Editorial Commentary

Can we successfully define and target BRCA-like breast cancers?

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Triple negative breast cancers (TNBCs) have long been associated with aggressive disease biology and a worse prognosis in the setting of advanced breast cancer (ABC). Despite advances in the treatment with protocols using immunotherapy and novel antibody drug-conjugates (ADCs), there remains an unmet need for patients with advanced TNBC. Homologous recombination deficiency (HRD) represents a disruption in the usual DNA repair process by the homologous recombination repair (HRR) pathway. The *BRCA 1* and *BRCA 2* genes are centrally involved in the double-strand DNA break repair process and pathogenic germline BRCA1 and BRCA2 mutations are identified in 10–20% of patients with TNBC, presenting a potential therapeutic target (1). The EMBRACA and the Olympiad studies sought to compare the efficacy of the PARP inhibitors talazoparib and olaparib, respectively, to standard chemotherapeutic agents in patients with ABC and germline mutations in BRCA1/2. Both studies established the role of poly (ADP-ribose) polymerase (PARP) inhibitors for the treatment of advanced HER2-negative breast cancer harbouring a pathogenic BRCA mutation, with a nearly 3-month progression-free survival (PFS) advantage and a doubling of the overall response rate (ORR) with talazoparib and olaparib, relative to standard single-agent chemotherapy (2,3). Additionally, combinations of veliparib with platinum doublet chemotherapy have previously shown an improvement in PFS in patients with pathogenic germline BRCA mutations, with minimal increase in hematological toxicity, in contrast to combination studies with other PARP inhibitors (4). Given the relatively low frequency of pathogenic BRCA1/2 germline mutations, it remains uncertain whether there is a potential role for PARP inhibitors in germline BRCA wildtype patients with evidence of HRD, although benefits have been demonstrated in similar populations with ovarian and prostate cancer (5).

The HRD phenotype is observed when there is a significant disruption in the usual DNA repair process by the HRR pathway. This is typically mediated through loss of function mutations in key genes, namely *BRCA1* and *BRCA2*, but may also involve other genes including *PALB2*, *ATM*, *RAD51*, amongst others, and can also be caused by epigenetic modification such as hypermethylation of the *BRCA1* promoter region (6). There has been speculation that 40–60% of TNBCs may express a BRCA-like phenotype in the absence of pathogenic BRCA mutations (7). However, the definition of HRD and refinement of what defines a BRCA-like phenotype remains ambiguous and the use of this as an informative biomarker to guide treatment in breast cancer has not proven fruitful thus far.

In the study accompanying this editorial published in *Lancet Oncology* in January 2023, Rodler *et al.* report the

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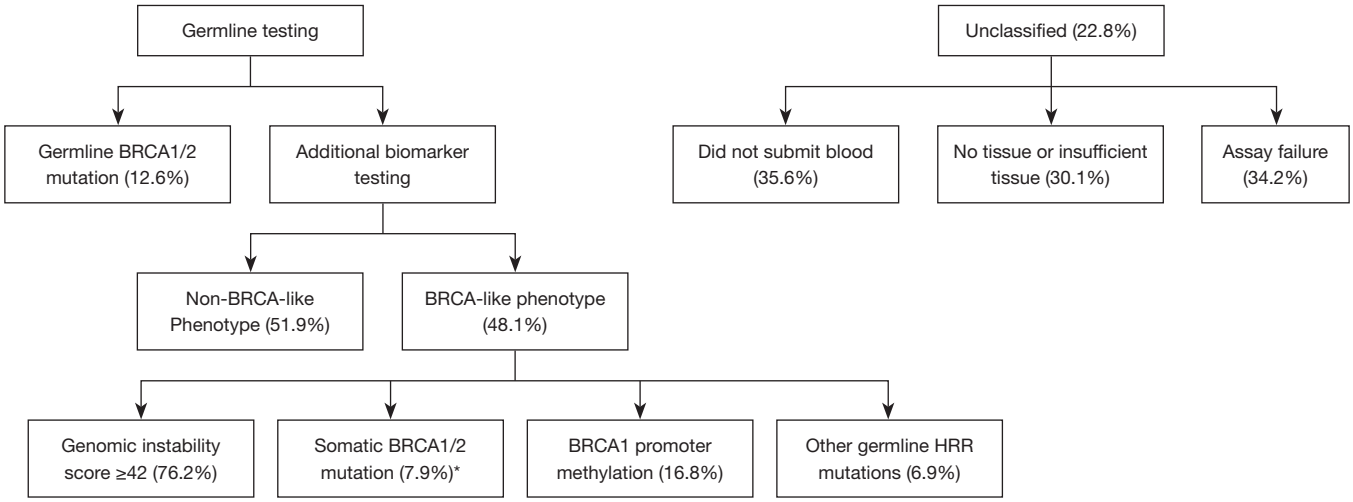

