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Management of early breast cancer in patients bearing germline BRCA mutations

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ABSTRACT

Women diagnosed with breast cancers (BCs) that harbor *BRCA*1/2 mutations have an increased lifetime risk of a second BC and ovarian cancer. They may benefit from risk-reducing surgical strategies such as mastectomy and salpingo-oophorectomy. In cases of triple negative BC with BRCA mutation, there is some evidence that adding platinum-agents in the neoadjuvant setting improves the pathologic complete response. Lastly, ongoing clinical trials testing the efficacy of PARP inhibitor therapy in tumors with *BRCA*1/2 mutations will be determinant for future guideline recommendations in selecting best adjuvant treatment options for this specific population. For pre-menopausal patients whose tumors have BRCA mutations and hormone-receptor positive BC, the option of combined bilateral annexectomy and hormonal therapy with aromatase inhibitor can be discussed with high-risk patients. This review summarizes the latest results from clinical trials evaluating treatment and prevention strategies for breast cancers harboring BRCA1/2 mutations and discusses the current management of this patient population.

Introduction

Breast cancer (BC) is the most frequent malignant tumor among women in developed countries [1]. Hereditary BC, caused by specific genetic mutations that increase the lifetime risk of developing BC, account for approximately 5-10% of the total number of BC cases. Management of hereditary BC cases requires specific measures and care concerning the available treatment options and over the past 2 decades significant progress has been made in the diagnosis, treatment, and prevention of hereditary BC. Identification and cloning of the genes for BC type 1 susceptibility protein (BRCA1) and BC type 2 susceptibility protein (BRCA2) associated with a better understanding of their role in the pathogenesis of BC have improved treatment modalities and specific prevention strategies. It is now well established that women that inherit mutations in the BRCA1 or BRCA2 genes suffer from homologous recombination DNA repair deficiency [Homologous Recombinant Deficiency (HRD)] caused by loss of function of the wild-type BRCA1 or BRCA2 allele, elevating their lifetime risk for developing early invasive BC [2]. It was hypothesized early on that the inherent HRD in BC could be exploited to develop specific systemic therapeutic modalities. Furthermore, breast tumors harboring wild type BRCA1 and BRCA2 respond differently to chemotherapy as compared to those BCs with mutant BRCA1 and BRCA2 [3].

In this review, we summarize the most recent advances in the management of early BC in patients with germline BRCA 1/2 mutations. We present an overview of the recent results from surgical and systemic neo- and adjuvant clinical trials and discuss the management of these patients, with a particular focus on systemic treatment options.

Impact of BRCA status on the management of early BC

Given our current understanding of the role played by BRCA status in cancer risk and tumor biology, it is important to know the BRCA status of a patient soon after a cancer diagnosis since it influences the choice of systemic therapeutic regimens and surgical options (Fig. 1). Therefore, the possibility of a hereditary BC should be fully explored. Based on the results of the genetic test, the therapeutic and prophylactic choices should always strike a balance between patient's preference, the pathological features of the tumor as well as the general health, life expectancy, and prognosis of the primary disease.

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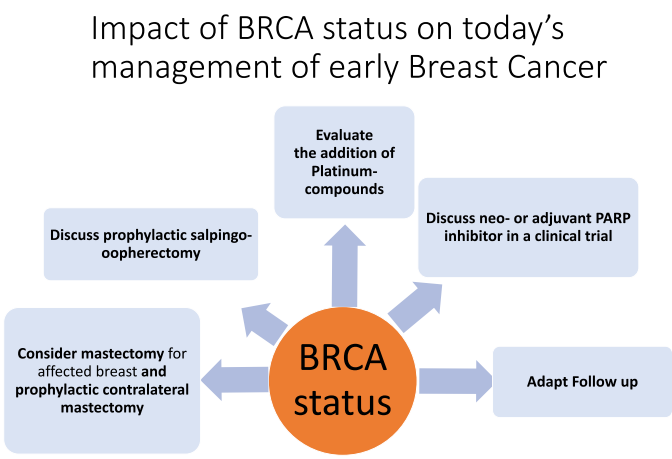

Fig. 1. Considerations for clinical management based on BRCA status.

