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Hot Topic

Parp-inhibitors in the therapeutic landscape of breast cancer patients with BRCA1 and BRCA2 pathogenic germline variants: An Italian consensus paper and critical review

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ABSTRACT

The introduction of PARP inhibitors has revolutionized the management and treatment of patients with pathogenic germline variants of BRCA1/2 who have developed breast cancer. The implementation of PARP inhibitors in clinical settings can be challenging due to their overlapping indications with other drugs, including both recently approved medications and those with proven efficacy. This study utilized the Delphi method to present the first Italian consensus regarding genetic testing, the use of PARP inhibitors in both early and metastatic settings, and strategies for managing the potential toxicity of these novel drugs. The Panel unanimously agreed on various issues, including the timing, techniques, and patient characteristics for BRCA1/2 genetic testing, and the appropriate placement of PARP inhibitors in the treatment algorithm for both early and advanced breast cancer. Nevertheless, some areas of divergence became evident, particularly regarding the use of axillary surgery for therapeutic purposes and the application of hormone replacement therapy in cases of bilateral mastectomy and risk-reducing salpingo-oophorectomy for patients treated for triple negative breast cancer. Additional research is needed in these particular domains to improve the care of patients with breast cancer who bear an increased genetic risk.

Introduction

Approximately 10 % of patients with breast cancer (BC) carry pathogenic germline variants (PGVs) in critical genes, including BRCA 1 and BRCA 2, predisposing to BC development [1]. Both are tumour suppressors playing a pivotal role in DNA double-strand breaks repairing, through the error-free homologous recombination mechanism. The presence of mutations in genes such as BRCA1 and BRCA2, located on chromosome 17 and 13 respectively, results in DNA instability, reduction in telomere length, and increased susceptibility to tumor development, especially for BC and ovarian cancer (OC). The prevalence of PGVs varies according to BC subtypes: 3–5 % in hormone receptor (HR)-positive BC, mostly BRCA2, and about 12 %-15 % in triple-negative (TN) BC, primarily BRCA1 [2,3].

The early detection of PGVs in the BRCA 1/2 genes has important implications both for the management of patients already diagnosed with BC and for the prevention of hereditary cancers in family members. Current Italian criteria for patient's eligibility to BRCA1/2 gene testing are shown in Table 1[4]. For patients diagnosed with early BC (eBC), the presence of BRCA1/2 PGVs may modify the treatment approach, including radical or conservative surgery, complementary radiotherapy, and optimal systemic treatment. Moreover, the identification of carriers within families may allow the implementation of special cancer surveillance and/or risk reduction strategies [5].

The initial therapeutic synthetic lethal interaction identified with BRCA1/2 deficiency was poly (ADP-ribose) polymerase [PARP] inhibition [6]. Synthetic lethality is a mechanism by which cells affected by BRCA1/2 mutations are more susceptible to PARP inhibitors [7]. This accumulation of DNA damage leads to cell mortality in BRCA1/2-mutated cells leaving wild type cells unaffected. Numerous experimental models have been proposed as cancer-specific altered pathways, including those that act on single-strand DNA breaks, capture PARP-1, or homologous recombination [8].

Accordingly, patients with BC and PGVs in BRCA1/2 can effectively benefit from PARP inhibitors in both early [9] and advanced setting [10].

Olaparib was approved in early setting for patients with HR-positive BC and TNBC based on the results of the phase 3 Olympia trial, in which patients were randomised to receive olaparib or a placebo as adjuvant treatment for a year following (neo)adjuvant chemotherapy (CT) [11]. Patients diagnosed with TNBC who underwent adjuvant CT were specifically required to have a pathologically assessed tumour greater than 2 cm or positive lymph node (LN), or to have failed to achieve pathological complete response (pCR) in the case of neoadjuvant therapy (NAT). For patients with HR–positive BC they were required to have at least 4 pathologically confirmed positive axillary LN, or have failed

Table 1
Indications for multigene testing for genetic, personal, and therapeutic causes. Adapted from criteria for BRCA1/2 testing in patients with a diagnosis of BC, actually from Italian Association of Medical Oncology (AIOM) guidelines for the treatment of early BCE 2023 (published on January 8th, 2024). [a]The presence of a first-degree family member (parent, sibling, child) exhibiting similar disease characteristics. When considering the paternal side of the family, it is important to also take into account second-degree relatives such as grandmothers and aunts. [b]The therapeutic indication for adjuvant PARP inhibitor olaparib pertains only to testing for BRCA1 and BRCA2 mutations. Abbreviations: BC, breast cancer; CDK4/6i, cyclin-dependent kinases 4/6 inhibitors; CT, chemotherapy; CPS/EG, clinical and pathological stage / estrogen-receptor status and histological grade; HR, hormone-receptor; LN, lymph node; NAT, neoadjuvant therapy; pCR, pathological complete response; T, tumour; TNBC, triple negative breast cancer; yo, years old.

Indication		Criteria
Genetic	Known pathogenetic variant in a predisposing gene in a family member	
Personal history	Without family history	Males, BC and ovarian cancer, females < 40 yo, TNBC, bilateral < 50 yo
	41–50 yo	First-degree relative with history of[a]: BC<50 yo, non-mucinous or borderline ovarian cancer at any age, bilateral BC, male BC, pancreatic cancer, prostate cancer
	> 50 yo	Family history of breast, ovarian, and pancreatic cancer in two or more first-degree relatives who are also related to each other (one of whom is a first-degree relative to the patient).
Therapeutic	HR-positive eBC[b]	≥ 4 LN; or No pCR after NAT and CPS/EG score ≥ 3
	HR-positive metastatic BC	Received CT with anthracyclines/taxanes (if not unfit for these treatments) and endocrine treatment progressing thereafter CDK4/6i for advanced disease.
	TNBC[b]	N≥1 or T≥2 cm If no pCR after NAT

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achieving pCR after NAT with a clinical and pathological stage (CPS) and estrogen-receptor status and histological grade (EG) score ≥ 3.

