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CASE REPORT

Management of PALB2-associated breast cancer: A literature review and case report

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Key Clinical Message

Germline pathogenic variants (PV) of the *PALB2* tumor suppressor gene are associated with an increased risk of breast, pancreatic, and ovarian cancer. In previous research, *PALB2*-associated breast cancer showed aggressive clinicopathological phenotypes, particularly triple-negative subtype, and higher mortality regardless of tumor stage, type of chemotherapy nor hormone receptor status. The identification of this germline alteration may have an impact on clinical management of breast cancer (BC) from the surgical approach to the systemic treatment choice. We herein report the case of a patient with a germline PV of *PALB2*, diagnosed with locally advanced PD-L1 positive triple-negative BC, who progressed after an immune checkpoint inhibitor (ICI)-containing regimen and then experienced a pathologic complete response after platinum-based chemotherapy. This case report hints a major role of the germline *PALB2* alteration compared to the PD-L1 expression as cancer driver and gives us the opportunity to extensively review and discuss the available literature on the optimal management of *PALB2*-associated BC. Overall, our case report and review of the literature provide additional evidence that the germline analysis of *PALB2* gene should be included in routine genetic testing for predictive purposes and to refine treatment algorithms.

KEYWORDS

breast cancer, immunotherapy, PALB2, PARP inhibitor

1 | INTRODUCTION

PALB2 (Partner and Localizer of *BRCA2*) is a tumor suppressor gene that plays a key role in the homologous recombination (HR) pathway as mediator between BRCA1 and the BRCA2/RAD51 complex.[1] As in *BRCA1/2* mutation carriers, the loss of both *PALB2* alleles causes the activation of the nonhomologous end joining (NHEJ), with consequent genomic instability.[2] Indeed, germline likely pathogenic or pathogenic variants (LPV/PV) in *PALB2* are associated with an increased risk of breast and pancreatic cancer,[3] while evidence for association with ovarian cancer is conflicting. It is estimated that 0.6%–3% of patients with BC harbor an LPV/PV in *PALB2*[4] and approximately 1% of patients with triple-negative BC (TNBC) carry such a mutation.[5,6] As already observed in g*BRCA*-associated BC,[7–9] PARP inhibitors showed promising activity in patients carrying *PALB2* LPV/PV in two small phase 2 studies.[10,11] Despite these results g*PALB2* genetic testing is not universally included in routine genetic testing for predictive purposes.[12,13]

We report the case of a patient with a germline PV of *PALB2*, diagnosed with locally advanced PD-L1 positive TNBC, who experienced a pathologic complete response after platinum-based chemotherapy. Our case report gives us the opportunity to review and discuss the available data on the optimal management of PALB2-associated BC.

2 | CASE PRESENTATION

In June 2021, a 58-year-old female patient presented to the emergency department complaining of severe and intense pain in her right breast. The pain was secondary to an ulcerated, excavated, and necrotic lesion believed to have appeared approximately 1 year earlier (Figure 1A). At physical examination, only the right axillary lymph nodes were palpable. Medical history was unremarkable, except for the previous removal of a uterine fibroid. Family history of breast or ovarian cancer was negative.

The punch biopsy of the lesion revealed a TNBC, grade 3, with a Ki-67 of 90% and a PD-L1 expression of more than 1%. Consequently, a total-body computed tomography (CT) scan revealed a highly colliquated hypodense process at the level of the right mammary gland, infiltrating the pectoralis muscle, along with multiple other metastatic right axillary lymph nodes, the largest of which measured 28 × 26 millimeters (mm). No distant metastases were detected. Serum carcinoembryonic antigen (CEA) and cancer antigen 15.3 (CA 15.3) were found to be in range. A multigene NGS-panel test was performed on peripheral blood and the heterozygous germline PV c.420del, p.(Lys140Asnfs*37) in the *PALB2* gene was identified.

Based on the immunohistochemical characteristics, a chemo-immunotherapy schedule was initiated, with nab-paclitaxel (100 mg/m^2) and atezolizumab (840 mg). After 3 cycles of therapy, a partial response of the breast mass was observed (Figure 1B) and the CT scan revealed an initial reduction in both the right mammary lesion and the ipsilateral axillary nodes (20 × 15 mm). Nonetheless, soon after the CT scan, a rapid clinical progression of the breast neoplasm was detected (Figure 1C). Second-line chemotherapy with carboplatin (AUC2) and gemcitabine (800 mg/m^2) was therefore started. After the first cycle, an impressive clinical response was observed (Figure 1D).