Surgery

Current surgical management for patients with an early BC harboring germline BRCA mutation requires discussion of the available surgical options, both for the ipsilateral and contralateral breasts. It is important to note, however, that although no study has demonstrated an impact of prophylactic bilateral surgery on overall survival (OS), the risk of a second BC is high and surgery remains the more efficient option for risk reduction in this group [4].

For the diseased breast, the choice of a mastectomy, instead of tumorectomy, may be the best option as it may render adjuvant radiotherapy needless and allow immediate reconstruction with better aesthetic outcomes than those obtained if reconstruction is performed after radiotherapy. Contralateral risk reduction mastectomy has to be discussed together with the different techniques of breast reconstruction, either immediately or at a future time point. Though 1 prospective study showed that contralateral risk reduction mastectomy improved OS in carriers of a mutant BRCA with a history of unilateral BC and strongly reduced the incidence of a contralateral BC in this same population [5], the assessment of impact on survival remains an unsolved issue linked to tumor features, age at the time of diagnosis and treatment options. Randomized trials between radical prophylactic surgery and conservative options are impossible for ethical reasons. So, the discussion of pros and cons of risk-reducing surgery remains the preferred option for the individual patient [6]. It is important to note that the nipple-sparing mastectomy compared to a modified radical mastectomy has proven to be safe in patients carrying a mutant BRCA, as both a therapeutic option and as regards risk-reduction, given its very low local recurrence rates [7,8].

Given the role of BRCA in DNA repair, concerns have been raised. about potential complications of radiation therapy in women with germline BRCA mutations and an early BC However, several studies have failed to find evidence of significant radiation complication rates, including toxicity or contralateral BC, between women with a BRCA-associated BC and a sporadic BC [9-11]. For patients who need chest wall and/or regional lymph nodes irradiation, an immediate breast reconstruction is significantly more prone to complications. So, if postoperative radiotherapy is needed, management becomes complex as it delays definitive breast reconstruction. Immediate breast reconstruction should not be allowed as it delays adjuvant radiotherapy. A balance must be struck between the need to comply with a radiotherapy indication and the patient's wish to immediately achieve a satisfying cosmetic result.

Therefore, the need for BRCA testing should be ascertained as soon as possible so as to have enough time for getting the result at the time of surgery – the growing trend towards neoadjuvant chemotherapy for triple negative BC (TNBC) patients, which lasts at least 4 to 6 months, offers the perfect opportunity for timely testing .

Screening for and prevention of second primaries

Screening for a second primary BC in patients with BRCA mutations treated with a conservative surgery is organized with alternating annual mammogram and breast MRI, according to international guidelines [12]. For patients treated by radical mastectomy and contralateral prophylactic mastectomy, current follow-up recommendations include annual breast examinations and self-examination without a need for breast imaging studies. Nevertheless, the pathologic features of the tumor and the type of reconstruction can be taken into consideration to adapt the modalities of follow-up.

Regarding ovarian carcinoma prevention, bilateral prophylactic salpingo-oophorectomy is recommended for carriers of a BRCA1 mutation before the age of 40 and around 45 for those who carry a BRCA2 mutation [13]. While the effectiveness of the risk-reducing salpingo-oophorectomy (RRSO) in reducing the ovarian cancer risk has been demonstrated, the impact of RRSO on BC risk remains conflicting [14,15] and agreement has not been reached regarding the population that benefits the most from this procedure. For the general oncologic point of view, we can consider that in pre-menopausal patients at high risk of recurrence with hormone-positive disease (independent of BRCA status), prolonged suppression of ovarian function combined with endocrine therapy has been associated with improved outcome [16]. Therefore, in the management of BC in pre-menopausal patient carrying a BRCA mutation the discussion of RRSO should be conducted early.