OlympiAD and EMBRACA phase 3 randomized clinical trial (RCT) demonstrated a significant benefit in progression-free survival (PFS) with olaparib and talazoparib, respectively, for patients with previously treated metastatic HER2-negative BC with PGVs of BRCA1/2, despite the lack of a statistically significant benefit in overall survival (OS) [12,13]. For such a therapeutic indication, TNBC patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant or metastatic setting and should have received platinum-derived drugs, unless patients were ineligible for these treatments. Patients who have undergone no more than three courses of treatment for metastatic HR-positive breast cancer can be prescribed talazoparib. To be noted that in the EMBRACA study, 7.80 % of patients who have been pretreated with CDK4/6 inhibitors[13].

In fact, the clinical use of PARP inhibitors may compete with alternative treatment options in both early and metastatic settings, and with the constraints of the local reimbursement policies, which are not always aligned with clinical evidence. Under these circumstances, a group of highly experienced Italian BC oncologists developed a series of statements regarding BRCA 1/2 genetic testing and the use of PARP inhibitors in the treatment of BC. These statements were presented to local oncologists to gauge their opinions and preferences.

Methods

A scientific board composed of 27 Italian internationally recognised BC experts (the Scientific Board), formulated relevant statements regarding BRCA genetic testing and the use of PARP inhibitors in therapeutic interventions between March and August 2023.

Subsequently, a sample of 60 Italian local oncologists of breast units was surveyed (30/08/2023–30/09/2023) using a modified Delphi method to measure the level of agreement and disagreement with the proposed statements.

In detail, the Delphi method represents a survey approach that aims at quantifying the level of agreement/disagreement to develop a consensus [14].

For each statement, the voters were asked to express a preference among the following options:

- Completely disagree (contributing to the “disagreement”)
- Partially disagree (contributing to the “disagreement”)
- Partially agree (contributing to the “agreement”)
- Agree (contributing to the “agreement”)
- Completely agree (contributing to the “agreement”)

Agreement or disagreement was considered as reached when > 66.6 % of the responses in one of the two possible directions. In all the other cases the consensus was considered not reached.

The results of this survey were then discussed in a meeting involving both the Scientific Board and the local Italian oncologists, using the Nominal Group Technique (NGT) (December 2023).

The areas covered by the survey were:

- Genetic testing of critical genes in BC
- Patterns of care in patients with PGVs of BRCA1/2
- Management of PARP inhibitors and follow-up

Descriptive statistics were applied to analyse data.

Results

(Dis-)agreement levels for each response option are shown in Sup. Table S1. The aggregated agreement/disagreement levels (agreement level [%] = partially agree + agree + completely agree; Disagreement level [%] = completely disagree + partially disagree) are shown below.

Of the 60 breast unit specialists, approximately two-thirds were affiliated with central hub centres (44/60), while 27.1 % were affiliated with peripheral spoke centres. Approximately 30 % of the participants held the position of breast unit coordinator. The study participants were dispersed across Italy, with the northern region providing the largest proportion, led by Lombardy with 30 %. Emilia Romagna, Lazio, and Veneto each contributed 10.2 % of the sample.

Genetic testing of critical genes in BC

Requirements for genetic test access

Consensus was reached on all statements regarding access the genetic testing reached the consensus agreements (Fig. 1a).

- For patients diagnosed with TNBC, it would be appropriate to suggest genetic testing for prognostic or therapeutic purposes prior to initiation of oncological treatment, regardless of family history, age, or gender.

  Consensus reached (agreement level = 98.3 %).

- For patients diagnosed with HR-positive BC that occurred at the age of 40 or younger, it would be appropriate to suggest genetic testing for prognostic or therapeutic purposes prior to initiating oncological treatment, regardless of family history, age, or gender.

  Consensus reached (agreement level = 100 %).

- For patients with BC and criteria already considered eligible due to family history, it would be appropriate to propose genetic testing for prognostic or therapeutic intentions.

  Consensus reached (agreement level = 100 %).

- For patients with HR-positive BC who underwent surgery with involvement of more than 4 lymph nodes, it would be appropriate to propose genetic testing for therapeutic purposes.

  Consensus reached (agreement level = 94.9 %).

- For patients with HR-positive BC treated with NAT, in the presence of residual disease and a high risk of relapse (CPS/EG score ≥ 3), it would be appropriate to propose genetic testing for therapeutic purposes.

  Consensus reached (agreement level = 96.6 %).

Single-gene vs. Multigene panel

Consensus was reached on both statements regarding the recommended genetic testing of patients (Fig. 1b).

- It would always be preferable to perform genetic testing using a multigene panel for inheritance of genes with high and moderate penetrance (e.g. < 50 genes) rather than searching for pathogenic variants exclusively of BRCA1/2.

  Consensus reached (agreement level = 91.3 %).

- It would be appropriate to use targeted testing only in the case of pathogenetic variants already established in the family.

  Consensus reached (agreement level = 89.7 %).

