) Axial fused images from PET/CT after eight cycles of treatment with nivolumab and olaparib show complete resolution of the primary GEJ mass (left) as well as the metastatic upper abdominal lymphadenopathy and right hepatic lesion (right).
CT, computed tomography; GEJ, gastroesophageal junction; ICI, immune checkpoint inhibitor; PARP, poly (ADP-ribose) polymerase; PET, positron emission tomography.

Growing evidence shows that PARP inhibitors and ICIs could synergistically act against tumor evasion *via* multiple mechanisms. Persistent DNA damage induced by PARP inhibition leads to potentiation of the immune response through increased expression of tumor neoantigens, enhancement of programmed cell death-ligand 1 (PD-L1) expression, activation of immune-activating pathways such as cGAS–STING (cyclic GMP-AMP synthase – stimulator of interferon genes) pathway, and modulation of the tumor immune microenvironment toward more aggressive T helper (T_H)1 state.[15–19] These mechanisms could enhance the immune system and accentuate the rate and durability of response from ICIs, making a combination of ICIs and PARP inhibitors an attractive option for tumors enriched in an immunosuppressive tumor microenvironment, including esophageal cancer.[20] Here, we describe an exceptional case of metastatic esophageal adenocarcinoma who achieved complete response with combination therapy of programmed cell death-1 (PD-1) inhibitor nivolumab and PARP inhibitor olaparib.

Case presentation

An 83-year-old male with a past medical history of type 2 diabetes, hypertension, diverticulitis, and basal cell carcinoma presented with 4 months of ongoing abdominal pain, 10 lb weight loss, intermittent constipation, and diarrhea. His baseline [Eastern Cooperative Oncology Group (ECOG)] performance status was 1. The initial workup was unremarkable, including a complete blood count and comprehensive metabolic profile. Contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis demonstrated an abnormal mass-like soft tissue thickening and edema at the gastroesophageal (GE) junction, abnormal necrotic lymph nodes in the celiac axis, and hypoenhancing hepatic lesions. CT chest demonstrated multiple sub-centimeter pulmonary nodules. Magnetic resonance imaging of the abdomen with and without contrast corroborated these findings. A subsequent whole-body positron emission tomography (PET) scan revealed hypermetabolic activity associated with the GE junction mass, upper abdominal adenopathy, and liver lesions [Figure 1(a)].

Esophagogastroduodenoscopy (EGD) revealed an ulcerated mass extending from the lower third of the esophagus into the GE junction and posterior stomach body. The biopsy of the esophageal mass revealed adenocarcinoma with human epidermal growth factor receptor 2 (HER2)

expression 2+ on immunohistochemistry (IHC) and equivocal by fluorescence *in situ* hybridization (FISH). Next-generation sequencing (NGS) of the tissue (*via* Tempus xT) revealed pathogenic BRCA2 mutations (germline c.3545_3546del p.F1182fs Frameshift – LOF and somatic c.2641G>T p.E881 – Stop gain – LOF), and somatic SMAD4, APC, and PHLPP1 mutations. The tumor was microsatellite stable, tumor mutational burden (TMB) was 4.2 mutations per megabase, tumor proportion score (TPS) was 5%, and combined positive score (CPS) was 5. Cell-free DNA (cfDNA) (*via* Tempus xF) analysis revealed similar findings – BRCA2 (c.3545_3546del p. F1182fs Frameshift – LOF and somatic c.2641G>T p.E881 – Stop gain – LOF) in addition to SMAD4 and APC mutations. Liver biopsy was then pursued, which revealed moderately differentiated adenocarcinoma, positive for CK7 and CDX2 and negative for CK20 and TTF-1, HER2 IHC expression 0. Hence, the patient was diagnosed with Siewert type II esophageal adenocarcinoma with biopsy-proven liver metastases.