Of note, fertility issues and guidance on fertility-preservation techniques should also be discussed with young pre-menopausal patients carrying a BRCA mutation before the initiation of treatment. Especially because there is a consistent trend for reduced reproductive potential, linked to the presence of the mutation itself, making cryopreservation strategies potentially less effective in patients carrying a. BRCA mutation [17].

Systemic therapy considerations

Platinum-based chemotherapy

In recent years, there has been a resurgence of interest in platinum-based chemotherapy, including the use of platinum in patients with early BC with BRCA mutations. Platinum salts are alkylating agents that result in DNA adducts and intra- and inter-strand crosslinks causing single- and double strand DNA breaks, with activation of the DNA damage response and eventually tumor cell apoptosis. Their ability to induce DNA damage led to the hypothesis that platinum salts could be effective in cancers associated with dysfunctional DNA repair caused by deficiency in the genes involved in homologous recombination (HRD) including BRCA mutations. Indeed, in both advanced and, later, in early disease settings, several studies have provided evidence that the response rates to platinum agents are influenced by the mutation status of germline BRCA1 and BRCA2 (Table 1).

In the metastatic setting, 3 trials reported between 2012 and 2015 evaluated cisplatin or carboplatin chemotherapy for BC. All demonstrated increased efficacy with overall response rate up to 80%. in patients with germline BRCA mutations. The largest trial to date is the TNT phase III trial that randomized 376 women with advanced TNBC or BC harboring BRCA mutations to either single-agent carboplatin or docetaxel [18]. Carboplatin was found superior in the subgroup of patients whose tumors harbored BRCA

Table 1
Published Results In Patients with Tumors Harboring BRCA Mutations.