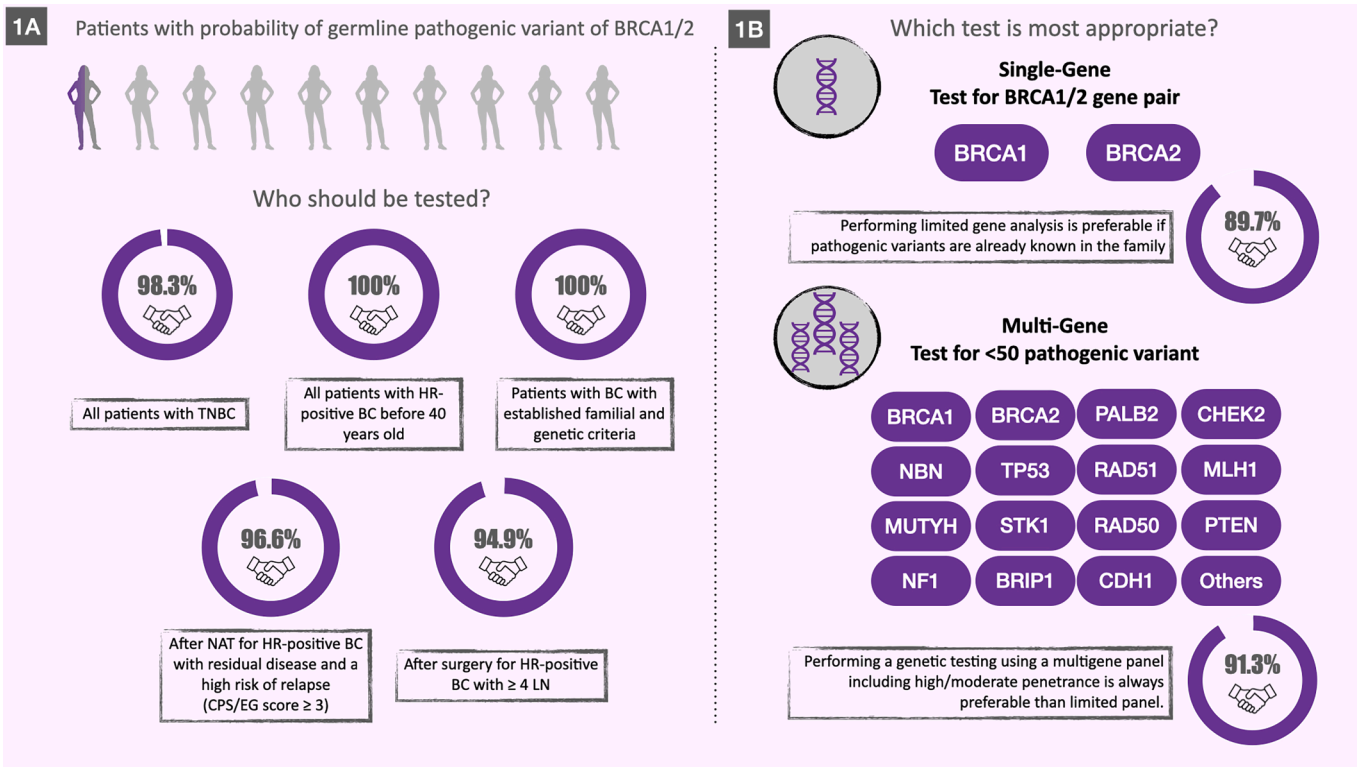

Fig. 1. Finding germline pathogenic variants of BRCA1/2 in patients with breast cancer. 1A) Determining the appropriate candidate for testing the germline pathogenetic variant of BRCA1/2 in breast cancer patients. 1B) Determining the most suitable gene testing option: single- versus multi-gene panel. *Abbreviations: CPS/EG: clinical and pathologic stage and oestrogen receptor status and histologic grade; HR: hormone receptor; LN: lymph node; NAT: neoadjuvant therapy; TNBC: triple negative breast cancer.*