Figure 1 Distribution of patients in the biomarker groups and proportion assigned to the BRCA-like phenotype based on the predefined qualifying markers (8). Germline testing was the first step for group allocation. If no germline mutation was identified, patients went on to have additional biomarker testing which comprised four predefined markers in rank order of priority, as listed from left to right. A positive result in any of these resulted in assignment to the BRCA-like phenotype. Those who underwent additional biomarker testing and could not be classified in the BRCA or non-BRCA phenotypes, comprising 22.8% of the overall study population, are shown in the right panel of this figure. *, total exceeds 100% as all 8 patients with somatic BRCA mutations had been classified in the BRCA-like phenotype by genomic instability score. HRR, homologous recombination repair.

results of the S1416 randomized double-blind, placebo-controlled phase 2 study of cisplatin 75 mg/m^2 with either veliparib 300 mg twice daily on days 1–14 or placebo for each 21-day cycle (8). Following randomisation, central testing was performed using the BROCA-HR test as the first step, which comprises a group of 40 genes with recognized involvement in hereditary breast and ovarian cancer or HRR. Patients were subsequently assigned to a BRCA 1/2-mutated, BRCA-like or non-BRCA like group (*Figure 1*). BRCA-like was defined using 4 markers, in rank order of priority, comprising either a genomic instability score of 42 or higher based on the myChoice CDX Plus assay from Myriad, a somatic BRCA1/2 mutation, BRCA1 promoter hypermethylation or germline mutations in HRR genes other than BRCA. Those assigned to the BRCA-like group had a median PFS of 5.9 months in the cisplatin and veliparib group versus 4.2 months in the cisplatin and placebo group, with a statistically significant hazard ratio of 0.57. In contrast, the patients in the non-BRCA like group derived no further benefit from the addition of veliparib, with a median PFS of 3–4 months.

This study is of interest for a number of reasons, primarily as it is one of the largest prospective studies to show a clinically relevant PFS advantage for patients with advanced TNBC and a BRCA-like phenotype, in the absence of a pathogenic germline BRCA mutation, and truly represents a concerted effort with accrual across 154 community and academic sites. Of additional interest is the fact that the rate of grade 3 hematological toxicity was not substantially higher with the addition of veliparib to high dose cisplatin, in contrast to combination studies utilizing other PARPs and cytotoxic drugs. This highlights the differences between the different PARP inhibitors and likely reflects the lower PARP trapping potency of veliparib (6,9), which may ultimately revive its role in the ABC space for combination strategies. The study also allowed for a discontinuation of the chemotherapy backbone after a minimum of 4 cycles, with a progressive uptake of monotherapy over time and may present an opportunity for a chemotherapy-free interval for some patients.

The study enrolled its first patient in 2016, and in the midst of the study, both talazoparib and olaparib were approved for use in germline BRCA-mutation positive patients. Thus, the sample size for the BRCA1/2-mutated group was smaller than projected and limits the conclusions that can be drawn for this group. Additionally, patients were randomised upfront and subsequently underwent biomarker panel testing. This resulted in a large cohort consisting

of 23% of subjects, defined as unclassified, due to a lack of blood/tissue or assay failure, with a particularly poor prognosis relative to the other groups. In fact, while the median follow-up was relatively short at 11.1 months, 84% of patients had died at the time of analysis despite the fact that nearly 70% had not received prior systemic therapy in the advanced setting, which truly underscores the poor prognosis and unmet need for these patients.