Trial	Author	Patients (n)	Phase	Study Scheme	Primary Objective	
PLATINUM COMPOUNDS – METASTATIC SETTING						
Open-Label, Non-Randomized Trial of Cisplatin Chemotherapy in BRCA1-Positive Metastatic Breast Cancer Patients (Cisplatin) [NCT01611727][42]	Byrski	20 BRCA1+	II	Cisplatin 75 mg/m² q3wk for 6 cycles	ORR = 80%; CR = 45%(9/16); PR = 35% (7/16)	
Platinum for Triple-Negative Metastatic Breast Cancer and Evaluation of p63/p73 as a Biomarker of Response [NCT00483223][43]	Isakoff	86 TNBC (11 BRCA+)	II	Cisplatin 75 mg/m² q3wk or Carboplatin AUC6	ORR = 25.6% ORR = 54.5% in germline BRCA1/2+	
TNT trial[18] **Triple Negative Breast Cancer Trial (TNT) [NCT00532727]**	Tutt	376 TNBC (43 BRCA+)	III	Carboplatin (AUC 6 q3wk) X 6-8 cycles or Docetaxel (100 mg/m² q3wk) x 6-8 cycles (cross over to the alternative treatment on confirmed progression)	15% improvement in ORR with C vs. D BRCA+ ORR 68% for C; 33,3% for D	
PLATINUM COMPOUNDS – NEOADJUVANT SETTING						
Cisplatin-monotherapy in the Treatment of BRCA1 Positive Breast Cancer Patients in Poland [NCT01630226][44]	Byrski	107 BRCA1+	0	Cisplatin 75 mg/m² q3wk for 4 cycles, followed by mastectomy and conventional chemotherapy	pCR rate = 63%	
PrECOG 0105[45] **A Phase 2 Study of Standard Chemotherapy Plus BSI-201 (a PARP Inhibitor) in the Neoadjuvant Treatment of Triple Negative Breast Cancer [NCT00813956]**	Telli	80 TNBC (19 BRCA+)	II	Gemcitabine (1,000 mg/m² d1-8) + carboplatin (AUC2 d1-8) + iniparib (5.6 mg/kg IV on D1, 4, 8, and 11) q3wk x 4 or 6 cycles	pCR rate = 36%	
GEPAR SIXTO trial - secondary analysis by BRCA status[21] **Addition of Carboplatin to Neoadjuvant Therapy for Triple-negative and HER2-positive Early Breast Cancer (GeparSixto) [NCT01426880]**	Hahnen	50 BRCA+	sub-analysis	Paclitaxel 80 mg/m² q1wk x 18 + Non-pegylated liposomal doxorubicin 20 mg/m² q1wk x 18 + bevacizumab 15 mg/kg q3wk X 6 ± carboplatin AUC 2 q1wk x 18	The high pCR rate observed in BRCA1 and BRCA2 mutation carriers [66.7%] was not increased further by adding carboplatin [65.4%]	
BrighTNess[46] **A Study Evaluating Safety and Efficacy of the Addition of ABT-888 Plus Carboplatin Versus the Addition of Carboplatin to Standard Chemotherapy Versus Standard Chemotherapy in Subjects With Early Stage Triple Negative Breast Cancer [NCT02032277]**	Loibl	634 TNBC (95 BRCA+)	III	Veliparib 50 mg bid + carboplatin AUC6 + paclitaxel 80 mg/m² q3w x 4 cycles or	pCR rate = 53.2%	
				Veliparib placebo + carboplatin AUC6 + paclitaxel 80 mg/m² q3w x 4 cycles or	pCR rate = 57.5%	
				Carboplatin placebo + paclitaxel 80 mg/m² q3w x 4 cycles	pCR rate = 31%	
				All followed by coxorubicin + cyclophosphamide (AC)	N/A	
PARP-INHIBITORS – METASTATIC SETTING						
Study to Assess the Efficacy and Safety of a PARP Inhibitor for the Treatment of BRCA-positive Advanced Breast Cancer (ICEBERG 1)[47] [NCT00494234]	Tutt	54 BRCA+	III	Olaparib 400 mg bid or Olaparib 100 mg bid	ORR = 41% ORR = 22%	
Study of Talazoparib, a PARP Inhibitor, in Patients With Advanced or Recurrent Solid Tumors[48] [NCT01286987]	De Bono	71 BRCA+ (14 BC)	I	Talazoparib 1mg/d	ORR = 50% (7/14) in all; 42% (5/12) in BRCA+	
BROCADE II[49] **The Study Evaluating Efficacy And Tolerability Of Veliparib in Combination With Temozolomide or In Combination With Carboplatin and Paclitaxel Versus Placebo in Subjects With BRCA1 and BRCA2 Mutation and Metastatic Breast Cancer [NCT01506609]**	Han	296 BRCA+	II	Veliparib 120 mg bid D1-D7 + carboplatin AUC6 + paclitaxel 175 mg/m2 on day 3 or	ORR = 77.8%	P = 0.027
				Veliparib placebo + carboplatin AUC6 + paclitaxel 175 mg/m2 on d3 or	ORR = 61.3%	
				Veliparib 40 mg bid D1-7 + temozolomide 150-200 mg/m² D1-5 q4w	ORR = 28.6%	
OlympiaD[28] **Assessment of the Efficacy and Safety of Olaparib Monotherapy Versus Physicians Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients With Germline BRCA1/2 Mutations. (OlympiAD) [NCT02000622]**	Robson	302 BRCA+	III	Olaparib 300 mg, 2x/d or	PFS = 7m	HR 0.58; 95%CI, 0.43, 0.80; P<0.001
				Physicians choice standard chemotherapy	PFS = 4.2 m	
EMBRACA[29] **A Study Evaluating Talazoparib (BMN 673), a PARP Inhibitor, in Advanced and/or Metastatic Breast Cancer Patients With BRCA Mutation (EMBRACA Study) [NCT01945775]**	Litton	431 BRCA+	III	Talazoparib 1 mg daily Physician's choice single-agent therapy choice (capecitabine, eribulin, gemcitabine, or vinorelbine q3wk	PFS = 8.6 m PFS = 5.6 m	HR 0.54; 95%CI, 0.41, 0.71; P<0.001.