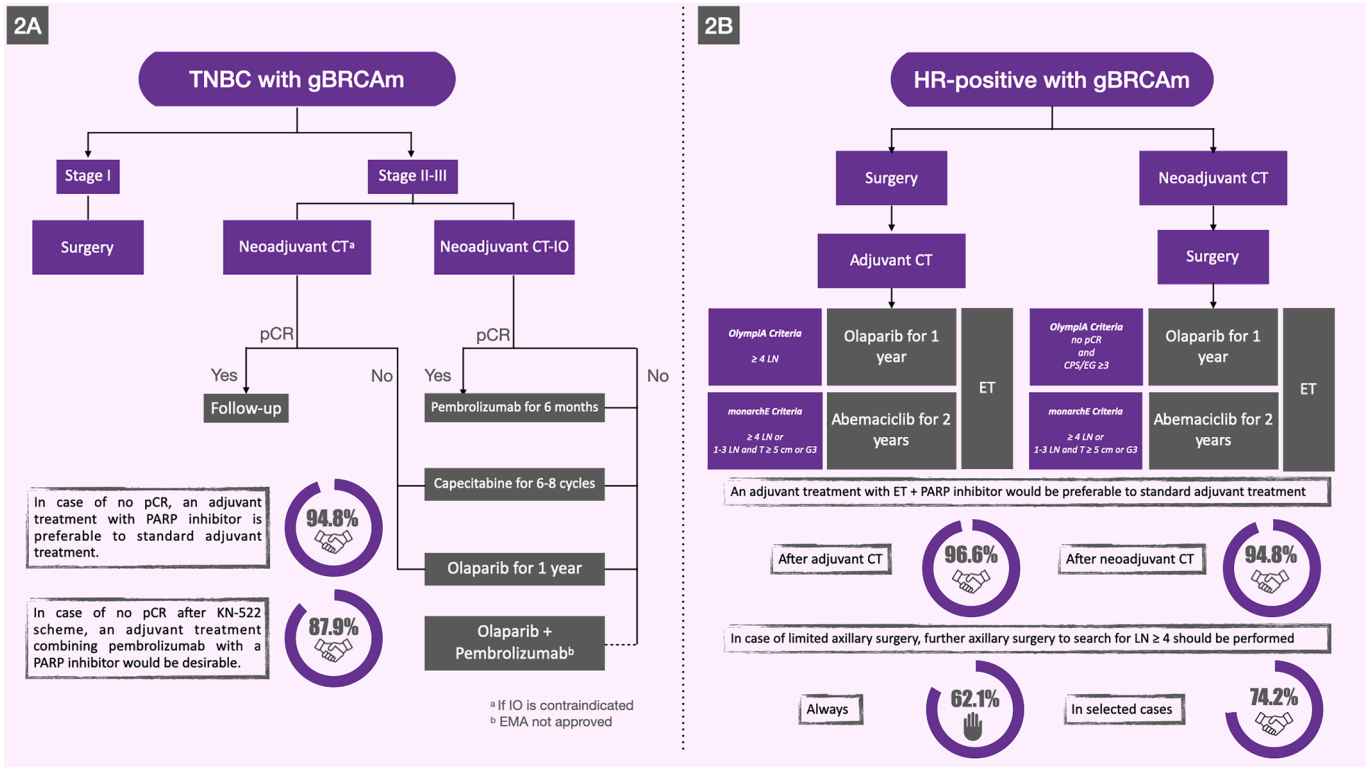

Fig. 2. Positioning of Olaparib for the treatment of early breast cancer for both TNBC (2A) and HR-positive (2B). *Abbreviations: CPS/EG: clinical and pathologic stage and estrogen receptor status and histologic grade; CT: chemotherapy; ET: endocrine therapy; gBRCAm: germline BRCA mutation; HR: hormone receptor; IO: immunotherapy; LN: lymph node; pCR: pathologic complete response; TNBC: triple negative breast cancer.*

Patterns of care in patients with PGVs of BRCA1-2

Olaparib in the treatment of eBC

Consensus was reached on five out of six statements regarding the positioning of olaparib in the algorithm for the treatment of patients with eBC bearing BRCA1/2 PGVs (Fig. 2).

- For patients with TNBC, stage II-III, with BRCA1/2 PGVs undergoing NAT based on anthracycline/taxanes and platinum salts with residual disease postNAT, an adjuvant treatment with PARP inhibitor is preferable to standard adjuvant treatment (capecitabine or continuation with pembrolizumab if KEYNOTE-522 scheme) (Fig. 2a).

  Consensus reached (agreement level = 94.8 %).

- For patients with TNBC, stage II-III, with BRCA1/2 PGVs undergoing NAT according to the KEYNOTE-522 scheme and with residual disease postNAT, an adjuvant treatment combining pembrolizumab with a PARP inhibitor would be desirable (Fig. 2a).

  Consensus reached (agreement level = 87.9 %).

- For patients with HR-positive BC, stage II-III, with BRCA1/2 PGVs who undergo NAT and eligible for olaparib, an adjuvant treatment with ET+PARP inhibitor would be preferable to standard adjuvant treatment (adjuvant ET+abemaciclib) (Fig. 2b).

  Consensus reached (agreement level = 96.6 %).

- For patients with HR-positive BC with BRCA1/2 PGVs with ≥ 4 positive LN who received surgery and after completion of adjuvant CT, treatment with ET+PARP inhibitor would be preferable to standard adjuvant treatment (adjuvant ET+abemaciclib) (Fig. 2b).

  Consensus reached (agreement level = 94.8 %).

- For patients with HR-positive BC with BRCA1/2 PGVs undergoing limited breast and axillary surgery, it would always be preferable to proceed with further axillary surgery (dissection or sampling) to search for LN≥4 for possible access to olaparib (Fig. 2b).

  Consensus NOT reached (agreement level = 62.1 % vs disagreement level = 37.9 %).

- For patients with HR-positive BC with BRCA1/2 PGVs undergoing limited breast and axillary surgery, it would be preferable to proceed with further axillary surgery (dissection or sampling) to search for LN≥4 per possible olaparib access only in selected cases.

  Consensus reached (agreement level = 74.2 %).

Olaparib in the treatment of ABC

Consensus was reached on all statements regarding the place of olaparib in the algorithm for the treatment of patients with BRCA1/2 PGVs in advanced setting (Fig. 3).

a) For patients with TNBC with BRCA1/2 PGVs, who have previously received anthracyclines/taxanes in the (neo) adjuvant setting:

a) If PDL-1 negative, first-line treatment with a PARP inhibitor would be preferable to standard CT.

Consensus reached (agreement level = 96.6 %).

b) If PDL-1 positive, first-line treatment with CT and immunotherapy (IO) would be preferable to PARP inhibitor.

Consensus reached (agreement level = 88 %).

b) For patients with TNBC with BRCA1/2 PGVs, already previously treated with CT-IO according to the KEYNOTE-522 scheme upon relapse of PDL1-positive disease, first-line treatment with PARP inhibitor would be preferable to CT-IO for advanced disease.