The patient was initiated on palliative leucovorin, 5-fluorouracil, oxaliplatin (FOLFOX), and nivolumab. Despite dose reductions, he was poorly tolerant of chemotherapy and developed grade 3 fatigue, grade 3 anorexia, grade 2 diarrhea, and grade 1 nausea per CTCAE v5.0 criteria. He started having frequent falls and became wheelchair-bound. After six cycles of chemoimmunotherapy, a CT scan of the chest, abdomen, and pelvis revealed stable disease per RECIST 1.1 criteria.

Given the declining performance status and poor tolerance of chemotherapy, the case was presented at the multidisciplinary precision oncology conference at Saint Luke's Cancer Institute, and the decision was made to initiate the combination of a PARP inhibitor and ICI. The patient was subsequently initiated on nivolumab 240 mg intravenously every 2 weeks in addition to olaparib orally 300 mg twice daily.

After two cycles, he developed grade 2 transaminitis (aspartate aminotransferase, 107; alanine transaminase, 73; and alkaline phosphatase, 101), and nivolumab was held for 2 weeks before being resumed after the resolution of transaminitis without any intervention. Two months after the initiation of treatment with the combination of PARP inhibitor and ICI, minimal residual disease (MRD) testing using a commercially available tumor-informed circulating tumor DNA (ctDNA) assay (Signatera MRD assay) was performed and it showed undetectable ctDNA levels, indicating a complete response. After eight cycles (4 months) of treatment with olaparib and nivolumab, a skull base to mid-thigh PET scan was performed which revealed a complete resolution of all previously noted hypermetabolic lesions with no evidence of new fluorodeoxyglucose avid lesions [Figure 1(b)]. After 5 months of treatment with this combination, nivolumab dosing was changed to 480 mg administered every 4 weeks, while olaparib was continued at the same dosage. An EGD with biopsy was performed after 10 months of treatment with the ICI and PARP inhibitor combination, with esophageal biopsies confirming a complete pathological response. Follow-up imaging and serial ctDNA MRD testing 18 months after diagnosis continued to indicate complete response. The patient experienced no additional side effects and returned to his baseline performance status. Thus, the patient has had a sustained complete response for around one and a half years and is still ongoing. The patient's timeline from diagnosis until the last follow-up is delineated briefly in Figure 2.

Discussion

DNA damage repair is a complex process involving several pathways and genes.[21] PARP inhibition interferes with the base excision repair (BER) pathway, which induces the formation of single-strand breaks (SSBs) in DNA.[22] Persistently unrepaired SSBs and the inability of autoPARylation (hindering the regular detachment of PARP enzymes from the DNA replication fork) further contribute to the formation of double-stranded breaks (DSBs) in DNA. In cancer cells with HRD, especially those with loss of function of BRCA1 or BRCA2, there is an inadequate repair of DSBs. This leads to the accumulation of DSBs, which culminates in cellular stress and ultimately results in cancer cell death, a phenomenon called 'synthetic lethality'.[23]

ICIs have proven to be an effective therapeutic approach in various cancers by blocking the interaction between immune checkpoint proteins and their receptors and allowing enhanced immune activation and, ultimately, a more powerful antitumor response.[24] Unfortunately, most patients have progressive disease or relapse with ICI monotherapy.[13] Multiple mechanisms have been