While this study provides renewed interest for combination approaches with PARPs, it also raises questions about the combination strategies, definition of homologous repair deficiency, BRCA-like phenotype and genomic instability or HRD scores. Although the combination of platinum drugs with a PARP inhibitor are a rational combination, they exploit a similar mechanism of action with DNA damage and repair deficiency leading to synthetic lethality. With the development of novel antibody-drug conjugates and the increasing use of platinums in early stage TNBC, the exploration of ADCs with a topoisomerase-1 inhibitor payload and other DNA-damaging payloads may be of greater interest for combination approaches given the intrinsic DNA damage repair deficiency in these patients. Additionally, combination strategies of immunotherapy with an ADC have shown promise in early phase trials and strategic combinations with a PARP inhibitor could be an interesting approach given the alteration to tumour microenvironment which could yield synergistic effects (10).

Moreover, defining HRD has been an evolving paradigm from the time of trial conception relative to today and there remains no standardized approach to distinguish homologous repair deficiency clinically nor do the tests align in this classification. Prior studies have demonstrated that HRD scores predict response to platinum-containing neoadjuvant chemotherapy in early stage TNBC (11). The Gepar Sixto study also demonstrated that HRD was an independent predictor of pathologic complete response (pCR) with a substantial increase in pCR rates when carboplatin was used in the HR deficient tumours, though this did not translate to a disease-free survival (DFS) advantage relative to the HR non-deficient group (12). Similarly, higher HRD scores have been associated with higher response rates in the advanced HER2-negative breast cancer setting with talazoparib (13), which has also been demonstrated in other tumour types. Therefore, there may be a role for exploration of the impact of the genomic instability score on ORR and clinical benefit rates. There is also a role for validation of other HRD blood and tissue based assays as we consider the optimal companion diagnostic assays and refine biomarker panels for use in routine clinical practice. The design of future trials could also likely incorporate dynamic markers of response and shed some light on mechanisms of resistance and greater sensitivity to PARP inhibitors, given that studies such as Olympiad reported a portion of long-term responders at the final overall survival (OS) analysis (14).

The study defined 7% of participants as harbouring HRR mutations other than BRCA1/2 although the genes involved were not described. Given that both olaparib and talazoparib have shown efficacy in patients with pathogenic PALB2 mutations (13,15), but not in other HRR-associated genes, supplementary data on this subgroup would be of interest. Additionally, it should be noted that the 8% of patients assigned to the BRCA-like group due to somatic BRCA 1/2 mutations had all been identified by other criteria, including the genomic instability score, which identified 76% of the included patients in the study (8). These findings, along with clinical trial data and mechanistic knowledge, add further support to the notion that patients with somatic BRCA mutations should be treated similarly to germline BRCA mutation carriers.

Lastly and perhaps most importantly, only 10% of patients enrolled in the study had received prior platinum therapy and 4% had received a checkpoint inhibitor. Thus, the mutational landscape and genomic instability in a modern cohort would perhaps differ due to selective pressures and acquired resistance in a patient population treated with standard of care treatment which frequently comprises carboplatin and pembrolizumab. That being said we would postulate that there may be more genomic instability observed for patients who relapse following exposure to platinum and checkpoint inhibition.

Ultimately, this study demonstrates that the combination of veliparib with high-dose chemotherapy is feasible in BRCA-like advanced TNBC without pathogenic germline BRCA1/2 mutations (8). The activity of PARP inhibitors in this group has not been demonstrated previously in the breast cancer space and paves the way for future research with biomarker-informed trials utilizing HRD. However, the clinical applicability of the trial results are limited due to the challenges in assigning patients to this group a priori, the large proportion of unclassified cases and the heterogeneity in defining HRD with inconsistent overlap across assays. The definition of BRCA-like and the optimal HRD testing assays require validation to define clearly responsive cohorts for future studies. Combinations of novel PARP inhibitors with lower myelosuppressive profiles

and newer agents including ADCs are likely to be of greater interest in light of these data supporting the benefits of veliparib beyond germline BRCA-mutated tumours. Can we successfully define and target BRCA-like tumours in breast cancer? We believe that this study supports this approach and presents a first step in an area that has potential to provide new options for the treatment of advanced TNBC.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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