After 6 cycles of platinum-based chemotherapy, a progressive disappearance of the ulcerated lesion and the ipsilateral palpable axillary lymph nodes was found (Figure 1E). In February 2022, a bilateral breast magnetic resonance imaging (MRI) was performed, highlighting a complete response of the ulcerated neoformation. Furthermore, a marked size reduction in the right axillary

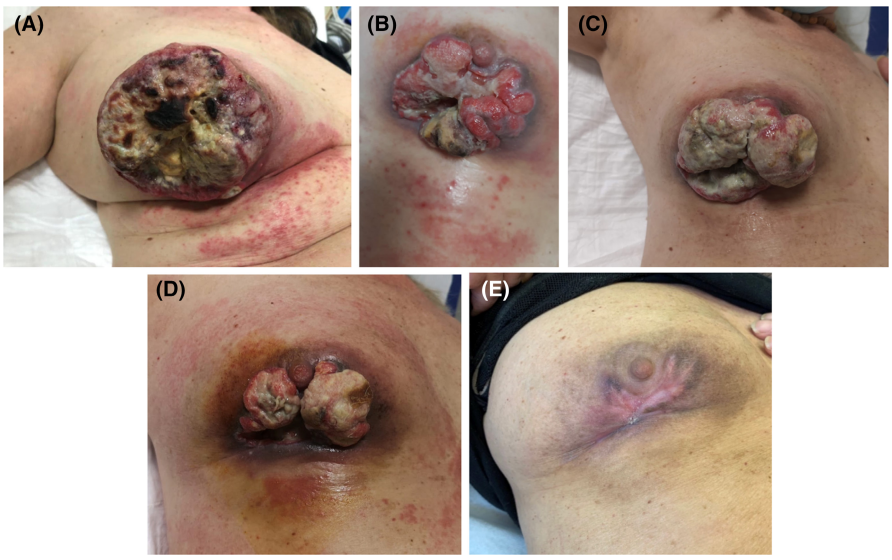

FIGURE 1 (A) Patient's breast at diagnosis. (B) Partial response after 3 cycles of nab-paclitaxel and atezolizumab. (C) Clinical progression after 4 cycles of nab-paclitaxel and atezolizumab. (D) Clinical response after 1 cycle of carboplatin and gemcitabine. (E) Disappearance of the ulcerated lesion after 6 cycles of carboplatin and gemcitabine.

nodes was observed, measuring a maximum diameter of 22 mm. In March 2022, the patient underwent a CT scan, which confirmed no distant metastases. A multidisciplinary team of oncologists and surgeons recommended right mastectomy with ipsilateral axillary dissection and enlargement of the deep muscle margin.

The histological examination of the resected primary malignancy and 16 lymph nodes showed no evidence of residual tumor and was therefore consistent with a pathologic complete response. To July 2023, the patient is still free from disease.

3 | THE TUMOR SUPPRESSOR *PALB2*

PALB2 is located on the chromosome 16p12.2[3] and it is responsible for BRCA2 nuclear localization and DNA damage repair.[14] *PALB2* plays a pivotal role in the DNA damage repair through two closely connected pathways: Fanconi anemia (FA) and homologous recombination (HR).[15] FA is a rare genetic instability syndrome due to biallelic PV in FA genes and associated with early-onset bone marrow failure and cancer predisposition.[16,17] *PALB2* belongs to the Group 3 proteins of the FA pathway that act as downstream effectors to facilitate DNA interstrand cross-link repair.[18]

HR is triggered by DNA double-strand break (DSB) during the S/G2 phase of the cell cycle, when the intact sister chromatid is available as a template. The MRN sensor complex recognizes DSBs and initiates DNA end-resection from 5′ to 3′, leading to the formation of single-strand DNA (ssDNA) at the extremity of the DSB repair.[19] After the ssDNA capping by RPA, BRCA1 recruits PALB2, which in turn allows loading of BRCA2 and RAD51 to DSB. In detail, the complex BRCA2-PALB2 removes RPA and facilitates the assembly of the RAD51 nucleoprotein filament.[20–22] The role of PALB2 in HR involves several protein domains described in Figure 2.[20–30]

