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BRIEF COMMUNICATION

Exceptional responses to PARP inhibitors in patients with metastatic breast cancer in oncologic crisis

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Abstract

Purpose Cancers deficient in homologous recombination DNA repair, such as those with *BRCA1* or *BRCA2* (*BRCA1/2*) mutations rely on a pathway mediated by the enzyme poly(adenosine diphosphate-ribose) polymerase (PARP). PARP inhibitors (PARPi's) have demonstrated efficacy in treating patients with germline (*g*)*BRCA1/2*, somatic (*s*)*BRCA1/2*, and *gPALB2* mutations in clinical trials. However, patients with a poor performance status (PS) and those with severe organ impairment are often excluded from clinical trials and cancer-directed treatment.

Methods We report the cases of two patients with metastatic breast cancer who had poor PS, significant visceral disease, and *gPALB2* and *sBRCA* mutations, who derived significant clinical benefit from treatment with PARP inhibition.

Results Patient A had germline testing demonstrating a heterozygous *PALB2* pathogenic mutation (c.3323delA) and a *BRCA2* variant of unknown significance (c.9353T>C), and tumor sequencing revealed *PALB2* (c.228_229del and c.3323del) and *ESR1* (c.1610A>C) mutations. Patient B was negative for pathologic *BRCA* mutations upon germline testing, but tumor sequencing demonstrated somatic *BRCA2* copy number loss and a *PIK3CA* mutation (c.1633G>A). Treatment with PARPi's in these two patients with an initial PS of 3–4 and significant visceral disease resulted in prolonged clinical benefit.

Conclusion Patients with a poor PS, such as those described here, may still have meaningful clinical responses to cancer treatments targeting oncogenic drivers. More studies evaluating PARPi's beyond *gBRCA1/2* mutations and in sub-optimal PS would help identify patients who may benefit from these therapies.

Keywords Breast cancer · BRCA · PALB2 · PARP · Performance status

Abbreviations

HR	Homologous recombination
PARP	Poly(adenosine diphosphate-ribose) polymerase
PARPi	PARP inhibitor/inhibition
PFS	Progression-free survival
HER2/neu	Human epidermal growth factor receptor 2
ECOG	Eastern Cooperative Oncology Group
PS	Performance status
ER	Estrogen receptor
PR	Progesterone receptor
XRT	Radiation therapy
NGS	Tumor next-generation sequencing
TMB	Tumor mutational burden
LFT	Liver function test
ALP	Alkaline phosphatase
AST	Aspartate transferase
ALT	Alanine transaminase
INR	International normalized ratio
RECIST	Response Evaluation Criteria in Solid Tumors
ASCO	American Society of Clinical Oncology
CDK4/6	Cyclin-dependent kinase 4/6
RB	Retinoblastoma
TNBC	Triple negative breast cancer

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Introduction

DNA repair aberrations are a hallmark of cancer, as they play a central role in giving rise to mutations that contribute to cancer development [1, 2]. Cancers deficient in homologous recombination (HR) DNA repair, such as those with *BRCA1* or *BRCA2* (*BRCA1/2*) mutations, rely on a repair pathway for single-strand breaks mediated by the enzyme poly(adenosine diphosphate-ribose) polymerase (PARP) [1–3]. PARP inhibitors (PARPi's) cause irreparable DNA damage in HR-deficient cancer cells, leading to death via synthetic lethality [1–4].

The OlympiAD and EMBRACA trials were phase III randomized studies in which patients with metastatic human epidermal growth factor receptor 2 (*HER2/neu*) negative breast cancer with germline (*g*)*BRCA1/2* mutations demonstrated significantly longer median progression-free survival (PFS) and better quality of life in groups treated with PARPi's compared to those treated with standard chemotherapy [3, 5, 6]. The phase III OlympiA trial, which compared the PARPi olaparib to placebo in patients with early stage *HER2/neu*-negative breast cancer with *BRCA1/2* mutations, showed significant improvements in invasive disease-free survival (85.9% for olaparib vs. 77.1% for placebo) [7]. The TBCRC048 trial was a nonrandomized, multicenter, phase II trial that assessed the response to olaparib in: (1) those with germline mutations in non-*BRCA1/2* HR-related genes such as *PALB2*, *ATM*, or *CHEK2* (cohort 1), or (2) those with somatic (s) mutations in these genes or *BRCA1/2* (cohort 2) [8]. Median PFS was 13.3 months for patients with *gPALB2* mutations and 6.3 months for those with *sBRCA1/2* mutations, suggesting benefit from PARPi's for patients with these mutations [8].

