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BREAKOUT

International Breast Cancer Biomarker, Standard of Care and Real World Outcomes Study

BREAKOUT was a cross-sectional study and a prospective cohort of human epidermal growth factor receptor 2 negative metastatic breast cancer patients who have started 1st line systemic cytotoxic chemotherapy. The study estimated the prevalence of germline breast cancer susceptibility gene in this patient population, and described the treatments administered. Exploratory analyses were undertaken to describe somatic breast cancer susceptibility gene and other homologous recombination repair gene mutations. The study also aimed at estimating the associated clinical outcomes of overall survival and progression-free survival amongst mutation carriers within the context of a low poly ADP ribose polymerase inhibitor treatment setting, yet these objectives were not fulfilled due to early termination of the study.

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STUDY REPORT SYNOPSIS

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International Breast Cancer Biomarker, Standard of Care and Real-World Outcomes Study

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Milestones:

25 November 2016: Final CSP
13 March 2017: First Patient In
30 April 2018: Last Patient In
20 June 2018: Last Patient Last Visit
11 July 2018: Database Lock
14 December 2018: Study Report

Phase of development: Not Applicable (observational study)

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This study was performed in compliance with Good Clinical Practice and Good Pharmacoepidemiology Practice.

Background/rationale:

Breast cancer is the most frequent cancer among women. Biomarkers are known to influence the risk of developing breast cancer, and may be targets for treatment, including the breast cancer susceptibility gene (*BRCA*). Several targeted therapies are currently in clinical development. The poly ADP ribose polymerase inhibitor (PARPi) olaparib was proven to be effective in targeting BRCA-mutated (*BRCA*m) breast cancers and has been tested in the Phase 3 OlympiAD trial in human epidermal growth factor receptor 2 negative (HER2-ve) metastatic breast cancer (MBC) population.

Among studies in unselected breast cancer patients, the prevalence of germline *BRCA* (g*BRCA*) mutations ranges from 1.2% to 8.8%, but limited epidemiological data exist on the prevalence of g*BRCA* and other gene mutations in HER2-ve MBC patients treated by 1st line cytotoxic chemotherapy, the natural history of this disease subtype and the standard of care treatments.

This can lead to uncertainty for payers, providers and other stakeholders in terms of the number of patients who might be available for future treatments with PARPi, whether the treatments used in regulatory studies are applicable locally and what the prognostic outlook might be for this patient population. It is imperative to understand the prevalence of g*BRCA* gene mutations among the eligible patient population and define the size of the target patient population for olaparib.

Objectives:

Primary objective

To estimate the prevalence of g*BRCA* gene mutations among the metastatic HER2-ve breast cancer patient population.

Secondary objectives

- To describe the standard of care treatments by line of therapy for g*BRCA* mutated (g*BRCA*m) metastatic HER2-ve breast cancer.[1]
- To estimate the progression-free survival (PFS) of g*BRCA*m metastatic HER2-ve breast cancer by line of therapy.[2]
- To estimate the overall survival (OS) of g*BRCA*m metastatic HER2-ve breast cancer by line of therapy.[2]

Exploratory objectives

- To estimate the prevalence of somatic *BRCA* (s*BRCA*) gene mutations among the metastatic HER2-ve breast cancer patient population.
- To estimate the prevalence of other homologous recombination repair (HRR) gene mutations among the metastatic HER2-ve breast cancer patient population.

[1] Due to early termination of the study, the standard of care treatments were presented for 1st line therapy, while other lines of therapy were mostly not collected.

[2] Due to early termination of the study, objectives related to PFS and OS assessments were not addressed.

- To describe the standard of care treatments by line of therapy for s*BRCA* gene mutated (s*BRCA*m) and other HRR gene mutated (HRRm) metastatic HER2-ve breast cancer.[1]
- To estimate the PFS of s*BRCA*m and HRRm metastatic HER2-ve breast cancer by line of therapy.[2]
- To estimate the OS of s*BRCA*m and HRRm metastatic HER2-ve breast cancer by line of therapy.[2]
- To explore the prevalence of other genomic alterations.[3]

Secondary and exploratory objectives on OS and PFS were not assessed.

Study design:

A cross-sectional study was conducted with HER2-ve MBC patients to assess the prevalence of g*BRCA* gene mutation. Patients who tested positive for a g*BRCA* gene mutation, and patients who tested positive for s*BRCA* or other HRR gene mutations (optional testing for those patients who tested negative for g*BRCA* gene mutations) were to be evaluated for treatment patterns, PFS and OS. However, only baseline data was collected and available for analysis due to the early termination of the study.

Data source:

Data was collected by the treating Investigator and/or other qualified research staff from individual patient medical records, to include baseline patient characteristics, medical and diagnostic history, and included an ongoing review of routine treatments and outcomes. This was collected from primary data sources and recorded into electronic case report forms (eCRF). Clinical visits were not mandated per protocol and were conducted in accordance with routine practice.