Monoallelic PALB2 LPV/PVs predispose carriers to multiple cancers such as BC, pancreatic cancer, and likely ovarian cancer.[14,31–33] g*PALB2* truncating LPV/PVs occurred in 1.1% of patients from a subset of BRCA-negative familial BC cases.[31] Subsequent studies showed that BC patients harbor a g*PALB2* LPV/PV in 0.4%–3% of the cases.[4,5,34–41] Multiple population-based studies reported a 2-30-fold higher risk of BC incidence in g*PALB2*-truncating variants carriers compared with noncarriers.[42–46] Furthermore, evidence shows that g*PALB2*-related BC is associated with aggressive clinicopathological features—such as triple-negative phenotype in the 22%–54% of the cases[41,47–54]—and higher mortality rate independently of tumor stage, type of chemotherapy, nor hormone receptor status.[41,55,56]

According to the NCCN guidelines,[57] screening with annual mammogram and breast MRI with contrast starting from 30 years of age is recommended for gPALB2 LPV/PV carries. Risk-reducing mastectomy may be considered based on family history, while risk-reducing salpingo-ovariectomy may be considered after 45 years of age. Pancreatic cancer screening in individuals who have g*PALB2* LPV/PV is not recommended unless there is additional family history of pancreatic neoplasia.

4 | LOCOREGIONAL TREATMENT OF PALB2-ASSOCIATED BREAST CANCER

Locoregional management in g*PALB2*-associated BC has not been fully elucidated yet. Women with germline *PALB2* mutations are at increased risk of developing contralateral BC (CBC).[58] A prospective cohort analysis published in 2015 showed that among 115 PALB2-mutated women there was a 5-year cumulative incidence of

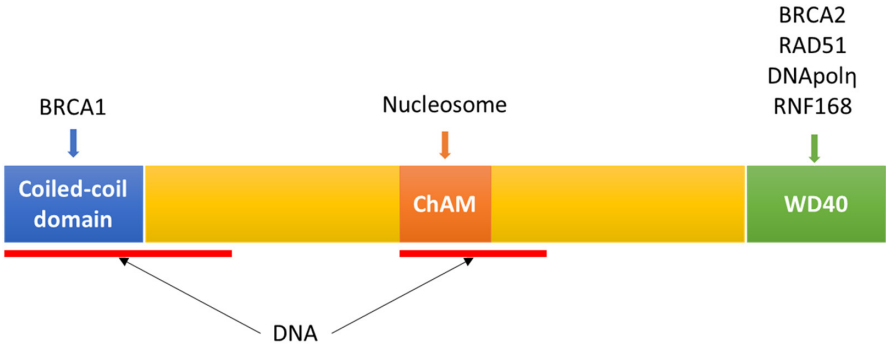

FIGURE 2 PALB2 protein structure. The coiled-coil domain is responsible for its interaction with BRCA1; the WD40 domain is involved in the interaction with BRCA2, DNA polymerase η (DNApolη), RAD51, and RNF168; the ChAM domain binds to nucleosome and participates to the formation of PALB2-BRCA2-RAD51 complex; two DNA-binding domains enhance the RAD51-mediated ssDNA invasion.

developing a second primary CBC of 10%,[41] which should be considered when approaching to newly diagnosed BC. Since indications for mutation carriers are lacking, the American Society of Clinical Oncology (ASCO), the American Society for Radiation Oncology (ASTRO), and the Society of Surgical Oncology (SSO) provided jointed guidelines for the management of BC in patients with germline mutations in the *BRCA1/2*, *PALB2*, *CHEK2*, or *ATM* genes.[59] A panel of 52 experts agreed that for women with newly diagnosed BC who have a mutation in a moderate-penetrance BC susceptibility gene, mutation status alone should not determine whether to perform contralateral risk-reducing mastectomy (CRRM), but additional predictors of CBC such as family history and age at diagnosis should be considered.[59] Consistent with these indications, the NCCN guidelines asserted that CRRM may be considered on an individual basis for women with unilateral BC and genetic predisposition to BC.[60,61] Breast-conserving therapy (BCT) represents a valid alternative for selected patients, who should undergo annual mammogram and breast MRI following surgery.[59]