These trials demonstrated the efficacy of PARP inhibition for patients with *g/sBRCA1/2* and *gPALB2* mutations. However, the OlympiA, OlympiAD, and TBCRC048 trials only enrolled patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, as did the EMBRACA trial, with the exception of a few patients with an ECOG PS of 2 [3, 5, 7, 8]. Patients with poor PS or with severe organ impairment are often excluded from clinical trials and few studies have explored the effects of chemotherapy or other novel drugs versus supportive care in these patients [9, 10]. We present two cases which demonstrate significant clinical benefit derived from PARPi's in patients with germline *PALB2* and somatic *BRCA* alterations with poor PS and in oncologic crisis.

Case report

Patient A was a 53-year-old woman with a history of coronary artery disease, hyperlipidemia, hypertension, morbid obesity, neuropathy, osteoarthritis, osteoporosis, and pulmonary embolism who noted a breast mass, for which imaging confirmed breast and axillary lesions. Biopsy revealed her tumor to be estrogen receptor (ER) positive at 75%, progesterone receptor (PR) 0, and HER2/neu 1+ (DISH *HER2/neu* to CEN17 ratio: 1; average *HER2* copy number: 1.9), with a Ki-67 of 30%. Her family history was notable for breast cancer in her mother and aunt. A 17-gene germline genetic testing panel performed in 2015 by Ambry Genetics revealed a heterozygous *PALB2* pathogenic mutation (c.3323delA) and a *BRCA2* variant of unknown significance (c.9353T>C). The patient underwent six cycles of neoadjuvant docetaxel and cyclophosphamide. She subsequently underwent a left partial mastectomy with axillary lymph node dissection demonstrating a pathologic complete response. She received radiation therapy (XRT) to the left breast and left supraclavicular nodal region, then started on tamoxifen but took it for less than 3 months before self-discontinuing therapy (Table 1).

The patient developed left buttock pain and back pain approximately 3 years later and was found to have a compression fracture at L4. A biopsy of L4 revealed breast cancer that was ER > 90%, PR 5–10%, and HER-2/neu 1+. Tumor next-generation sequencing (NGS) by TEMPUS was notable for *PALB2* (c.228_229del and c.3323del) and *ESR1* (c.1610A>C) mutations, and a tumor mutational burden (TMB) of 15.8 m/MB (Table 2). The c.3323del *PALB2* mutation detected by tumor NGS was consistent with that found in the patient's initial germline testing, with the second somatic mutation indicating possible bi-allelic inactivation. The patient received radiation to L2–L5 and was subsequently restarted on tamoxifen. Two months later, she underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy to allow for transition to endocrine therapy, consisting of letrozole and palbociclib with intravenous zoledronic acid. While she initially experienced disease control, restaging scans 8 months later revealed progression of the patient's cancer to her liver. She was started on nab-paclitaxel in addition to her letrozole; however, she experienced progression in her liver and bones 6 months later, prompting transition to gemcitabine and carboplatin.

Patient A was referred to the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center at that time. Laboratory evaluation showed a total bilirubin of 4.5 mg/dL. However, less than 2 weeks later, she presented to the emergency department for jaundice, nausea, and fatigue. Liver function tests (LFTs) demonstrated markedly elevated total bilirubin (16.7 mg/dL), alkaline phosphatase (ALP, 776 U/L), aspartate transferase (AST, 893 U/L), and alanine transaminase (ALT, 471 U/L), with evidence of hepatic insufficiency [low albumin (3.3 g/dL) and platelets (67 K/cu mm); elevated INR (1.24) and prothrombin time (12.9 s)].