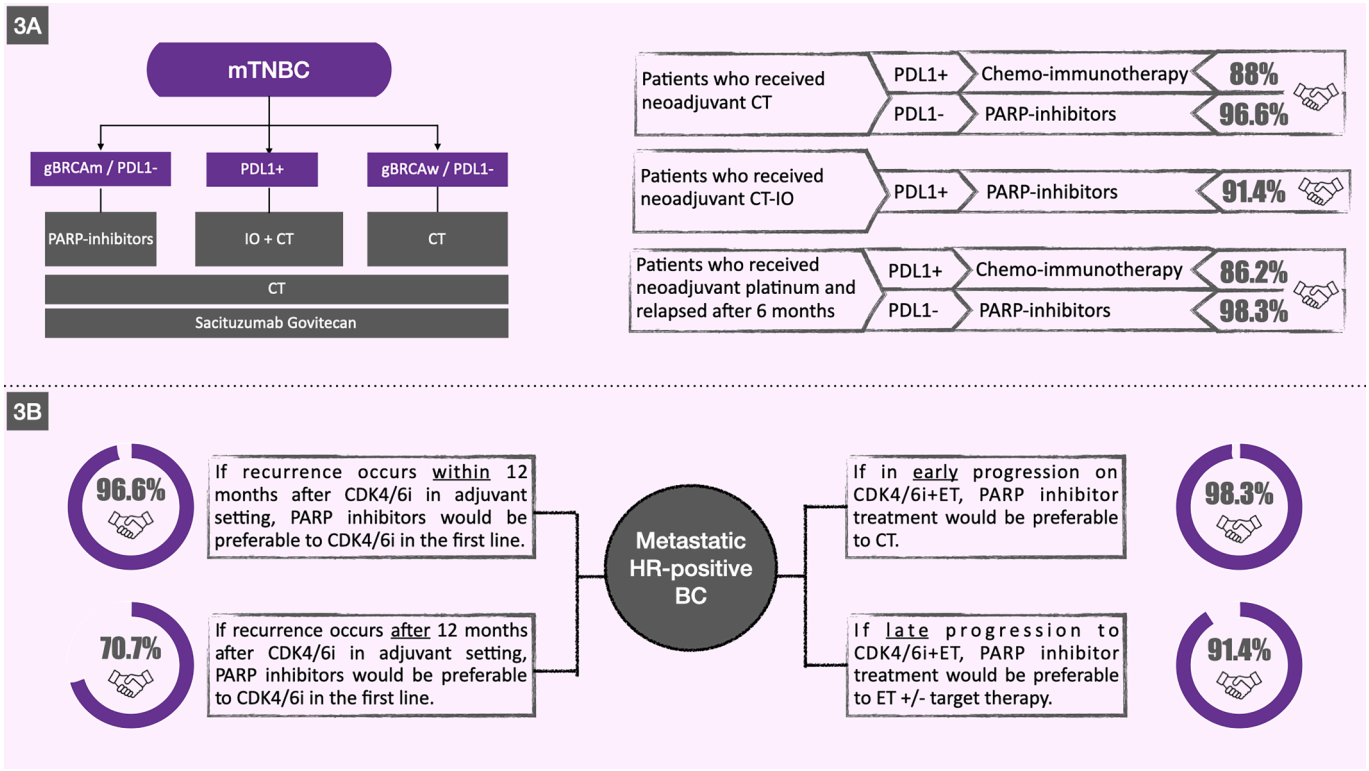

Fig. 3. Positioning of Olaparib for the treatment of metastatic breast cancer for both TNBC (3A) and HR-positive (3B). *Abbreviations: CDK4/6i: cyclin dependent kinases 4/6 inhibitors; CT: chemotherapy; ET: endocrine therapy; gBRCAm: germline BRCA mutation; gBRCAw: germline BRCA wild type; HR: hormone receptor; IO: immunotherapy; TNBC: triple negative breast cancer.*

Consensus reached (agreement level = 91.4 %).

c) For patients with TNBC with BRCA1/2 PGVs, already previously treated with CT with a regimen containing platinum salts in the (neo) adjuvant phase with relapse after 6 months:

d) If PDL-1 negative, first-line treatment with PARP inhibitor would be preferable to standard CT.

Consensus reached (agreement level = 98.3 %).

e) If PDL-1 positive, first-line treatment with CT-IO would be preferable to PARP inhibitor.

Consensus reached (agreement level = 86.2 %).

f) For patients with TNBC with BRCA1/2 PGVs, who have received first-line therapy (CT or CT-IO), therapy with a PARP inhibitor would be preferable to sacituzumab govitecan or another ADC, if accessible to prevent progression.

Consensus reached (agreement level = 91.4 %).

All statements regarding the treatment of metastatic TNBC are represented in Fig. 3A.

g) For patients with HR-positive BC with BRCA1/2 PGVs:

a) After failure of CT, ET and CDK4/6i in the (neo)adjuvant setting, treatment with a PARP inhibitor would be preferable to CDK4/6i in the first line in case of relapse within 12 months.

Consensus reached (agreement level = 96.6 %).

b) After failure of CT, ET and CDK4/6i in the (neo)adjuvant setting, treatment with a PARP inhibitor would be preferable to CDK4/6i in the first line in case of relapse after 12 months.

Consensus reached (agreement level = 70.7 %).

c) In the case of early progression on CDK4/6i with ET, treatment with a PARP inhibitor would be preferable to CT.

Consensus reached (agreement level = 98.3 %).

d) In the case of late progression on CDK4/6i with ET, PARP inhibitor treatment would be preferable to ET +/- targeted therapy.