Existing biomarker test results for g*BRCA* gene mutations were used for study purposes, but were not considered when enrolling patients, in order to obtain a representative study population. If unavailable from the patient medical records, g*BRCA* gene mutation status was tested using a blood sample. Where sufficient quality and quantity of archival tumor specimen was available, and patients had consented to tumor specimen testing (optional consent), the FMI Lynparza HRR assay (Foundation Medicine Inc. [FMI], Cambridge, Massachusetts, USA) may have taken place.

Study population:

The study population included eligible metastatic HER2-ve breast cancer patients who had initiated a 1st line systemic cytotoxic chemotherapy within 90 days prior to enrollment. Patients were enrolled from 14 countries.

[1] Due to early termination of the study, the standard of care treatments were presented for 1st line therapy, while other lines of therapy were mostly not collected.

[2] Due to early termination of the study, objectives related to PFS and OS assessments were not addressed.

[3] Other genomic alterations results obtained as part of FMI archival sample testing were not included into the clinical dataset of BREAKOUT.

Inclusion/exclusion criteria:

Patients were only included in the study if they met all the following inclusion criteria and none of the exclusion criteria.

Inclusion:

1. Provision of, written, signed and dated informed consent.
2. Adult females (according to the age of majority/adulthood as defined by local regulations).
3. Histologically or cytologically confirmed HER2-ve breast cancer with evidence of metastatic disease.
4. Initiated treatment with 1st line systemic cytotoxic chemotherapy (not hormonal therapy) for MBC in the last 90 days and, and at that time, were considered to have exhausted hormone therapy (HT) options (if hormone receptor [HR] positive [HR+ve]).[4]

Exclusion:

1. Previous enrollment in this study.
2. Involvement in the planning and/or conduct of this study (applied to both AZ staff and/or staff at the study site).
3. Current participation in a clinical study with an investigational oncology product.
4. Previous PARPi therapy, including, but not limited to, participation in a previous clinical study that included PARPi therapy.
5. Current commencement of PARPi treatment.

Statistical methods:

A comprehensive statistical analysis plan was prepared and finalized before database lock.

Analyses planned for the primary and secondary objectives were intended to evaluate:

- Prevalence of g*BRCA* gene mutations
- Distribution of demographic variables, disease characteristics, comorbidities among patients with and without a g*BRCA* gene mutation
- Distribution of regimens for 1st line therapy among patients with and without a g*BRCA* gene mutation

Additionally, exploratory analyses were planned to evaluate:

- Prevalence of s*BRCA* and other HRR gene mutations
- Distribution of demographic variables, disease characteristics, comorbidities among patients with and without a s*BRCA* gene mutation and other HRR gene mutations
- Distribution of regimens for 1st line therapy among patients with and without a s*BRCA* gene mutation and other HRR gene mutations

[4] A global communication via booster emails to all sites, as well as a protocol clarification letter addressed to sites in Taiwan, were sent in order to further explain the inclusion criterion #4: where a patient had HR+ve, HER2-ve MBC, and had completed prior HT they would be suitable to enter into the BREAKOUT study if the current or currently planned choice of treatment for the patient did not include a HT. Patients with 2nd line chemotherapy initiated before the enrollment were eligible as long as the 1st line chemotherapy was initiated within 90 days. Additionally, a second protocol clarification letter was sent to Taiwan sites to specify that patients treated concurrently with HT and cytotoxic chemotherapy were not eligible to this study.

- Prevalence of other genomic alterations

Due to early termination of the study, some of the planned secondary and exploratory analyses were not performed because of the limited number of recruited patients with g*BRCA*, s*BRCA*, and any HRR gene mutations as well as the absence of follow-up data for the description of treatment patterns and associated clinical outcomes. As a result, the secondary and exploratory analyses related to PFS and OS assessments were not performed. The standard of care treatments were presented for 1st line therapy only, while other lines of therapy were presented as a listing. The Eastern Cooperative Oncology Group (ECOG) performance status, the site and number of metastases were summarized at initiation of the 1st line therapy.

Results:

Patient disposition

The total number of consented patients was 384, of which 43 patients were excluded from analysis (39 due to violation of the eligibility criteria and four due to missing blood draws); therefore, the Full Analysis Set (FAS) included 341 patients. Among the FAS patients with a negative g*BRCA*m test, 64 were tested for HRR and s*BRCA* mutations and were included in the exploratory somatic analysis set (ESAS).

Of all FAS patients (N=341), 23.2% (n=79) were recruited from Turkey, 13.2% (n=45) from South Korea, 12.9% (n=44) from Japan, 9.4% (n=32) each from Russia and the United Kingdom (UK), 7.3% (n=25) from the United States (US), 5.3% (n=18) from Spain and the remainder (n=66, 19.4%) from the following countries: Bulgaria, Taiwan, Poland, Canada, Italy, Australia and Hungary.