Table 1 Germline and somatic genetic sequencing

Patient	Tumor mutational burden	Sequencing type	Gene	Mutation	VAF (%)	Biological relevance[a]
Patient A	15.8 m/MB 93rd percentile	Germline[b]	*BRCA2*	c.9353T>C p.M3118T		VUS
			PALB2	c.3323delA		Pathogenic
		Tumor NGS	*PALB2*	c.228_229del p.I76fs	62.8	Potentially actionable
			ESR1	c.1610A>C p.Y537S	33.5	Potentially actionable
			PALB2	c.3323del p.Y1108fs	15.7	Potentially actionable
			MAP3K1	c.3236dup p.N1079fs	31.8	Biologically relevant
			LRP1B	c.8787_8811del p.E2929fs	11.9	Biologically relevant
			KMT2C (*MLL3*)	c.3471_3496del p.Q1158fs	11.9	Biologically relevant
			CKS1B	Copy number gain		Biologically relevant
			ELF3	Copy number gain		Biologically relevant
			ERCC4	c.2585A>G p.N862S	87.1	VUS
			BRCA1	c.1561G>A p.A521T	82.2	VUS
			BRCA2	c.9353T>C p.M3118T	61.2	VUS
			ACVR1	c.656A>T p.Y219F	59.0	VUS
			MAP3K7	c.54G>A p.M18I	51.0	VUS
			ZNF471	c.1315G>T p.D439Y	39.2	VUS
			WNK1	c.2268_2270delinsCCT p.PP756PL	37.6	VUS
			CXCR4	c.544G>A p.D182N	33.6	VUS
			SMARCA4	c.3539C>G p.P1180R	33.6	VUS
			MYCN	c.250C>T p.Q84	33.1	VUS
			ATR	c.6286G>C p.D2096H	30.9	VUS
			SRP14	c.275A>C p.D92A	30.3	VUS
			MEF2B	c.925G>A p.A309T	30.1	VUS
			DEFB119	c.83_84delinsGT p.H28R	30.1	VUS
			ALK	c.1432T>A p.F478I	29.8	VUS
			PDGFRB	c.2109C>G p.H703Q	29.0	VUS
			CTNNA1	c.1872_1894del p.I625fs	27.5	VUS
			ATIC	c.1211T>C p.V404A	25.5	VUS
			CBL	c.1566T>C p.A522A	24.4	VUS

Table 1 (continued)

Patient	Tumor mutational burden	Sequencing type	Gene	Mutation	VAF (%)	Biological relevance[a]
			LRP1B	c.8663-6_8663-5del	20.1	VUS
			ACVR1B	c.1569_1583del p.A524_A528del	17.0	VUS
			SYNE1	c.13909G>A p.D4637N	16.6	VUS
			TANC1	c.388A>C p.S130R	10.4	VUS
			ERCC1	c.925C>A p.L309I	9.8	VUS
			KMT2C (*MLL3*)	c.1127C>T p.T376I	5.0	VUS
Patient B	7.4 m/MB 84th percentile	Germline[c]	None			
		Tumor NGS	*PIK3CA*	c.1633G>A p.E545K	10.1	Potentially actionable
			BRCA2	Copy number loss		Potentially actionable
			LRP1B	c.6412C>T p.R2138	27.5	Biologically relevant
			RUNX1	c.508+1G>T	25.5	Biologically relevant
			ARID1B	c.5309C>T p.A1770V	82.6	VUS
			RAD21	c.100G>C p.E34Q	44.9	VUS
			MIB1	c.2716C>T p.R906	35.5	VUS
			ERBB4	c.1806T>A p.S602R	21.8	VUS
			MKI67 (*Ki-67*)	c.2195G>A p.R732Q	20.8	VUS
			CALR	c.194-3C>A	20.7	VUS
			HIST1H1E	c.62A>G p.K21R	20.1	VUS
			LAG3	c.1533_1538dup p.E513_P514insPE	19.9	VUS
			MYH11	c.2005C>T p.R669C	19.0	VUS
			CALR	c.397+5G>T	14.2	VUS
			QKI	c.164A>G p.D55G	14.0	VUS
			TBX3	c.734_739del p.M245_H246del	9.9	VUS
			SYNE1	c.16667G>A p.W5556	8.7	VUS
			ARID1B	c.2510G>T p.S837I	8.5	VUS
			APOB	c.13146G>A p.M4382I	8.3	VUS
			PTPN13	c.4570G>T p.D1524Y	5.5	VUS

NGS next-generation sequencing; *LOF* loss of function; *GOF* gain of function; *VAF* variant allele fraction; *VUS* variant of unknown significance

[a]Tumor NGS was conducted by TEMPUS. Biological relevance is as determined and reported by TEMPUS in 2022 for Patient A and in 2020 for Patient B