At the 2022 San Antonio Breast Cancer Symposium, a subanalysis of the Carriers study[53] aimed to assess the risk of CBC among 15,104 women treated with ipsilateral surgery for invasive BC. Over a median follow-up of 11 years, there were seven CBC events among 97 carriers of *PALB2* PV. In an adjusted analysis, the risk of CBC was increased only for *PALB2* PV carriers with a diagnosis of estrogen receptor (ER)-negative BC (HR, 2.9; 95% CI, 1.4–6.4; $p = 0.006$).[6] *PALB2* PV carriers with ER-negative BC showed a 10-year CBC risk of 19.7%. Interestingly, premenopausal PV carriers are at a higher risk of CBC compared with postmenopausal carriers, whereas the CBC risk in PV carriers among women over age 65 years appears to be similar to noncarriers.

Data regarding radiation therapy (RT) outcomes in *PALB2*-related BC are scarce. The jointed ASCO/ASTRO/SSO guidelines underline that, for women with BC who are treated with BCT or with mastectomy for whom RT is considered, RT should not be withheld because of mutation status. Data showed no increase of radiation toxicity related to *PALB2* mutations.[58,62]

5 | SYSTEMIC TREATMENT OF PALB2-ASSOCIATED BREAST CANCER

5.1 | Immune-checkpoint inhibitors

Our patient was diagnosed with an inoperable PD-L1 positive triple-negative breast cancer. First-line therapy with nab-paclitaxel and atezolizumab was therefore prescribed, based on results from the Impassion130 study.[63] At the time, pembrolizumab according to the results of Keynote-355 study[64] was not available in Italy. No efficacy data of immunotherapy in g*PALB2*-associated BC are available yet, and also the role of *BRCA1/2* alteration in immunotherapy remains controversial across different tumor types.[65] *BRCA*-associated tumors have been found to contain more neoantigens than tumors with no alterations in genes of the HR pathway, harbor an increased number of tumor-infiltrating lymphocytes, and have an elevated PD-L1 expression as compared to HR-proficient tumors.[66] Nevertheless, the role of BRCA1/2 and PALB2 alterations in tumor immunotherapy remains conflicting. Indeed, there is a growing body of evidence suggesting that HR-deficient tumors show heterogeneous immune landscapes, and this might impact on rates of patient response to ICIs. Previous studies reported of improved response to immunotherapy in BRCA2-deficient tumors and limited response with BRCA1-loss.[67] Nevertheless, definitive evidence will require prospective evaluation of ICIs response in cohorts of patients with *BRCA1* and *BRCA2* mutations apart.

Concluding, *BRCA* altered tumors have shown enhanced immunosurveillance in several preclinical studies, but their correlation with immunotherapy outcomes remains unclear. In two early phase randomized clinical trials, the MEDIOLA trial[68] and the TOPACIO/KEYNOTE-162 trial,[69] combining PARP inhibitors with ICIs have shown promising results in *BRCA*-mutated BC. On the contrary, data on immunotherapy in g*PALB2*-associated BC are lacking. A recent pooled analysis[70] of five independent cohorts of 672 advanced melanoma patients showed that *PALB2* mutations was associated with a higher tumor mutation burden and tumor neoantigen burden level. Additionally, the *PALB2* patients had significantly improved objective response rate (ORR) of immunotherapy and median overall survival (mOS) than the *PALB2* wild-type group. According to these results, it seems that *PALB2* may serve as a positive predictor of immunotherapy (particularly CTLA4 inhibitors) in patients with advanced melanoma. Indeed, the clinical value of g*PALB2* mutations in predicting immunotherapy response warrants further investigation.