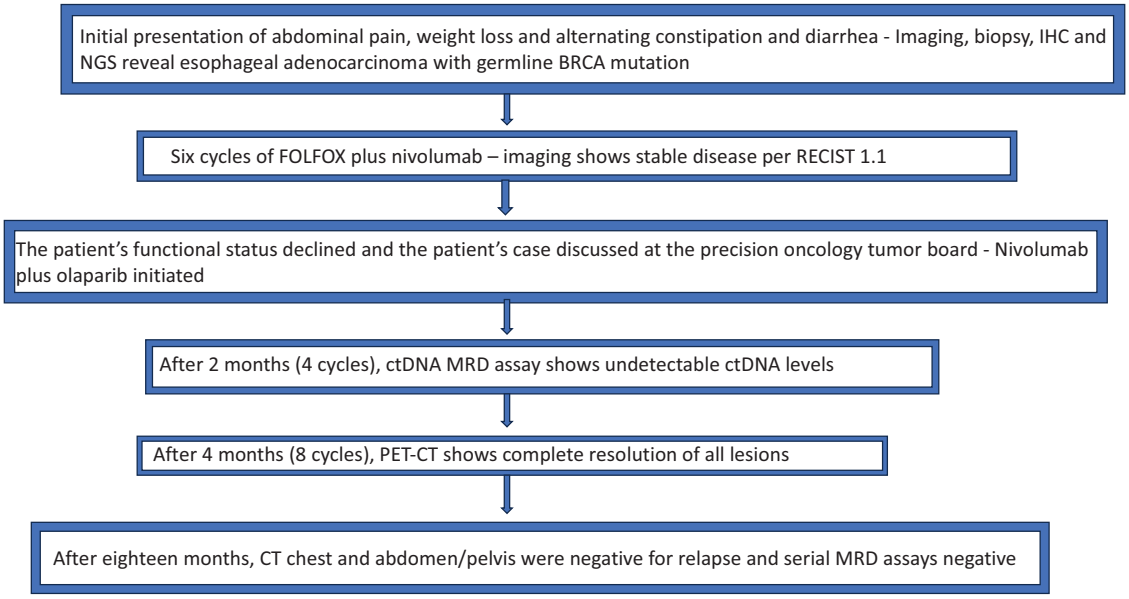

Figure 2. Timeline of events.
The figure shows the timeline of events from diagnosis to last follow-up.
ctDNA, circulating tumor DNA; FOLFOX, 5-fluorouracil plus oxaliplatin; MRD, minimal residual disease; NGS, next-generation sequencing.

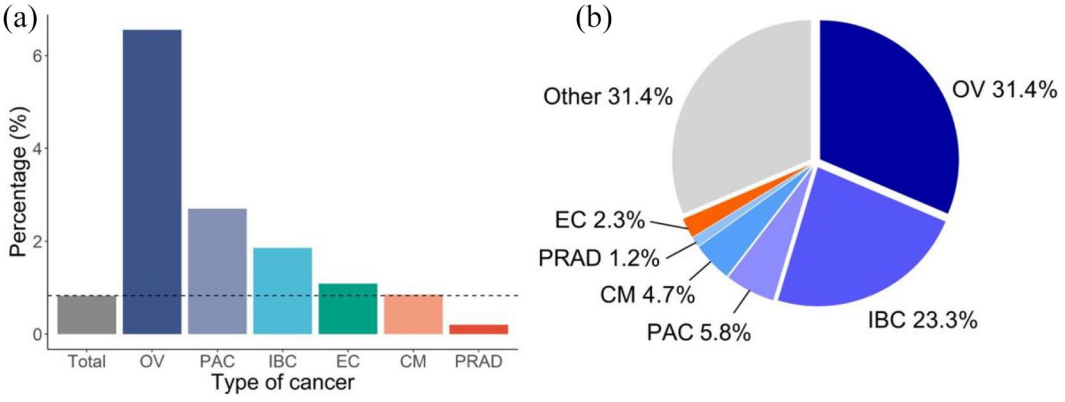

Figure 3. Prevalence of germline *BRCA2* mutation (a) compared to the total number of cases in a particular type of cancer (b) compared to the total number of cases with germline *BRCA2* mutations.
CM, cutaneous melanoma; EC, esophageal carcinoma; IBC, invasive breast carcinoma; OV, ovarian carcinoma; PAC, pancreatic adenocarcinoma; PRAD, prostate adenocarcinoma.

proposed for the loss of response to ICI. First, insufficient neoantigens may lead to a weaker immune response as less repertoire can be primed to attack the tumor.[25] Second, excessive secretion of immunoregulatory cytokines and metabolic inhibitors, such as interleukin-19 (IL-19), transforming growth factor-β (TGF-β), and kynurenine, also inhibits immune cell activity.[25] Third, tumor microenvironments that favor tumor immunosuppression, including the inadequate infiltration of T effector cells, excessive regulatory T cells, and over-expression of inhibitory signaling pathways, could inhibit cytotoxic T cells from mounting immune responses against tumor cells.[25]