[b]Germline sequencing for Patient A was reported by Ambry Genetics in 2015. Seventeen genes were analyzed as part of this panel: *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *MRE11A*, *MUTYH*, *NBN*, *NF1*, *PALB2*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *TP53*

[c]Germline sequencing for Patient B was reported by Color Health in 2018. Thirty-one genes were analyzed as part of this panel: *APC*, *ATM*, *BAP1*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A* (*p14ARF*), *CDKN2A* (*p16INK4a*), *CHEK2*, *EPCAM*, *GREM1*, *MITF*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PMS2*, *POLD1*, *POLE*, *PTEN*, *RAD51C*, *RAD51D*, *SMAD4*, *STK11*, *TP53*

Table 2 Treatment summary

Patient	Receptor status	Treatment history[a]
Patient A	Early stage: ER 75%, PR 0, HER2/neu 1+ Metastatic (bone): ER > 90%, PR 5–10%, HER-2/neu 1+	Early stage – Neoadjuvant docetaxel and cyclophosphamide – Left partial mastectomy with axillary lymph node dissection – Radiation therapy to the left breast and left supraclavicular nodal region Metastatic – Radiation therapy to L2–L5 – Tamoxifen – Total abdominal hysterectomy and bilateral salpingo-oophorectomy – Letrozole and palbociclib with intravenous zoledronic acid – Nab-paclitaxel – Gemcitabine and carboplatin – Olaparib – Trastuzumab-deruxtecan
Patient B	Breast: ER > 90%, PR > 90%, HER2/neu 1+ Metastatic (bone): ER 80%, PR 80%, HER2/neu 0	Metastatic – Tamoxifen and palbociclib with denosumab and zoledronic acid – Radiation therapy to spine – Vertebroplasty – Exemestane, goserelin, and everolimus – Olaparib

ER estrogen receptor; *PR* progesterone receptor; *HER2/neu* human epidermal growth factor receptor 2

[a]Treatments are listed in chronological order by date of initiation

Her ECOG PS was 4 at the time of her emergency department visit. After discussions regarding her prognosis and goals of care, given her *PALB2* mutations, the patient and her treating oncologist decided to discontinue chemotherapy and start olaparib at a dose of 300 mg twice daily, and she was co-enrolled in hospice. Within 2 months, her condition had significantly improved; her LFTs began to normalize (Fig. 1A), she reported increased strength and mobility, and her ECOG PS decreased to 2. Her main treatment-related toxicity was anemia, which required red blood cell transfusions. After a few months, she decided to return to work. She met Response Evaluation Criteria in Solid Tumors (RECIST) for radiographically stable disease in her liver on olaparib for 7 months (Fig. 2). However, restaging scans at month 9 demonstrated new hepatic metastases, indicative of progressive disease (Fig. 2). At this time, she was transitioned from olaparib to trastuzumab deruxtecan given her *HER2*-low status; unfortunately, she acutely decompensated and passed away shortly after her first dose.

Patient B is a 66-year-old man with a history of type 2 diabetes mellitus, hypertension, obesity, hepatitis C with hepatic fibrosis, prescription drug use disorder, and 73.5 pack-year tobacco use disorder, who noted a breast mass, with imaging confirming a breast abnormality. Biopsy of the left breast mass revealed poorly differentiated invasive carcinoma with signet ring cell features, ER > 90%, PR > 90%, HER2/neu 1+, and Ki-67 of 40–50%. Staging scans demonstrated metastases in his lumbar spine, which biopsy confirmed to be ER 80%, PR 80%, and HER2/neu 0 breast cancer. His family history was significant for breast cancer in his mother, colon cancer in his maternal aunt, and colon cancer in his maternal uncle. A 31-gene germline genetic testing panel performed in 2018 by Color Health was negative for pathologic *BRCA* mutations; however, tumor NGS by TEMPUS indicated somatic *BRCA2* copy number loss, a *PIK3CA* mutation (c.1633G>A), and TMB of 7.4 m/MB (84th percentile) (Table 2). The patient was started on tamoxifen, denosumab (later transitioned to zoledronic acid), and received XRT for his spinal metastases, followed by vertebroplasty for pathologic fractures of his L1 and L2 vertebrae. Palbociclib (125 mg) was then added. However, after three cycles of therapy, restaging scans revealed progressive disease in his thoracic and lumbar spine. Tamoxifen and palbociclib were discontinued and he was started on exemestane, goserelin, and everolimus. While he experienced approximately 2 years of disease control with this regimen, his course was complicated by osteonecrosis of the jaw and back pain secondary to his pathologic compression fracture status post-radiation therapy and vertebroplasty. He also developed a brain abscess requiring IV antibiotics, and had bilateral lower extremity edema and pain. Restaging scans approximately 2 years later demonstrated mildly progressed diffuse osseous metastatic lesions, new multiple FDG-avid hepatic lesions, and an increase in size of non-FDG-avid mediastinal lymph nodes, consistent with progressive disease. Unfortunately, his course was further complicated by SARS-CoV2 infection at this time, and he continued to clinically deteriorate, demonstrating forgetfulness, difficulty ambulating, and increased pain. The cumulative burden of these conditions along with progressive cancer caused his performance status to deteriorate.

