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MEETING REPORT

Part 2 – Highlights of the San Antonio Breast Cancer Symposium 2023

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1. Introduction

The annual SABCS combines the principles of multidisciplinary management with the basic science underlying pathobiological processes in breast cancer. The 46th meeting was held at the Henry B Gonzales Convention Centre in downtown San Antonio, TX, USA on 5–9 December 2023. The symposium delivers a range of presentations covering basic, translational and clinical sciences. Important trials that are potentially practice changing are often presented as late breaking news and published concurrently or shortly thereafter. This is the second of a two-part report highlighting important presentations and focuses on topics relating to pregnancy after breast cancer in BRCA mutation carriers, CDK 4/6 inhibitors for early and advanced breast cancer and immunotherapy with checkpoint inhibitors for breast cancer. Breast screening and loco-regional treatments for breast cancer were covered in the first part of this meeting report.

1.1. Pregnancy & breast cancer

More than 12% of young women with breast cancer are carriers of pathogenic gene variants (PGV) in BRCA-1 and BRCA-2 genes [1]. There are potential concerns about the detrimental prognostic effect of pregnancy following a breast cancer diagnosis among BRCA carriers. There is limited evidence for the safety of pregnancy in this group of women and it is unclear whether there is a negative effect of a PGV on reproductive potential. Matteo Lambertini (University of Genoa and San Marino Hospital, Genoa, Italy) reported results of an international multicenter retrospective cohort study that examined the likelihood of pregnancy among young BRCA mutation carriers with a personal history of breast cancer. This large study recruited almost 5000 patients from 78 centers around the world over a 20 years period between January 2000 and December 2020. All patients had stage I–III breast cancer and were aged $\leq$40 years with a PGV in BRCA-1 or BRCA-2. The primary end points were pregnancy rates and disease-free survival (DFS) and it was commented that a relatively high proportion of breast cancer patients became pregnant at 10 years (22%) compared with other studies. Interestingly, more hormone receptor negative than positive patients successfully conceived (26 vs 18%) and two-thirds of pregnant patients had hormone receptor negative disease. This might be attributable to lack of hormonal treatment that increased the chance of pregnancy – especially in the era of extended hormonal therapy. The mean time to pregnancy was 3.5 years and this was significantly shorter for hormone receptor negative (3.2 years) compared with hormone receptor positive (4.3 years) disease ($p < 0.01$). There were no significant differences in rates of breast cancer recurrence between pregnant and nongravid women at a median follow-up of 7.8 years (Hazard ratio (HR): 0.99; 95% CI: 0.81–1.2). A rather curious finding was significantly longer Breast cancer-specific survival (HR: 0.59. 95% CI: 0.41–0.86) and OS (HR: 0.58, 95% CI: 0.4–0.85) for the pregnant group of women. Lambertini emphasized that there was no obvious explanation for this observation and the key message from this study was not to imply that pregnancy was protective but rather to convey the safety of pregnancy after breast cancer for mutation carriers in terms of recurrence risk (only 0.9% babies were born with congenital abnormalities). Continuing the pregnancy theme, Hatem Azim (Technologico Del Monterrey, Mexico) discussed results of a secondary analysis of the POSITIVE trial that was presented the previous year at SABCS2022 [2]. His team evaluated the effects of fertility preservation and assisted reproductive technologies (ART) among a group of 497 patients who had paused endocrine therapy in an attempt to become pregnant. Three-quarters of these women become pregnant at a median follow-up of 41 months since enrolment into the trial within 1 month of stopping endocrine therapy. a third (36%) had used embryo/oocyte preservation and just under

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half (43.3%) some form of ART (e.g., ovarian stimulation). The majority of women who used cryo-preserved embryo transfer (82.4%) or ART (67.5%) achieved conception with pregnancy rates more likely for younger women (<35 years) and those reliant on embryo transfer – the latter was independently associated with an increased chance of pregnancy (OR = 2.41). Furthermore, cryo-preservation with ovarian stimulation did not increase the risk of breast cancer compared with non users (9.7 vs 8.7%).

1.2. Immunotherapy with checkpoint inhibitors for early stage breast cancer

Joyce O'Shaughnessy (Baylor University Medical Centre, Houston, TX, USA) presented results of the Phase III KEYNOTE-756 study that evaluated addition of pembrolizumab to chemotherapy in high risk early stage hormone receptor positive, HER2 negative breast cancer patients. A total of 1278 patients from Eastern Europe, China and other countries were randomized 1:1 to receive immunotherapy ($n = 635$) or not ($n = 634$). Stratification of patients was based on several factors including PD-L1 status (combined positive score [CPS] $\geq$10 vs <1) and nodal status (positive or negative). Dual primary end points were pathological complete response (pCR) and event-free survival with pCR defined as ypT0Tis and ypN0. Residual cancer burden at the time of surgery was an exploratory end point within this study that has a median follow-up of 33.2 months at final pCR analysis. There was a significantly higher rate of pCR from addition of pembrolizumab to chemotherapy and endocrine therapy within the intention-to-treat population (24.3 vs 15.6%) with an estimated absolute difference of 8.5% (95% CI: 4.2–12.8). There was consistent benefit across all pre-specified subgroups for immunotherapy but pembrolizumab treatment effect increased with CPS ($\leq$1 vs $\geq$10). Results for event-free survival remained immature at the time of analysis and further follow-up is awaited.