PARPi could overcome this loss of immune effect from ICIs *via* several pathways. Tumors with HRD have been associated with higher mutational load and thus enhanced neoantigen accumulation, culminating in more antigenic peptide presentation, increased T-cell priming, and a

stronger immune response against cancer.[11] PARP inhibitors create DSBs and higher expression of neoantigens, which may potentiate immune response.[26] Furthermore, PARP inhibitors have been shown to activate the cyclic GMP-AMP synthase (cGAS)-STING pathway.[15,19] This pathway facilitates interferon type I response, which enhances antigen presentation by increasing the immune proteasomal activity in antigen-presenting cells.[27]

Moreover, it instigates the release of chemokines, such as CXCL10 and CCL5, that enhance T-cell chemotaxis and increase peri-tumoral T-cell infiltration.[27] PARP inhibitors have also been shown to upregulate PD-L1 expression by inactivating glycogen synthase kinase 3β, a glycogen metabolism modulator, in a dose-dependent manner *via* the inhibition of proteasomal degradation.[17,28] PARP inhibitors may also induce elevated PD-L1 expression by altering DNA damage response *via* the ATM-ATR-Chk1 pathway.[29] Though modest, PARP inhibitors may also switch the immune effect from chronic low-level inflammation to a more aggressive T_H1 immune response.[16] In summary, with multiple potential mechanisms of immune enhancement, PARP inhibitors may accentuate response with ICIs and increase the durability of response.

Multiple clinical studies have established the benefit of ICIs in the first or later lines of treatment for esophageal cancer. Multiple phase III randomized-controlled trials (RCTs) utilizing ICIs showed statistically significant improvements in survival outcomes for the first-line treatment. CheckMate 648 compares nivolumab plus chemotherapy (CMT), nivolumab plus ipilimumab, and CMT alone in advanced esophageal squamous cell carcinoma (ESCC). ICI-containing regimens were shown to have superior overall survival (OS) and progression-free survival (PFS) regardless of PD-L1 expression.[30] CheckMate 649 compared nivolumab plus CMT *versus* CMT alone in advanced gastric cancer (GC), gastroesophageal junction (GEJ) cancer, and esophageal adenocarcinoma. The combination of nivolumab and CMT had significantly better OS and PFS than CMT alone, especially in those with PD-L1 CPS $\geqslant$ 5.[4] KEYNOTE-590 is a study comparing pembrolizumab plus CMT *versus* placebo plus CMT in advanced ESCC and esophageal adenocarcinoma, which demonstrated significantly improved OS and PFS with pembrolizumab compared to chemotherapy in patients who had a PD-L1 CPS $\geqslant$ 10, regardless of cell type.[5] KEYNOTE-181 is a phase III RCT comparing pembrolizumab *versus* CMT in advanced ESCC and esophageal adenocarcinoma. OS benefit was observed only in patients who had ESCC with PD-L1 CPS $\geqslant$ 10.[31] Finally, ATTRACTION-3 is a phase III RCT comparing nivolumab *versus* CMT for individuals with advanced ESCC, which showed superior OS but not PFS for individuals treated with nivolumab.[32]

By contrast, a limited number of studies have been conducted to determine the clinical utility of PARP inhibitors in GE cancer. A phase III RCT (GOLD trial) compared olaparib plus paclitaxel *versus* placebo plus paclitaxel in GC or GEJ as later-line therapy.[33] Unfortunately, the combination of olaparib and paclitaxel did not meet its primary endpoint of improving OS, including in patients with ATM mutation.[33] Despite the negative result, there is still value in determining the population that might benefit from PARP inhibitors in this setting, as there is emerging evidence that esophageal cancer could harbor genomic alterations involving the homologous recombination pathway.