His ECOG PS was 4; thus, after discussions of prognosis and goals of care, the patient and his oncology team decided to discontinue exemestane, goserelin, and everolimus, and to start olaparib at a reduced dose of 200 mg twice daily, based on his elevated serum creatinine of 1.4 mg/dL (creatinine clearance of 46.8 mL/min). The patient responded well to olaparib, as his functional mobility improved, and

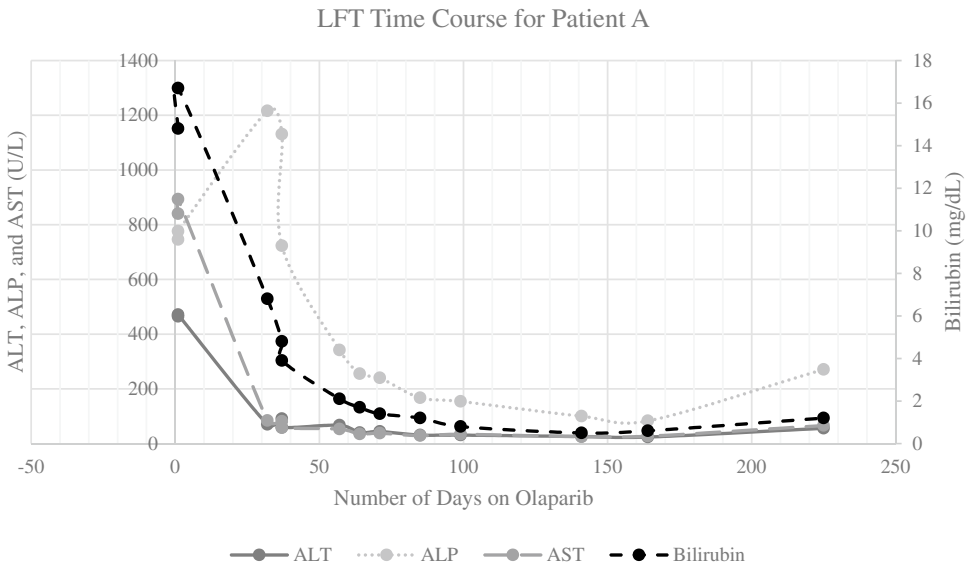

Fig. 1 LFT time course for Patient A

LFT, liver function test; ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate transferase.

his PS improved to 3. Restaging scans after 4 months exhibited markedly decreased radiotracer avidity of hepatic and osseous lesions and decrease in activity at the left breast mass and axilla, compatible with treatment response. After 1 year of stable disease on olaparib, scans revealed diffuse extensive mixed osteolytic and sclerotic lesions in the calvarium, facial bones, cervical spine, and upper thorax, suggesting possible progression, as well as worsening mandibular osteonecrosis. The patient was hospitalized again for altered mental status, lethargy, and hypercalcemia. He ultimately enrolled in hospice and passed away 3 months later.

Discussion

The American Society of Clinical Oncology (ASCO) recommends against cancer-directed treatment for patients with a poor performance status (ECOG PS 3–4), as low PS has been associated with poor survival, reduced response, and worse chemotherapy-related toxicity [9]. Poor PS and inadequate organ function also typically preclude inclusion in clinical trials, further limiting treatment options for these patients [3, 5, 8, 10]. However, targeting oncogenic drivers of disease may possibly result in rapid and profound treatment responses that can potentially reverse oncologic burden and improve patient outcomes. For example, the literature demonstrates that targeting *ALK*, *EGFR*, and *BRAF* gene mutations have resulted in remarkable responses in critical patients [11–14].