There were 33 patients (9.7%) identified with g*BRCA*m disease.

Patient baseline characteristics

The mean age at enrollment for the FAS was 55.6 (standard deviation [SD] 12.38) years; 75.3% (n=256/340) were post-menopausal at enrollment, and 21.8% (n=74/340) were pre-menopausal. The mean age at breast cancer diagnosis was 51.3 years (SD 12.31, available for 338 patients). The majority of the 341 FAS patients were White (n=223, 65.4%), followed by Asian (n=66, 19.4%).

In the g*BRCA*m subgroup, 57.6% (n=19/33) of patients were post-menopausal and 30.3% (n=10/33) were pre-menopausal at enrollment. On average, patients with g*BRCA*m disease were around eight years younger at diagnosis (mean 43.7 years, SD 12.24), and at enrollment (mean 47.9 years, SD 11.79), compared to the FAS.

Most patients with data on nicotine use (n=263/332, 79.2%) reported that they never smoked, and 13.0% (n=43/332) were former smokers; the proportion of current smokers was 7.8% (n=26/332).

ECOG performance status was captured at the initiation of 1st line chemotherapy. Most patients scored 0 (n=175/341, 51.3%) or 1 (n=143/341, 41.9%). Where reported, 26.7% (n=91/341) of the FAS patients had past medical conditions, 34.0% (n=116) had current comorbid conditions. Vascular disorders (n=59/341, 17.3%) were the most common comorbidities.

Where reported, family history of breast or ovarian cancer was present for 19.4% (n=66/340) of the FAS patients, 16.6% (n=51/307) of the patients without g*BRCA* mutation, and 45.5% (n=15/33) of the patients with g*BRCA* mutation. Age at diagnosis of these cancers was ≤50 years for one third of the relatives.

Disease characteristics

The median time from original diagnosis to study enrollment was 29.8 months (first and third quartiles 7.2, 76.8) for the FAS, and 28.1 months (first and third quartiles 13.4, 73.0) for the g*BRCA*m patients.

More than half of the FAS population (n=198/341, 58.1%) was post-menopausal at original diagnosis, and 37.8% (n=129/341) was pre-menopausal. Conversely, in the subgroup of g*BRCA*m patients, 57.6% (n=19/33) were in pre-menopausal status, and 36.4% (n=12/33) in post-menopausal status at the time of the original tumor diagnosis.

The most frequent tumor locations at original diagnosis were the upper-outer quadrant of the breast (n=141/336, 42.0%) or the upper-inner quadrant (n=48/336, 14.3%). Among the g*BRCA*m patients, 24.2% (n=8/33) had the primary tumor located in the upper-inner quadrant, and 21.2% (n=7/33) in the upper-outer quadrant.

The most frequent histology type at original diagnosis was invasive carcinoma, including invasive ductal breast cancer (n=207/341, 60.7%), invasive carcinoma not otherwise specified (NOS) (n=47/341, 13.8%), and invasive lobular breast cancer (n=26/341, 7.6%). Of the g*BRCA*m patients, 66.7% (n=22/33) had an invasive ductal breast cancer at original diagnosis, and 21.2% (n=7/33) had an invasive carcinoma NOS.

Most of FAS patients had either poorly differentiated (Grade 3) (n=118/336, 35.1%) or moderately differentiated (Grade 2) (n=111/336, 33.3%) tumors at original diagnosis. A higher proportion of g*BRCA*m patients had poorly differentiated (Grade 3) tumors (n=15/33, 45.5%) at original diagnosis.

Patients were staged according to the American Joint Committee on Cancer (AJCC) classification in use at the date of original diagnosis. From the 336 FAS patients for which stage at initial diagnosis was available, 34.8% (n=117/336) were diagnosed at stage II, and 26.2% (n=88/336) were diagnosed at stage III, and 27.1% (n=91/336) of patients were diagnosed at stage IV. The distribution of AJCC stages at initial diagnosis was similar in patients with g*BRCA*m disease.

For the FAS population, a median of 2.8 months (first and third quartiles 1.5, 11.0) elapsed from the diagnosis of metastatic disease to study enrollment. Of the 714 metastatic sites reported for the 341 FAS patients at enrollment, bone metastases were the most frequent site of distant metastases (n=175 sites, 24.5% of metastatic sites), and 20.9% (n=149) of the 714 metastatic sites were lymph nodes. The majority of patients in the FAS had two metastatic sites or more (n=214/311, 68.8%), whereas 50.0% of g*BRCA* mutation carriers had one metastatic site.