Consensus reached (agreement level = 91.4 %).

All statements regarding the treatment of metastatic HR-positive are represented in Fig. 3B.

Management of PARP inhibitors and follow-up

Toxicity prophylaxis of PARP inhibitors

Both statements concerning prophylactic measures to prevent toxicities in patients receiving PARP inhibitors did not achieve consensus.

h) The use of erythropoietin for the treatment of iatrogenic anemia would be appropriate.

Consensus NOT reached (agreement level = 55.1 % vs disagreement level = 44.9 %).

i) Regular use of 5-HT3 receptor antagonists as primary prophylaxis for iatrogenic emesis would be appropriate.

Consensus NOT reached (agreement level = 56.8 % vs disagreement level = 43.2 %).

Toxicity management PARP inhibitors

All statements regarding the management of patients receiving PARP inhibitors have achieved consensus agreements.

1. Total blood count should be carefully monitored every two weeks during the first two months of treatment

   Consensus reached (agreement level = 89.7 %).

2. In case of grade 2 non-hematological adverse reaction, the recommended dose should be decreased by one level

   Consensus reached (agreement level = 82.8 %).

3. Monthly clinical evaluation for the initial four to six months should be considered

   Consensus reached (agreement level = 98.3 %).

4. Following an initial period of 4–6 months of therapy with PARP inhibitors, if well tolerated, patients should undergo clinical evaluation every three months.

   Consensus reached (agreement level = 88 %).

Special consideration of follow-up management

Radiological surveillance after bilateral mastectomy

In patients with pathogenetic variants of BRCA who have had BC and undergone bilateral mastectomy, it is preferable to perform breast MRI as the first post-surgical check-up to define any residual glandular tissue and, if absent, continue the follow-up with only a physical examination and breast ultrasound every 6—12 months.

Consensus reached (agreement level = 84.5 %).

Hormone replacement therapy (HRT) after bilateral mastectomy and salpingo-oophorectomy

In young patients with pathogenetic variants of BRCA who received surgery for TNBC and subjected to bilateral mastectomy and risk-reducing salpingo-oophorectomy (RRSO), it would be appropriate to consider HRT until the age of physiologic menopause.

Consensus NOT reached (agreement level = 62.1 % vs disagreement level = 37.9 %).

Discussion

The study covers the most important issues regarding the management of patients with BC and PGV of BRCA1/2 using a modified Delphi approach to capture levels of agreement/disagreement among a scientific panel of internationally recognized BC oncologists (Table 2). Its goal was to establish a consensus based on expert opinion supported by both evidence and routine clinical practice. The overall results from this survey indicate a substantial consensus among the panel for most of the statements discussed, with some relevant issues raised during the debate process that are worth of sharing.

Genetic testing of critical genes in BC

Historically, the genetic testing for BRCA1/2 has been performed via polymerase chain reaction (PCR) amplification of specific exons and adjacent intronic sequences[15]. The Panel recognized the increasing importance of the implementation of massively parallel next-generation DNA sequencing (NGS) technology, which enables the analysis of a greater number of genes[16]. These include sequencing of several high-to-moderate penetrance genes beyond BRCA, including ATM, CHEK2, PALB2, PTEN, BARD1, RAD51C, RAD51D and TP53[17]. Besides providing accurate genetic sequencing at a single time, NGS offers an increased power to detect new or rare pathogenic variants along with an increasing number of variants of uncertain significance (VUS)[18]. NGS panels examine other genes that are less frequently encountered and whose contribution to cancer development remains unknown. Consequently, interpreting NGS panel's findings can be challenging due to these complexities. Because of the continuous advances in cancer genetics, the Panel discussed the opportunity of using an individual trace-back approach, both to identify any previously undetected alterations in patients who were tested in the past with outdated techniques and to capture the repositioning of VUS over-time.

As the demand for genetic testing in BC patients is rapidly increasing, the Panel emphasized the need to expedite the testing's process and discussed about the novel methods of genetic counselling. A method that is universally recommended is the *mainstream-consent pathway*[19]. In

Table 2
Summary of Key Areas and Consensus Recommendations. Abbreviations: BC: breast cancer; CDK4/6i: cyclin-dependent kinases 4/6 inhibitor; HR: hormone receptor; IO: immunotherapy; LN: lymph node; MRI: magnetic resonance imaging; PARP: poly(ADP-ribose) polymerase.

Area	Recommendation	Key Issue
Genetic testing	Offer genetic testing to TNBC Offer HR-positive patients < 40 years old	Use of multigene panels vs. single-gene testing for BRCA1/2
Early BC	Use adjuvant Olaparib for TNBC with residual disease irrespectively from neoadjuvant regimen Use adjuvant Olaparib for HR-positive with ≥ 4 LN.	Integration/Decision of pembrolizumab and olaparib post-KEYNOTE-522
Advanced BC	Consider PARP inhibitors after progression to CDK4/6i in HR+BC Consider first-line IO even in BRCA	Sequencing of IO and PARP inhibitors in treatment
Toxicity management	Regular monitoring and timely intervention for hematologic toxicities	Primary prophylaxis of nausea and anemia
Follow-up strategies	Use MRI for initial post-surgical check-up post-mastectomy	Evidence supporting continued MRI surveillance

certain circumstances, the oncologist may request genetic testing directly from the consultation to the consent process, provided that specific criteria are met (family history and predefined clinicopathological factors according to guidelines). This approach is currently being used in several hospitals since it facilitates the process in terms of time and resources, if the characteristics of the patients to be tested are clearly defined[20,21]. Another option under evaluation, is the somatic-to-germline pathway, already adopted in other contexts but not in BC, which considers first the tumor BRCA genetic sequencing and then the targeted germline confirmation in case of pathogenic somatic variant, eventually favoring the enrichment in PGV detection [22].