5.2 | Chemotherapy

After modest and brief partial clinical response to atezolizumab and nab-paclitaxel, the disease continued to progress and second-line therapy with carboplatin and gemcitabine was started. Mutations in the HR pathway have been shown to improve sensitivity to DNA-targeting agents, including platinum-based chemotherapeutics.[1]

Increased sensitivity to platinum agents has been previously described in a variety of solid tumors that harbor *PALB2* mutations.[71–73] In 2018, in particular, the cases of two metastatic *PALB2*-associated BC patients were published and showed rapid and durable responses to platinum chemotherapy.[71]

In our case report, the platinum-based treatment offered an advantage over the ICI, suggesting a major role of the germline *PALB2* alteration compared to the PD-L1 expression, and highlighting how the germline genetic profile of our patients should remain the target of our interventions. Pembrolizumab offers the opportunity to prescribe carboplatin/gemcitabine or taxanes along with the ICI in this setting,[64] therefore germline genetic testing including the evaluation of PALB2 assumes a renewed role for the selection of the proper backbone to immunotherapy.

5.3 | PARP inhibitors

Beyond alkylating agents, polyp (ADP-ribosome) polymerase (PARP) inhibitors exploit the HR deficiency induced by *BRCA* LPV/PV to induce cancer cell death through the inhibition of single-strand break repair. *PALB2* represents a possible further biomarker for PARP inhibitor-based therapy. Indeed, several studies in prostate cancer have suggested that some patients with mutations in HR-related genes other than *BRCA1/2* may benefit from PARP inhibitors, although which genes are consistently associated with response is not yet clear.[74–76] Furthermore, mutations in the *BRCA1/2* or in other HR-associated genes or methylation of HR genes may converge in a high HRD score. Therefore, tumors with high HRD scores are a promising subset to consider for PARP inhibitor therapy, as already demonstrated in ovarian cancer.[77]

In this context, the phase II TBCRC-048 study[10] enrolled 55 metastatic BC patients with germline mutations in non-*BRCA1/2* HR-related genes or somatic mutations in these or *BRCA1/2 genes*. Among patients with germline mutation other than g*BRCA1/2*, all responses were in patients with a g*PALB2* mutation.

Similar data have been found in a phase II trial that evaluated talazoparib in patients with advanced HER2-negative BC or other solid tumors with germline or somatic alteration in HR-related genes other than BRCA.[78] Among the six patients with g*PALB2* mutations, the ORR was 50% (95% CI, 19%–81%), all five breast cancers had tumor shrinkage as the best response. On these grounds, PARP inhibitors could soon be alternative options for patients carrying *PALB2* LPV/PV, but further research in this setting is ongoing.

6 | ONGOING STUDIES AND FUTURE PERSPECTIVES

Seventeen phase I/II clinical trials (Table 1) and two observational studies have been identified in our literature research. Here we report a list according to the tumor type.

6.1 | PALB2-associated breast and ovarian cancer

The ongoing studies on breast and ovarian cancer bearing HRD mutations mainly involve different types of PARP inhibitors in many diverse combinations.

A phase I study will determine whether olaparib can be safely combined with navitoclax in TNBC with *BRCA1/2* or *PALB2* mutations and in recurrent high-grade serous epithelial ovarian cancer who have progressed greater than 6 months since their last platinum containing chemotherapy.[79] Another phase II trial will evaluate the association of pembrolizumab with olaparib in advanced HER2 negative BC with germline mutation in *BRCA1/2* irrespective of tumor HRD status (cohort 1), or a germline mutation in *ATM*, *BARD1*, *CHEK2*, *FANCC*, *PALB2*, *RAD51C*, *RAD51D*, *SLX4*, and *XRCC2* irrespective of tumor HRD status (cohort 2), or a centrally confirmed high tumor HRD status, but no deleterious germline mutation in *BRCA1/2* and abovementioned genes (cohort 3).[80] Finally, the RADIOLA trial is a phase II study that will evaluate olaparib in unresectable BC in two cohorts, the first one made of patients with mutation of *BRCA1/2*, *PALB2*, or *RAD51C/D* and the latter characterized of BC with RAD51-foci low score in wild-type HRR tumors. The primary objective is to assess the capacity of the RAD51-foci score to predict the efficacy of olaparib in *BRCA1/2*, *PALB2*, or *RAD51C/D* mutated advanced BC.[81]

A phase II study will investigate the role of niraparib with dostarlimab as neoadjuvant treatment for patients with *BRCA1/2* and *PALB2* mutation and stage I to III BC.[82] Additionally, another phase II study will explore the potential benefit of niraparib in patients with metastatic BC developing in germline-*PALB2* mutations carriers and *BRCA1/2* wild type.[83] Finally, a phase II clinical trial will evaluate the efficacy and safety of talazoparib monotherapy in advanced BC bearing *PALB2* mutation.[84]