mutations doubling the ORR to 68% compared to 33% with docetaxel, with better tolerance. Progression-free survival (PFS) also favored carboplatin for women whose tumors harbored BRCA mutation (6.8 *v*4.4 months) but there was no difference in OS. The high response rate seen with carboplatin was similar to that reported for the combination of carboplatin and paclitaxel in in the reference comparator arm of a very similar population in the phase II BROCADE trial, supporting the notion that carboplatin monotherapy is highly active in this patient group. Indeed, tumors harboring impaired DNA repair mechanisms linked to HRD, have increased sensitivity to platinum agents inducing DNA damages and replication stress.

Following these findings, 4 major studies have been published evaluating the impact on pathologic complete response (pCR) rate of the addition of platinum agents to standard neoadjuvant chemotherapy in the early setting, with heterogeneous results (Table 1). Of note, pCR, defined as the absence of invasive carcinoma in the breast and axillar lymph nodes (ypT0 ypN0) after neoadjuvant chemotherapy, is regarded as an independent factor predictive of a favorable clinical outcome and is considered a suitable surrogate marker for long term outcome in patients with TNBC [19]. Interestingly, the BrighTNess study which compared a taxane alone versus carboplatin plus a taxane and which also assessed the PARP-inhibitor, veliparib in combination with carboplatin plus a taxane, demonstrated that patients treated with carboplatin plus a taxane had a pCR rate of 57.5% compared to 31% in patients treated only with taxanes (P value <0.001). The addition of veliparib to neoadjuvant carboplatin plus paclitaxel did not improve the proportion of patients with pCR (53%) suggesting the improvement in pCR was due to the use of carboplatin, without a substantial contribution from veliparib in patients not selected for BRCA mutations [20]. In parallel, the secondary analysis focused on the BRCA mutant population of the neoadjuvant GeparSixto study determined that addition of carboplatin improved the pCR rate of BRCA WT tumors. Patients with TNBC harboring BRCA mutations did not have superior response rates with the addition of carboplatin, likely because they already have a significantly better response rate with standard chemotherapy regimens (anthacyclines plus taxanes) [21]. Given these controversial results, the transfer of the results from the neoadjuvant TNBC trials to clinical practice has generated an intense debate. To date, platinum salts have not been endorsed by clinical practices guidelines as a new standard of care for unselected patients with TNBC [22,23]. However, considering the strong biologic rationale, and more consistent results in pCR in favor of platinum salts in patients whose tumors harbor a BRCA mutation, the detection of a BRCA mutation is an incentive for many oncologists to add platinum in the neoadjuvant setting for this population. The impact of platinum agents on long term survival outcomes – disease-free survival and OS rates - as well as the potential benefit of additional therapy in the post-neoadjuvant setting (being investigated in the EA1131 {NCT02445391} trial) have to be demonstrated in clinical trials.

PARP inhibitors

In 2005, simultaneous publications by Bryant et al[24] and Farmer et al [25] demonstrated that pathogenic mutations of the BRCA1 or BRCA2 genes resulted in deficiencies of homologous recombination (used to repair DNA double strand breaks) and sensitized cancer cells to the inhibition of poly- (ADP-ribose) polymerase (PARP) enzymatic activity. In cancers harboring specific DNA-repair defects such as BRCA1 or BRCA2 mutations, inhibition of PARP enzymes is a potential synthetic lethal therapeutic strategy. Several PARP inhibitors (PARPi) including olaparib, veliparib, talazoparib, niraparib, and rucaparib are currently under investigation, either as monotherapy or in combination with other cytotoxic agents or with immunotherapy. Combination with immunotherapy seems a particularly interesting option that has already been demonstrated safe and active in metastatic TNBC and ovarian carcinoma [26]. By interfering with the mechanisms of DNA repair, these drugs can increase the tumor mutational burden and neoantigen expression that have been associated with response to immune checkpoint blockade as seen in non small cell lung cancer [27].