The Panel unanimously agreed that genetic testing is essential prior to initiating treatment in patients with TNBC regardless of age, and for HR-positive patients younger than 40 years, regardless of family history or gender. Moreover, the Panel endorses genetic testing for therapeutic intent in HR-positive eBC with at least 4 LN after axillary dissection or with a CPS/EG score ≥ 3 after NAT. These agreements fully support the new criteria for genetic-testing (Table 1) and reasonably expand the population of probands in line with both epidemiological estimates and current treatment indications.

Patterns of care in patients with BC and PGVs of BRCA1/2

The second section of the survey aimed to capture the therapeutic attitude of the Panel when various treatment alternatives are available for BC patients with PGV of BRCA1/2.

Since the OlympiA study is the only adjuvant RCT to have demonstrated a significant OS benefit in selected cases of eBC at higher risk of recurrence [23]. The alternative of adding adjuvant abemaciclib in high-risk HR-positive/HER2-negative patients, as in the monarchE trial, still lacks the OS advantage, although a promising PFS benefit has been documented so far [24]. The critical issue is the intricate interaction among CDK and BRCA that is still unclear. It has been suggested that the patients harboring PGV of BRCA2 may exhibit a lower susceptibility to CDK4/6 inhibitors, possibly because of RB1 target-loss, located in close proximity to altered BRCA2.

The survival benefit of adjuvant olaparib for patients with eTNBC has not yet been matched by the introduction of both pembrolizumab and capecitabine in the (neo)adjuvant setting because of the uncertainty of the OS benefit as observed in the KEYNOTE 522 trial [25] and in GEICAM-COBOMA trial [26], especially for basal-like tumors [27]. Nonetheless, the integration of olaparib with other treatment options is now considered with interest and finally the Panel expressed a preference for the combination/sequencing of pembrolizumab and olaparib in selected cases, based on the encouraging results reported in metastatic BC [28,29]. However, conclusive data demonstrating the combination is more effective than a PARP inhibitor alone in the curative setting are still lacking.

The requirement for a minimum of 4 pathological LN at surgery to prescribe adjuvant olaparib in HR-positive eBC was another issue addressed in the survey. Clinical trials have shown that the axillary LN dissection (ALND) in the setting of limited nodal involvement has no impact on survival and local control in case of patients with eBC and limited nodal involvement. Therefore, an increasing number of patients are now receiving the sentinel LN biopsy alone as mean of de-escalation surgery. The Panel has reached a consensus to recommend ALND only in specific cases, leading to safer procedures with fewer surgical complications and reduced morbidity [30,31].

In the advanced setting, the Panel was asked about different clinical situations depending on subtypes and predictive biomarkers.

The landscape of first-line treatment in metastatic TNBC changed dramatically since the introduction of IO in PD-L1 positive disease [32], based on the results of two pivotal RCTs (IMpassion-130 and KEYNOTE-355) that reported a survival advantage with the addition of immune-check-point inhibitors (ICI) to standard CT [32–35] Accordingly, the Panel expressed a strong preference for IO over PARP inhibitors in eligible patients, reserving PARP inhibitors as a viable option in the subsequent lines of treatment following IO [36].

Similarly, for HR-positive metastatic BC, after progression on a first-line CDK 4/6 inhibitors, the Panel favored treatment with PARP inhibitors over ET and targeted therapy or conventional CT. In this context, patients who received PARP inhibitors significantly increased PFS, doubled ORR and showed a delayed global QoL deterioration compared to those treated with different types of standard CT[13]. It is important to clarify that patients who present with de novo metastatic disease typically undergo treatment with CDK4/6 inhibitors, except for visceral crisis, followed by a sequence of ET and CT. PARP inhibitors are approved following treatment with anthracyclines and taxanes, which are commonly preferred in later stages. This is because clinical trials showed promising results particularly when administered early in the treatment algorithm, as 40.8 % of pa- tients receiving first-line treatment in the olaparib arm were alive at 3 years compared with 12.8 % of controls[37].

Patients with BRCA1/2 PGVs may have a higher vulnerability to platinum-based salts[38]. However, there are no direct comparison between platinum-derived salt and PARP inhibitors as these were absent in the control arms of the main studies. Translating the knowledge from studies on OC the response to PARP inhibitor may be influenced by the presence of resistance or sensitivity to platinum[39]. A retrospective analysis revealed that patients who had a platinum-free interval of more than 6 months had longer PFS and a higher disease control rate with treated with PARP-inhibitors[40]. In contrast, the efficacy of platinum following PARP inhibitors is poor. The subgroup analysis of OlympiAD demonstrated a benefit in PFS regardless of receiving prior platinum, received by 30 % of patients[41].

It must be acknowledged that when this consensus was conducted the only therapeutic options available after CDK4/6 inhibitors were fulvestrant and the combination of exemestane and everolimus. The availability of oral SERD, PIK3CA and AKT inhibitors would have likely impacted the response. Nevertheless, there is limited evidence regarding the optimal sequencing following the first-line treatment with CDK4/6 inhibitors and further data are eagerly awaited to support an informed

decision, especially in patients with BRCA1/2 PGVs.