As regards local therapies, a phase II study will investigate prophylactic irradiation to the contralateral breast in patients with *BRCA1*, *BRCA2*, and *PALB2* mutation diagnosed with stage 0-III BC undergoing lumpectomy or mastectomy within 1 year.[85] Moreover, another phase II trial will study how well surgery (risk-reducing salpingo oophorectomy vs. interval salpingectomy with delayed oophorectomy) works in preventing ovarian cancer in

TABLE 1 Phase I/II clinical trials bearing PALB2 mutation and listed according to the tumor type.

Intervention/Treatment	Phase	Tumor	Status	Mutated genes
Olaparib and navitoclax	I	Breast and ovarian cancer	Not yet recruiting	*BRCA1*, *BRCA2*, and *PALB2*
Pembrolizumab and olaparib	II	Advanced breast cancer	Not yet recruiting	*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *CHEK2*, *FANCC*, *PALB2*, *RAD51C*, *RAD51D*, *SLX4*, and *XRCC2*
Olaparib	II	Advanced breast cancer	Recruiting	*BRCA1*, *BRCA2*, *PALB2*, and *RAD51C/D*
Niraparib and dostarlimab	II	Stage I to III Breast Cancer	Recruiting	*BRCA1*, *BRCA2*, and *PALB2*
Niraparib	II	Metastatic breast cancer	Not yet recruiting	*PALB2*
Talazoparib	II	Advanced breast cancer	Not yet recruiting	*PALB2*
Prophylactic breast irradiation	II	Breast cancer	Recruiting	*BRCA1*, *BRCA2*, and *PALB2*
Preventive surgery	II	Ovarian cancer risk	Active and not recruiting	*BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *RAD51C*, *RAD51D*, and hereditary breast and ovarian cancer syndrome
Genetic screening	I	Breast cancer	Recruiting	*BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *RAD51C*, and *RAD51D*
Melphalan, BCNU, low-dose ethanol, vitamin B12b and vitamin C in association with autologous hematopoietic stem cell infusion	I	Metastatic breast and pancreatic cancer	Recruiting	*BRCA 1*, *BRCA2*, and *PALB2*
Talazoparib	II	Recurrent or metastatic tumors other than breast and ovary	Active and not recruiting	*ATM*, *BRCA1*, *BRCA2*, and *PALB2*
Niraparib	II	Advanced breast, colon, lung, urologic, pancreatic, esophageal, endometrial, head and neck cancers, and melanoma	Recruiting	*PALB2*
CX-5461	Ib	Pancreatic, ovarian, prostate, and breast cancers	Recruiting	*BRCA1*, *BRCA2* and *PALB2*
Olaparib	II	Metastatic biliary tract cancer	Recruiting	*ARID1A*, *ATM*, *ATR*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *EMSY*, *Fanconi anemia complementation group*, *MRE1*, *NBN*, *PTEN*, and *RAD51*
Olaparib	II	Resected pancreatic cancer	Recruiting	*BRCA1*, *BRCA2*, and *PALB2*
Irinotecan liposome, fluorouracil, and rucaparib	I/II	Metastatic pancreatic, gastric, esophageal, colorectal, and biliary cancer	Recruiting	*BRCA 1*, *BRCA2*, and *PALB2*
Carboplatin or olaparib	II	Metastatic prostate cancer	Recruiting	*BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK1*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*

patients with genetic mutations at risk of developing ovarian cancer.[86]

Concluding, the MAGENTA (MAking GENetic Testing Accessible) trial is a randomized study designed to compare the effectiveness of online genetic education with pre- and post-test telephone genetic counseling to three potentially more accessible alternative approaches: online genetic education with optional

telephone counseling, online genetic education with required pretest telephone genetic counseling, and online genetic education with required posttest telephone genetic counseling.[87]

6.2 | Multiple PALB2-associated solid tumors

The SHARON study is a phase I, single-arm trial that will assess the safety and the efficacy of melphalan, carmustine, low-dose I.V. ethanol, vitamin B12b, and vitamin C in association with autologous hematopoietic stem cell infusion in metastatic breast and pancreatic cancer patients who harbor a g*BRCA1*, g*BRCA2*, or g*PALB2* mutation.[88]