A germline mutational analysis of 10,389 cases from The Cancer Genome Atlas (TCGA) PanCanAtlas cohort revealed that 1.09% of all cases with esophageal cancer carried germline BRCA2 mutation, slightly higher than the prevalence in all cancers combined (0.83%). In addition, of all cases from TCGA with a germline BRCA2 mutation, esophageal cancer constituted 2.33% of the cases [Figure 3(a) and (b)].[34] This population of patients with germline BRCA mutations might benefit from PARP inhibitor therapy, and several ongoing trials using PARP inhibitors with or without CMT or ICIs for GE cancer are being tested to determine the efficacy of these treatment regimens (Table 1).

Based upon the possible synergistic effect of PARP inhibitors and ICIs, there has been some progress in translating this combination treatment for other types of cancer. A phase I/II MEDIOLA basket trial studied the effectiveness of olaparib and durvalumab combination in advanced small-cell lung cancer, breast cancer, ovarian cancer, and GC. For patients with relapsed GC, the overall response rate (ORR) and the 3-month disease control rate (DCR) were 10% and 26%, respectively. The median duration of response was 11.1 months.[35] Similar efficacy was also found in

Table 1. Ongoing studies with treatment using PARP inhibitors with or without ICI in gastroesophageal cancer.

PARPi	ClinicalTrials.gov identifier	Phase	Population	Estimated number of patients	Treatment regimen	Primary outcome	Status
Olaparib	NCT04592211	I/II	Second-line recurrent/ advanced GC/GEJ with HRR mutation and MSS	71	Olaparib + pembrolizumab + paclitaxel	PFS, dose-limiting toxicity	Not yet recruiting
	NCT03008278	I/II	Second-line recurrent/ metastatic GC/GEJ	49	Olaparib + ramucirumab	ORR, dose-limiting toxicity	Active, not recruiting
Niraparib	NCT03840967	II	Second-line advanced/ metastatic GC/GEJ/EAC with HRD or LOH-high	43	Niraparib	ORR	Active, not recruiting
Rucaparib	NCT03995017	I/II	Second-line advanced/ metastatic GC/GEJ/EAC	34	Rucaparib + ramucirumab ± nivolumab	ORR	Active, not recruiting
Talazoparib	NCT04511039	I	Second-line advanced/ metastatic GC/GEJ/EAC and CRC	21	Talazoparib + trifluridine/ tipiracil	Adverse events	Recruiting

CRC, colorectal cancer; EAC, esophageal adenocarcinoma; GC, gastric cancer; GEJ, gastroesophageal cancer; HRD, homologous recombination deficiency; HRR, homologous recombination repair; ICI, immune checkpoint inhibitor; LOH, loss of heterozygosity; MSS, microsatellite stable; ORR, objective response rate; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival.

patients with small-cell lung cancer.[36] Of note, patients with platinum-sensitive relapsed ovarian cancer and germline BRCA1/2-mutated breast cancer had a remarkably better 3-month DCR of 81% and 80%, respectively.[37,38] Core biopsy and plasma samples from patients with ovarian cancer before and during treatment revealed that PARP inhibitor–ICI treatment combination accentuated interferon-gamma/CXCL9/CXCL10 expression and T lymphocyte tumor infiltration, forming an immunoenhancing microenvironment.[39] The phase I/II TOPACIO trial was a larger study evaluating niraparib in combination with pembrolizumab for patients with ovarian or triple-negative breast cancer with mutated *versus* wild-type BRCA and revealed an ORR of 25% and DCR of 68%. However, for patients with BRCA mutations, both ORR and DCR were greater at 45% and 73%, respectively.[40,41] ORR was also higher at 33% in PD-L1-positive compared to 15% in PD-L1-negative tumors, highlighting the potential utility of PD-L1 as a predictive biomarker for therapeutic response to this combination therapy.[40] Anti-CTLA-4 therapy plus PARPi therapy is another promising approach that warrants further exploration in addition to anti-PD1/PD-L1 therapy.[42]

ICI and PARPi have non-overlapping and manageable toxicity profiles. In the MEDIOLA trial, grade 3 or 4 toxicity occurred in less than 10% of patients.[37] The TOPACIO trial also showed that the combination treatment was well tolerated, and there were no new safety signals.[40] Our patient had grade 1 elevated liver function tests, which resolved quickly after a brief discontinuation and could then tolerate reinitiation of the PARPi plus ICI combination.