The two cases we present demonstrate that PARP inhibition can result in dramatic responses in patients with homologous recombination DNA repair aberrations beyond germline *BRCA*. Patient A had a pathogenic *gPALB2* mutation with an additional somatic mutation likely representing biallelic inactivation, and patient B had *sBRCA2* and *sPIK3CA* mutations. Like *BRCA1/2*, the *PALB2* gene is involved in HR DNA repair, and *PALB2* mutations are associated with an increased risk of breast cancer and reduced survival [15, 16]. Patients with *PALB2* mutations may also benefit from treatment with PARPi's [8, 17–19]. TBCRC048 is currently one of the only prospective trials demonstrating response to olaparib in patients with breast cancer and *sBRCA1/2* mutations and *gPALB2* mutations [8]. Another single institution phase II trial that investigated the PARPi talazoparib in patients with advanced *HER2/neu*-negative breast cancer and HR pathway gene mutations found that all five patients with a *gPALB2* mutation experienced reduction in target lesions and that three patients achieved a RECIST response [18]. A follow-up study to this phase II trial, focused on evaluating the ORR of talazoparib monotherapy specifically in patients with g/s*PALB2* mutation-associated advanced breast cancer, is currently ongoing [20]. A retrospective, real-world analysis of the Flatiron Health-Foundation Medicine Clinico-Genomic Database also demonstrated benefit with olaparib in four patients with *gPALB2* mutations and nine patients with *sBRCA* mutations [21].

TBCRC048 required participants to have an ECOG PS of 0–1 and adequate organ function, while the talazoparib trials required an ECOG PS of 0–2 [8]. Furthermore, the pharmacokinetics of olaparib have only been studied with