Currently, based on the results of the the OlympiAD and EMBRACA trials, the PARP inhibitors olaparib and talazoparib are both approved for use in the metastatic setting [28,29]. In the randomized phase-3 OlympiAD trial, compared with standard chemotherapy, olaparib monotherapy achieved a PFS gain of 2.8 in HER2 negative BC harboring BRCA mutations months in the metastatic setting for [28]. Shortly thereafter, the large randomized phase-3 EMBRACA study showed similar results with the new dual mechanism PARP inhibitor, talazoparib, namely a significantly gain of PFS of 3 months compared to physician's choice single agent chemotherapy [30]. Although modest in magnitude, these results provide a proof of concept for PARP inhibition in BC harboring BRCA mutations and demonstrate a favorable therapeutic index in patients with tumors that have genetic loss of function of BRCA1- or BRCA2-associated DNA repair. A more recent sub-group analysis of the OlympiAD trial confirmed a gain of OS in first line for those patients whose tumors harbored BRCA mutations (22.6 *v*14.7 months), suggesting the possibility that the therapeutic benefit might be even better impact in the early management of the disease [31].

Thus far, in the early setting, the available data is sparse. The comparison between the veliparib + carboplatin + taxane versus carboplatin + taxane in BrighTNess suggests no added advantage for the use of veliparib [20]. It is important to note however that only 15% of patients in this study had tumors that harbored a mutant BRC. In 2019, the first results of the TALA study (NCT02282345), evaluating neo-adjuvant talazoparib for BCs harboring BRCA mutations provided very promising results with an encouraging rate of pCRs with manageable toxicity [32]. These observations suggest that PARP inhibitors as single oral targeted therapy, have the potential to play an effective role also as therapeutic strategies. PARP inhibitors have relatively tolerable toxicity profiles and can therefore be administered to patients over long periods of time.

Table 2 summarizes ongoing studies in the early setting. Thus far PARPi have been shown to amplify the effect of chemotherapeutic agents when used in combination and have been approved for use as monotherapy in advanced disease.

The concept of HRD deficient tumors may be identified by presence of mutations (using Next Generation Sequencing) in HRD-related genes, like PALB2, CHEK2 or ATM, or by functional assays of HR capacity (by measures of genomic instability). These tumors are today often grouped under the overarching umbrella of "BRCAness," a phenotype that is closely related to that of patients and/or tumors with BRCA mutations. HRD-BRCA wild type (BRCAwt) should also respond to systemic therapies including anthracyclines [33], platinum agents and/or PARP inhibitors [34]. BRCAness status has a prognosis and predictive value and it becomes easier today, with more sophisticated assays to identify BRCAness [35]. It remains unclear what constitutes the best predictor of a favorable response to a drug that targets HRD, such as a PARP inhibitor or a platinum salt. Trials are ongoing to determine the real benefit of using the BRCAness status in the early setting. One example, is the I-SPY2 neoadjuvant umbrella trial program where the results in 72 patients with TNBC treated with veliparib plus carboplatin (VC) concurrently with weekly paclitaxel were compared to the outcomes in 44 patients who received weekly paclitaxel alone. Following paclitaxel ± VC, all pa-

Table 2
Ongoing trials with PARP inhibitors.