Results of the ALEXANDRA/Impassion030 trial were presented by Michall Ignatiadis (Institute Jules Bordet, France). This randomized Phase III trial assessed the potential benefit of administering adjuvant immunotherapy following primary surgery for smaller triple negative breast cancers (TNBC). Hence all patients underwent initial surgical resection of the tumor and were subsequently randomized 1:1 to receive immunotherapy with the anti-PD-L1 monoclonal antibody atezolizumab ($n = 1101$) or not ($n = 1098$). This was given simultaneously with chemotherapy and continued for 12 months. Patients were stratified for type of surgery, nodal and PD-L1 status. At a median follow-up of 25.3 months, there was no improvement in the primary end point of invasive DFS (HR: 1.12, 95% CI: 0.87–1.45). There was a similar lack of benefit from immunotherapy in PD-L1 positive patients who experienced equivalent numbers of events for atezolizumab ($n = 77$) and placebo ($n = 73$) (HR: 1.03, 95% CI: 1.02–1.96). These results therefore do not support use of adjuvant atezolizumab for patients undergoing primary surgery for TNBC and Ignatiadis postulated that the absence of tumor at the time of administration of immunotherapy might lead to less robust T-cell activation. The majority of TNBC (stages II and III) receive upfront chemotherapy combined with immunotherapy that continues as adjuvant therapy [3].

1.3. CDK 4/6 inhibitors for breast cancer

The prospective Phase II PARSIFAL study evaluated fulvestrant and letrozole as the preferred endocrine partner for *combined* therapy with a CDK 4/6 inhibitor (palbociclib) for advanced hormone receptor positive, HER2 negative previously untreated breast cancer [4]. There were no significant differences in progression-free survival (PFS) between the two endocrine combinations of palbociclib + fulvestrant or palbociclib + letrozole. Antonio Llombart-Cussac (University Hospital Arnau de Vilanova, Spain) explained how the follow-on PARSIFAL-LONG study aimed to determine whether more prolonged follow-up was associated with an OS benefit from either endocrine partner. No significant differences emerged between these two endocrine combinations at a median follow-up of 65.4 months (95% CI: 57.8–70) for OS and 33.2 months (95% CI: 27.7–39.5) for PFS. However, a combined analysis for PFS and OS for both endocrine partners (plus palbociclib) identified a group of early progressors with a median PFS <12 months. It was concluded that this group of patients had a less favorable outcome compared with those remaining progression-free at 12 months with median OS of 18 versus 27 months respectively (HR: 0.67, 95% CI: 0.51–0.9).

Gabriel Hortobagyi (University of Texas, MD Anderson Cancer Center, Houston, TX, USA) presented results from the final analysis of the NATALEE trial that explored the efficacy and safety of the CDK 4/6 inhibitor ribociclib combined with endocrine therapy for hormone receptor positive, HER2 negative early breast cancer [5]. More than 5000 female and some male patients with stage IIA, IIB and III disease were recruited and in contrast to the MonarchE trial [6], some node negative patients were eligible for inclusion if deemed higher risk based on grade (III), proliferation index (Ki67 $\geq$ 20%) and genomic risk profiling (Oncotype $\geq$ 26). Endocrine therapy was either anastrozole or letrozole with premenopausal women and men receiving an Luteinizing hormone-releasing

hormone analogue. The primary outcome measure was invasive DFS. A previous interim analysis had revealed significant improvement in invasive DFS for stage II and III disease, including node negative patients. The final protocol-specific analysis was undertaken at a median follow-up of 33.3 months when 42.8% of patients had completed 3 years of treatment with ribociclib. Approximately a third of patients (35.5%) discontinued treatment with CDK 4/6 inhibitor either in isolation or together with endocrine therapy. More than two-thirds of patients allocated to endocrine treatment remained on endocrine therapy alone. There was continued improvement in the primary outcome measure for the combination of ribiciclib and endocrine therapy compared with endocrine alone with invasive DFS of 90.7 versus 87.6%, respectively. There was benefit across all subgroups with a proportional benefit of 30% for stage II (HR: 0.7) and 25% for stage III [HR: 0.75] in terms of risk reduction. Furthermore, there was a 28% risk reduction for node negative patients which potentially broadens the indications for CDK 4/6 inhibitors as a component of systemic adjuvant therapies in higher risk patients (not exclusively node positive ones). Hortobagyi commented that CDK 4/6 inhibitors were still in the 'early days' of development and overall results from the NATALEE study remain immature. Nonetheless, this class of therapeutic agents offer a potential strategy to overcome innate tumor dormancy and emergence of recurrence up to 20 years after initial treatment of hormone receptor positive, HER2 negative breast cancer. There was consensus on the urgent need for development of biomarkers to identify patients with greatest benefit from CDK 4/6 inhibitors – and conversely those who derive minimal benefit.