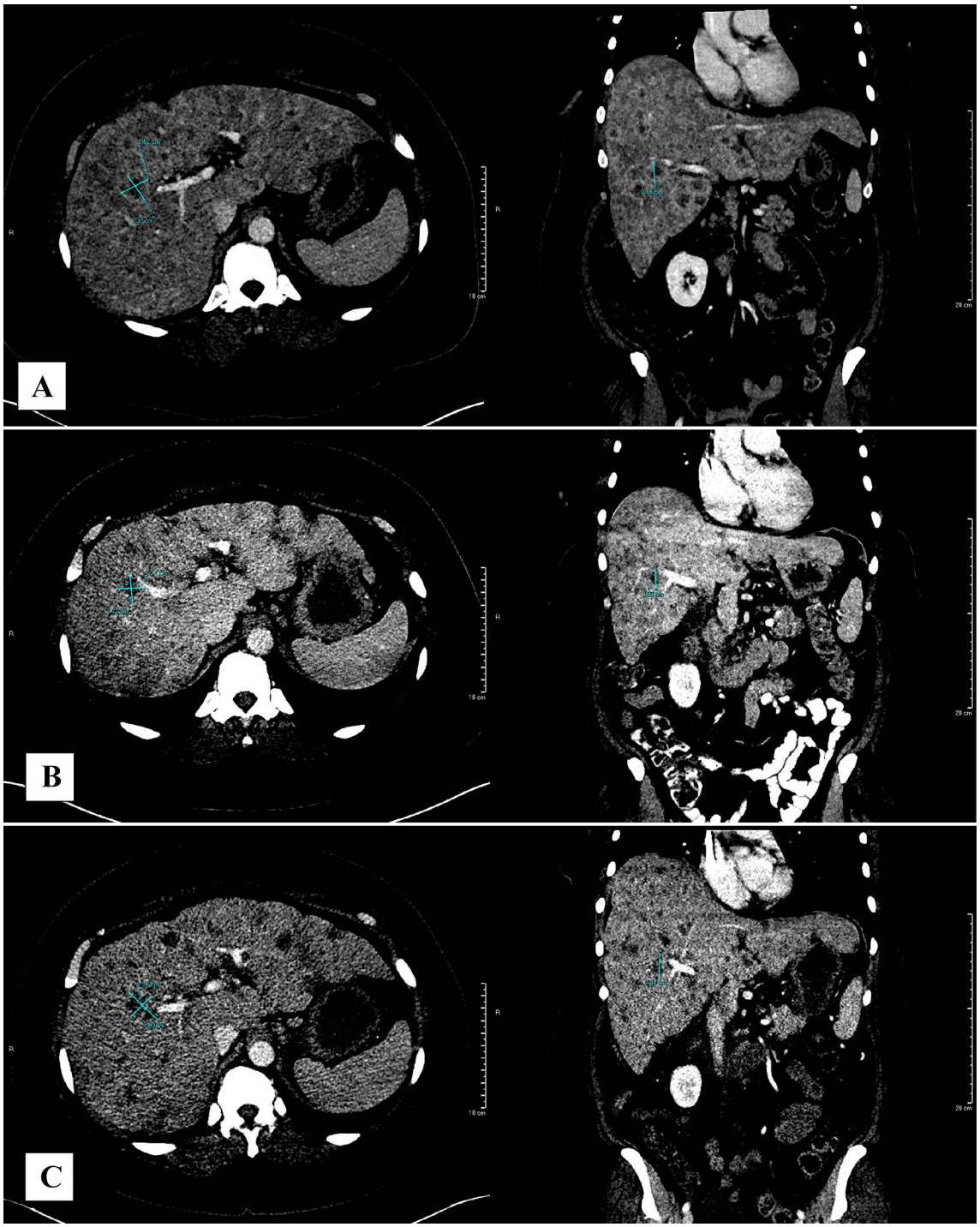

Fig. 2 CT imaging for Patient A. CT abdomen/pelvis demonstrating a segment 5/8 lesion measuring 2.5 × 2.4 × 2.7 cm at baseline (initiation of olaparib) (**A**), 2.2 × 2.1 × 2.3 cm post-treatment at 7 months (**B**), and 3.3 × 2.3 × 2.5 cm post-treatment at 9 months (**C**). RECIST stable disease was observed between **A** and **B**. RECIST progressive disease was observed between **B** and **C**

mild and moderate hepatic impairment [22]. In our report, Patient A was treated with olaparib for 9 months, despite her initial PS of 3–4 and evidence of hepatic failure. Although Patient B had an initial PS of 3–4, multiple comorbidities, and poor prognosis, he responded to olaparib for 1 year. Despite the poor performance status of these two patients at the time of treatment initiation, both tolerated olaparib well with limited side effects and demonstrated improvement in performance status with treatment response. These cases illustrate the therapeutic potential in targeting beyond

gBRCA1/2 mutations using PARPi's, despite clinically critical situations. Future research is also needed to identify other patient populations that may benefit from PARPi, but also in overcoming PARPi resistance, and developing optimal combination strategies.

Conclusion

Patients with a poor ECOG PS that is being driven by their cancer burden still have the potential to have meaningful clinical responses to cancer treatments targeting oncogenic drivers, such as using PARPi's to target *gPALB2* and *g/sBRCA* mutations. Clinical trials have supported the efficacy of PARP inhibition in treating patients with *g/sBRCA1/2* and *gPALB2* mutations and a PS of 0–2. We have described two cases of patients with a PS of 3–4 and significant visceral disease who demonstrated remarkable clinical responses to treatment with PARPi's. While not all patients in such oncologic crisis may benefit from PARPi's, more studies evaluating PARPi's beyond *gBRCA1/2* mutations and in sub-optimal PS would help identify patients who may benefit from these therapies.

Author contributions All authors contributed to the study conception and design. The first draft of the manuscript was written by JMC and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Competing interests Cesar A. Santa-Maria, MD MSCI disclosures: Research funding: Astra Zeneca, Pfizer, Merck, BMS, Genentech, GSK/Tesaro. Advisory board (paid): Seattle Genetics, Genomic Health, Athenex. Advisory board (not paid): BMS, Merck. Joyce M. Cheng, Jenna Canzoniero, Seoho Lee, Sudeep Soni, Neha Mangini has no financial or non-financial disclosures.

Ethical approval This is a case report of two patients. The Johns Hopkins University Institutional Review Board has confirmed that ethical approval is not required for retrospective analyses of up to three clinical cases.

Consent to participate The Johns Hopkins University Institutional Review Board does not classify this case report as human subjects research; therefore, informed consent was not required.

Consent to publish The Johns Hopkins University Institutional Review Board does not classify this case report as human subjects research; therefore, informed consent was not required.

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