Study name (NCT)	Phase	Setting	Investigational arm(s)	Comparator arm(s)	Primary endpoint	Study status
OLAPARIB						
OLYMPIA (NCT02032823)	III	ADJ	Olaparib monotherapy	Placebo	IDFS	*Ongoing but not recruiting patient*
PARTNER (NCT03150576)	II/III	NADJ	Olaparib + carbo/taxol	carbo/taxol	pCR rate	R
VELIPARIB						
BROCADE (NCT01506609)	II	ADV	Veliparib + (Temozolomide) or (CBDCA + PTX)	Placebo + CBDCA + PTX	PFS	R
(NCT02163694)	III	ADV	Veliparib + CBDCA + PTX	Placebo + CBDCA + PTX	PFS	R
TALAZOPARIB						
ABRAZO (NCT02034916)	II	ADV	Talazoparib monotherapy	Single arm study	ORR	R
(NCT02282345)	II	NADJ	Talazoparib monotherapy	Single arm study	Safety	R
NIRAPARIB						
BRAVO (NCT01905592)	*III*	*ADV*	*Niraparib monotherapy*	*Physician's choice CT*	*PFS*	*closed earlier*
RUCAPARIB						
(NCT01074970)	*II*	*ADJ*	*Rucaparib + Cisplatin*	*Cisplatin*	*2y-DFS*	*Ongoing but not recruiting patient*

ADJ = adjuvant; ADV = advanced; CBDCA = carboplatin; CT = chemotherapy; IDFS = interval disease-free survival; NADJ = neoadjuvant; NR = not yet recruiting; ORR = objective response rate; PFS = progression-free survival; PTX = paclitaxel; R = recruiting; 2y-DFS = 2-year disease-free survival.

tients received doxorubicin and cyclophosphamide. pCR was estimated to be 51% in the VC arm versus 26% in the standard arm [36]. Further, in a subgroup analysis, patients who had a BRCA1-like signature, called BRCA1ness, experienced an improved tumor response if they had been randomized to the V-C arm compared to those with BRCA1ness assigned to the control arm (50% *v*23.5%) [37].

Interestingly, clinical benefit of these classes of agents, platinum compounds and PARP inhibitors has been observed in patients with cancers associated with BRCA mutations and those with a WT BRCA if their tumors have a BRCAness phenotype [37].

Immunotherapies

As previously mentioned, the combination of PARP with immune checkpoint blockade may emerge as a promising therapeutic strategy for patients with tumors harboring BRCA mutations. These tumors appear as more "immunogenic" due to their higher mutational burden, their higher levels of tumor-infiltrating lymphocytes and expression of immune checkpoint inhibitory molecules compared to BCs with WT BRCA [38]. A recent study using preclinical models demonstrated that the combination of platinum-based chemotherapy with immune checkpoint inhibitors delayed the growth of tumors with mutant BRCA1 and improved survival [39]. In the phase III trial, IMPASSION 130, the combination of nab-Paclitaxel and atezolizumab as first line treatment with in patients with PD-L1 immune cell-positive locally advanced or metastatic TNBC achieved a statistically significantly longer PFS and a clinically meaningful OS benefit [40]. About 15% of the patients had BRCA mutations, however, BRCA status was not predictive of response to the combination. In patients with BRCA1/2 mutation, the combination showed a clinical benefit only in patients with PD-L1 positive tumors. This promising combination is still under evaluation in several other clinical trials, and the predictive value of BRCA status (germline and somatic) as a biomarker should be further investigated [41–49].

Conclusion

While most cases of BC are not hereditary, the cases in which BC is an inherited condition merit highly specialized multidisciplinary care to assist in the decision-making process regarding the best treatment options for both local and systemic treatment. Deleterious mutations in BRCA1 or BRCA2 impair homologous recombination DNA repair, rendering these tumors uniquely sensitive to chemotherapy (the specific addition of platinum-agents however is still a matter of debate) and PARPi therapy. Numerous PARP inhibitors are currently under evaluation in phase III trials for several indications, including BCs harboring BRCA1/2-mutations in early settings. Because of their "immunogenic" profile, the addition of the immunotherapy as a treatment for BCs harboring BRCA mutations could be soon a promising therapeutic option. The results of these trials will likely have a major influence on the management of early BC.

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