Of note, there are still several unanswered questions about this treatment combination. The synergy of this combination acting through various mechanisms needs further characterization for routine clinical utility. Our case demonstrated an exceptional response in a type of cancer where current evidence for the use of this combination is limited. The best biomarkers to predict treatment responses are still not clearly elucidated. These are mainly due to the complex interplay of intratumoral and intertumoral heterogeneity and effects from the tumor microenvironment. Biomarkers more specifically predictive of response to the combination of ICI and PARPi may enable us to identify the subset of patients who are likely to derive stronger clinical benefit from the combination approach. Moreover, the mode of tumor sampling (tissue sequencing *versus* ctDNA), the type of mutation (germline *versus* somatic), and the PD-L1 expression level could also play roles in determining the treatment responses.[43]

Conclusion

We illustrate the case of a patient with metastatic esophageal adenocarcinoma with a germline BRCA2 mutation who only achieved a stable treatment response with the current standard-of-care chemotherapy and ICI combination. Complete resolution of the tumor was then achieved within 4 months of initiation of maintenance PARP inhibitor–ICI therapy. The combination also had a favorable safety profile, consistent with previous studies. This demonstrates that the combination of PARPi and ICI may have synergistic activity through multiple distinct mechanisms in cancers possessing HR deficiencies like BRCA mutations and lead to superior patient outcomes with a tolerable safety profile. Further studies are needed to determine the population that would most benefit from PARP inhibitor–ICI combination treatment strategy to guide therapy in difficult-to-treat cancers and overcome treatment resistance from single-agent PARP inhibitors or ICIs.

Methods

IHC and cytology

Histological evaluation was performed by a pathologist at Saint Luke's Hospital. IHC of HER2 expression level and HER2 FISH were tested with FDA-cleared rabbit clone 4B5 antibody using Ventana automated platform utilizing an ultra-View Universal Detection Kit at Saint Luke's Hospital. CPS and TPS were determined using the DAKO PD-L1 22C3 qualitative immunohistochemical assay.

Molecular studies

A tumor sample was obtained from the GE mass *via* cold forceps biopsies during EGD, then preserved in formalin solution. Tempus xT containing a 648-gene panel DNA sequencing and whole transcriptome RNA sequencing was performed. MSI and TMB were measured using the same panel as well. In addition, the Tempus xF cfDNA panel was used for tumor-normal match and detection of germline alterations, with blood being used as the normal tissue and GEJ mass biopsy as the tumor tissue. Serial ctDNA monitoring was performed during the treatment course using the signatera MRD assay.

The reporting of this study conforms to the CARE guidelines (CARE Checklist – PARPi plus ICI).

Declarations

Ethics approval and consent to participate

The patient provided written informed consent for all investigations and treatment, including imaging, histological testing, tumor DNA, and RNA sequencing. The local institutional review board (IRB – at Saint Luke's Hospital of Kansas City, MO, USA) exempted this study from IRB review.

Consent for publication

The patient provided written informed consent for case report publication.

Author contributions

Himil Mahadevia: Conceptualization; Data curation; Formal analysis; Methodology; Resources; Writing – original draft; Writing – review & editing.

Ben Ponvilawan: Formal analysis; Methodology; Writing – review & editing.

Ammar Al-Obaidi: Methodology; Writing – review & editing.

Jennifer Buckley: Methodology; Writing – review & editing.

Janakiraman Subramanian: Methodology; Writing – review & editing.

Dhruv Bansal: Conceptualization; Methodology; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The authors declare that data in this study, including the de-identified targeted panel

sequencing report, are available through the electronic medical records of Saint Luke's Hospital of Kansas City. Further inquiries may be directed to the corresponding author.

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Supplemental material

Supplemental material for this article is available online.

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