Management of PARP inhibitors

The most common side-effects of PARP inhibitors are hematologic toxicity (neutropenia, anemia and thrombocytopenia), nausea, and fatigue. In the OlympiA study, 23.5 % of participants experienced some degree of anemia, 8.7 % of which classified as severe. As a result, approximately 25 % of patients had their dose reduced and 5.8 % of patients required blood transfusion. Overall, the discontinuation rate was 9.9 %, mainly due to nausea (2 %) and anemia (1.8 %). These results were consistent with the findings observed in the metastatic setting, where severe anemia appeared to be more pronounced with talazoparib compared to olaparib (38.5 % vs 16.8 %) while nausea was common with both drugs and could be effectively managed with antiemetics [42,43]. In a Bayesian fixed-effects indirect treatment comparison, it was predicted that olaparib would have a lower risk of common hematologic adverse events of any grade (anemia, thrombocytopenia, and neutropenia; odds ratios (OR) 0.37, 0.23, and 0.54, respectively) and alopecia (OR 0.22), compared to talazoparib. On the contrary, there was an increased risk of nausea (OR 2.39) and vomiting (OR 2.13) compared to talazoparib[44].

Regarding the implementation of primary prophylaxis for both anemia and nausea, the Panel was divided but there was consensus on the need for a strict monitoring during the first months of treatment with recommendation for a timely intervention to mitigate toxicities through supportive care and/or dose-adjustment approach.

Follow-up of patients with BC and BRCA1/2 PVGs

Bilateral mastectomy is a preventive surgical option for patients carrying BRCA1 or BRCA2 GVPs at risk of developing contralateral BC [45]. In a study conducted by Metcalfe et al., 18.4 % of 810 women with stage I or II BC and BRCA1/2 PGVs developed a contralateral breast cancer. Women with BRCA1 had a 15-year actuarial risk of contralateral BC of 36.1 %, while those with BRCA2 had a risk of 28.5 % [46]. Similarly, another prospective cohort study of 6036 BRCA1 and 3820 BRCA2 female carriers reported a 20-year cumulative risk of contralateral BC around 40 % for BRCA1 and 26 % for BRCA2[47]. This risk is reduced by 90 % with bilateral mastectomy[48]. The Panel discussed a first post-surgical breast MRI assessment after preventive surgery to detect any residual glandular tissue and to calibrate to optimal subsequent surveillance. In the presence of residual glandular tissue, continued MRI surveillance should be recommended in a case-by-case basis and otherwise omitted[1]. Residual fibroglandular breast tissue is associated with a remaining local oncologic risk following mastectomy, as indicated in the study by Deutschmann which supports the rationale for initial MRI post-mastectomy to accurately assess any residual tissue and inform subsequent follow-up strategies[49]. However, there is a lack of validated tools to measure and quantify residual breast tissue, and this is an important area for research and diagnostic improvement[50,51].

To mitigate the high risk of developing ovarian cancer in patients with BRCA1/2 PGVs[52], RRSO is recommended between ages 35 and 40 for BRCA1 and between ages 40 and 45 for BRCA2. The risk of ovarian cancer is approximately 39–44 % for patients with BRCA1 PGVs and 11–17 % for those with BRCA2 PGVs[47,53]. Surveillance of these patients is challenging because no current technique can effectively detect early ovarian cancer. Although the benefit is uncertain, international guidelines suggest ovarian screening with transvaginal ultrasound every six months and serum CA125 determination until RRBSO is performed[1]. A *meta*-analysis conducted by Eleje et al. showed an increase in overall survival among women who had RRSO versus women without RRSO who were BRCA1 GPV carriers (HR 0.30, 95 % CI 0.17 to 0.52) and BRCA2 GPV carriers (HR 0.44, 95 % CI 0.23 to 0.85)[54]. The panel was questioned about the use of HRT in pre-menopausal patients who underwent bilateral mastectomy and RRSO for eTNBC, but no consensus was reached. HRT usually helps relieve menopausal symptoms, as urogenital and vasomotor symptoms and showed some advantages on cardiovascular system and bone-health[55]. Nonetheless, there is a reduced level of awareness of the impact of menopausal symptoms and the potential benefits of different types of HRT. Moreover, patients with a high genetic risk of BC are likely to overestimate the negative effects of HRT while underestimating its positive health effects [56]. Several studies have reported reassuring evidence in HR-negative BC patients receiving HRT and a metanalysis of more than 1100 women with PGV of BRCA showed there was not a significantly higher BC risk with HRT after RRSO (HR=0.98; 95 % CI 0.63–1.52)[57]. However, available data on the role of HRT in BC survivors and BRCA1/2 PGVs are limited and further research using contemporary different types of HRT is needed to draw definitive recommendation.

Conclusions

This document represents the first Italian consensus on the treatment of patients with BC and BRCA1/2 genetic alteration with special focus on the use of PARP inhibitors. We have addressed several practical topics, including genetic testing access, the patterns of care in BC patients with BRCA1/2 PGVs, and the clinical management of PARP inhibitors and follow-up. A structured methodology was adopted to provide a set of prioritized considerations/consensus statements reflecting the Panel position. The most relevant findings were thoughtfully discussed and, for statements not reaching the consensus threshold, possible interpretations were put forward.

While the Panel converged on the majority of the topics regarding BRCA1/2 genetic testing and the use of PARP inhibitors, nonetheless there were still some areas of divergence (i.e. axillary surgical dissection for therapeutic purposes and the use of HRT in bilateral mastectomy and RRSO) whereby a renewed research effort is required to potentially enhance the management of patients with a higher genetic susceptibility.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2024.102815.

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