1.4. PARP inhibitors for BRCA gene mutation carriers in breast cancer

Hope Rugo (University of California at San Francisco, CA, USA) discussed the issue of safe and effective maintenance treatment for advanced breast cancer patients for whom it is important to take account of both quality of life and duration of survival. The KEYNOTE-355 trial had previously shown a benefit in terms of PFS and OS from addition of a PD-L1 inhibitor (pembrolizumab) to platinum-based chemotherapy as first-line therapy for PD-L1 positive TNBC in the metastatic disease setting [7]. It is important to sustain any clinical benefits after initial induction therapy; the randomised KEYLINK-009 trial evaluated the poly(ADP)-ribose polymerase (PARP) inhibitor olaparib as maintenance therapy for locally recurrent (inoperable) or metastatic TNBC treated with platinum-based chemotherapy (at least 4–6 cycles). Following chemotherapy, patients with complete/partial response or stable disease were randomised to pembrolizumab plus either olaparib ($n = 135$) or chemotherapy ($n = 136$) with continuation of the latter two therapies until disease progression or excessive toxicity. This trial had dual primary end points of PFS and OS with secondary end points of PFS and OS in BCRA mutation carriers. At a median follow-up of 17.2 months, there was no significant improvement in primary outcomes for olaparib compared with chemotherapy when combined with immunotherapy (5.5 vs 5.6 months for median PFS and 25.1 vs 23.4 months for median OS). Of note, a numerical improvement in PFS was observed for the pembrolizumab-olaparib combination among BRCA gene mutation carriers (median PFS 12.4 vs 8.4 months [HR: 0.7 95% CI: 0.33–1.48]) but not those with higher PD-L1 levels (CPS $\geq$10) (median PFS 5.7 vs 5.7 months [HR: 0.92 95% CI: 0.59–1.43]). However, there was no OS benefit from olaparib treatment for BRCA mutation carriers or patients with high PD-L1 levels. Interestingly, there was halving of grade 3 or higher adverse effects in the olaparib group compared with chemotherapy (32.6 vs 68.4%).

1.5. Population diversity

The MAMMO-50 trial was based on a UK screened population. Although uptake of screening is recognized as being lower among ethnic minority groups, according to 2021 consensus data, 82% of the population in England and Wales are White, while 18% belong to Black, Asian, mixed or other ethnic groups. Likewise, the ICARO study drew on real-world data from Europe, North America, South America, Southeast Asia and Turkey. It is likely that the proportion of White patients in routine clinical practice within Europe is less than 18% while, in some parts of the United States, estimates from 2021 show that 59.3% of the population are White, 18.9% are Hispanic or Latino and 12.6% are Black. The NSABP trial reported racial characteristics that were well balanced in both groups (RNI and no RNI): 8% Asian, 17% Black/African American, 69% White and 6% unknown or other. The results from these studies are therefore generalizable, although the proportion of ethnic patients in MAMMO-50 is likely less than 18% due to lower rates of compliance. The study reported by Lambertini focused on pregnancy after breast cancer in young women with germline pathogenic variants. It involved nearly 5000 patients from 78 centers worldwide (across 26 countries and four continents), reflecting a broad range of ethnic groups, although individual percentages are not recorded. Similarly, the POSITIVE trial recruited 518 patients from 116 centers in 20 countries. Notably, the KEYNOTE-756 study predominantly recruited patients

from Eastern Europe and China, which may limit generalizability if a high proportion of patients were of East Asian descent.

The SABCS2023 featured work of many investigators not mentioned above but who have worked incessantly to reduce the burden of breast cancer from more effective prevention and treatment strategies. More importantly, the symposium continues to demonstrate the courage of thousands of women around the world who have participated in clinical trials and contributed to advances in the field of both clinical and translation research. International collaboration with collection of real-world data from large numbers of sites can produce robust evidence for acceleration of treatment de-escalation and reduce morbidity without risk of oncological compromise. Hence lesser forms of treatment can become standard of care sooner than would otherwise be the case if awaiting results of randomised clinical trials.

Author contributions

Both authors (JR Benson and I Jatoi) have contributed significantly to this manuscript in terms of conception, execution and interpretation of data. JR Benson has written the manuscript that has been critically reviewed by I Jatoi and both authors agree to publication of this article in Future Oncology. Likewise, both JR Benson and I Jatoi have reviewed and agreed all versions of the article before submission and will review the final version that is accepted for publication and agree to any changes introduced at the proofing stage. Moreover, both JR Benson and I Jatoi agree to take responsibility and be accountable for the contents of the article and to share responsibility to resolve any questions raised about the accuracy or integrity of the published work.

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Competing interests disclosure

JR Benson was on the Planning Committee and I Jatoi the Executive Committee for the above meeting. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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