Another phase II trial will explore the efficacy of talazoparib in relapsed, unresponsive, or metastatic cancers that have alterations in *BRCA1*, *BRCA2*, *PALB2*, or *ATM* genes. Patients will be enrolled in one of six cohorts: (1) somatic mutations of *BRCA1/2*, (2) somatic deletions of *BRCA1/2*, (3) mutations or homozygous deletions in other *BRCA* pathway genes, (4) mutations or homozygous deletions in *PTEN* and/or PTEN loss by IHC, (5) homologs recombination defects, (6) germline *BRCA1/2* mutations (not breast or ovarian cancer).[89]

Another phase II trial will investigate the efficacy and safety of niraparib in patients with locally advanced or metastatic solid tumors (including breast, colon, lung, urologic, pancreatic, melanoma, esophageal, endometrial, head, and neck cancers). Participants must have received all standard therapies for their tumor type and stage and must have tested positive for a pathogenic or likely pathogenic *PALB2* gene mutation.[89]

Finally, a phase Ib expansion study will assess a tolerable and safe dose of CX-5461 in patients with selected solid tumors and associated to HRD mutations. CX-5461 is a synthetically-derived small molecule that selectively kills HR-deficient cancer cells through the binding and stabilization of G4 DNA structure offering an alternative in destabilizing the DNA compared to PARP inhibitors.[90]

6.3 | PALB2-associated gastrointestinal tumors

A phase II study will explore olaparib in monotherapy in patients with advanced biliary tract cancer with aberrant DNA repair gene mutations.[91] Additionally, the APOLLO trial is a randomized phase II double-blind study that will evaluate olaparib compared to placebo in patients with resected pancreatic cancer and a pathogenic *BRCA1*, *BRCA2*, or *PALB2* mutation. After completion of study treatment, patients are followed up at 30 days, every 4 months for year one, then every 6 months for following years.[92]

Another phase I/II trial will investigate safety and efficacy of liposomal irinotecan and rucaparib when given together with fluorouracil and leucovorin calcium in patients with metastatic pancreatic, colorectal, gastroesophageal, or biliary cancer.[93]

6.4 | PALB2-associated prostate cancer

An open-label phase II study is comparing the efficacy of carboplatin as first-line followed by second-line olaparib versus olaparib as first-line followed by second-line carboplatin in the treatment of patients with metastatic castration-resistant prostate cancer.[94]

6.5 | Observational studies

The first observational study aims to evaluate a cascade genetic testing intervention by looking at how often genetic testing occurs when healthcare providers have permission to reach out to family members to recommend genetic testing and to help those who are interested get tested.[95] The second one, instead, is a study that investigates the quality of life post preventive salpingo-oophorectomy in healthy *BRCA1/2* and *PALB2* mutation carriers.[96]

7 | CONCLUSIONS

Our manuscript provides additional evidence that the analysis of g*PALB2* gene should be included in routine genetic testing for predictive purposes. Particularly, our case suggests that platinum agents should be included in the frontline treatment of gPALB2-associated TNBC, and should be preferred to nonalkylating agents. Additionally, the presence of a g*PALB2* mutation may impact on surgical management of these patients and soon will open room for new targeted strategies such as the use of PARP inhibitors.

AUTHOR CONTRIBUTIONS

Angela Toss: Conceptualization; writing – original draft. **Ornella Ponzoni:** Conceptualization; writing – original draft. **Beatrice Riccò:** Conceptualization; writing – original draft. **Claudia Piombino:** Writing – original draft. **Luca Moscetti:** Writing – review and editing. **Francesca Combi:** Visualization. **Enza Palma:** Visualization. **Simona Papi:**

Visualization. **Elena Tenedini:** Methodology. **Giovanni Tazzioli:** Visualization. **Massimo Dominici:** Writing – review and editing. **Laura Cortesi:** Writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

CONSENT

Written informed consent has been obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ETHICS STATEMENT

IRB approval was not required per Area Vasta Emilia Nord (AVEN) Ethical Committee guidelines, and all additional relevant ethical considerations were complied with.

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