HER2 and HR receptor status

All patients had HER2-ve status. The HR status (missing for seven patients) was positive (estrogen receptor [ER] and/or progesterone receptor [PR] positive) for 64.4% (n=215/334) of the FAS patients, conversely, 35.6% (n=119/334) of the FAS patients had triple-negative

breast cancer (TNBC). ER status was positive for 61.8% (n=207/335) and PR status was positive for 49.4% (n=159/322) of the FAS patients. Similar distributions were found regardless of the g*BRCA* mutation status.

Treatment history prior to metastatic disease

Slightly more than half (n=176/331, 53.2%) of the FAS patients and 64.5% (n=20/31) of g*BRCA*m patients with reported information received past chemotherapy since their original breast cancer diagnosis and before MBC. The median number of months that elapsed between the end of the most recent chemotherapy before MBC and the date of enrollment was 35.7 months (first and third quartiles 16.9, 77.3). On average, FAS patients received 5.6 (SD 3.03) cycles of their most recent chemotherapy before MBC.

A total of 549 chemotherapy agents administered before MBC were recorded for the FAS patients. The most commonly used (regardless of g*BRCA* mutation status) was cyclophosphamide that represented 30.4% (n=167) of all agents; followed doxorubicin (n=85, 15.5%), fluorouracil (5FU, n=78, 14.2%), docetaxel (n=69, 12.6%), epirubicin hydrochloride (n=65, 11.8%), and paclitaxel (n=41, 7.5%). More than half of these agents (n=307/547, 56.1%) were used as adjuvant treatments, and 41.9% (n=229) were used as neo-adjuvant therapy.

Non-chemotherapy treatments were administered to 38.2% (n=129/338) of the FAS patients and 30.3% (n=10/33) of the g*BRCA*m patients before MBC. The most common were tamoxifen (n=81/183, 44.3% of agents), followed by letrozole (n=40, 21.9%) and anastrozole (n=37, 20.2%). Most agents (n=141/181, 77.9%) were used in the adjuvant setting. The median number of months that elapsed between the end of the most recent non-chemotherapy before MBC and the date of enrollment was 12.8 months (first and third quartiles 2.6, 41.8) in the FAS patients, and 8.6 months (first and third quartiles 2.7, 54.9) in the subgroup of g*BRCA*m patients.

Treatments received for metastatic disease before 1st line chemotherapy

Non-chemotherapy treatments were administered in the metastatic setting before 1st line chemotherapy to 30.3% (n=103/340) of the FAS patients with available information, including 24.2% (n=8/33) of the g*BRCA*m patients.

A total of 228 non-chemotherapy agents were reported for the FAS patients. Overall, the most common was letrozole (n=41/228, 18.0%), followed in decreasing frequency by fulvestrant (n=34, 14.9%), exemestane (n=32, 14.0%), bevacizumab (n=27, 11.8%), and everolimus (n=25, 11.0%).

Primary objective: prevalence of gBRCA mutations

Within the FAS population, the prevalence of g*BRCA* mutations (g*BRCA1* and/or g*BRCA2*) was estimated at 9.7% (n=33/341; 95% confidence interval [CI] 6.8%, 13.3%). The g*BRCA* mutations were distributed as follows: 4.7% (n=16; 95% CI 2.7%, 7.5%) of the FAS patients presented with g*BRCA1* mutations only; 3.5% (n=12; 95% CI 1.8%, 6.1%) had g*BRCA2* mutations only; and 1.5% (n=5; 95% CI 0.5%, 3.4%) had both g*BRCA1* and g*BRCA2* mutations.

Among the 44 patients recruited in Japan, the prevalence of g*BRCA* mutations was estimated at 15.9% (n=7/44; 95% CI 6.6%, 30.1%). The g*BRCA* mutations were distributed as follows: 6.8% (n=3; 95% CI 1.4%, 18.7%) of the Japanese patients had g*BRCA1* mutations only, and 9.1% (n=4; 95% CI 2.5%, 21.7%) had g*BRCA2* mutations only. No patients were found to have both g*BRCA1* and g*BRCA2* mutations.

Subgroup analyses

The prevalence of any g*BRCA* mutation was comparable in Europe (n=18/199, 9.0%; 95% CI 5.4%, 13.9%) and North America (n=3/33, 9.1%; 95% CI 1.9%, 24.3%) and it was slightly higher in Asia (n=11/104, 10.6%; 95% CI 5.4%, 18.1%).

The prevalence of any g*BRCA* mutation in FAS was 12.9% (n=22/171; 95% CI 8.2%, 18.8%) in patients aged ≤50 years at breast cancer diagnosis, and 5.4% (n=9/167; 95% CI 2.5%, 10.0%) in patients >50 years of age at initial diagnosis. This difference was mainly due to the g*BRCA1* mutations. In Japan, g*BRCA* mutations were observed only in patients diagnosed at ≤50 years of age. The estimated prevalence of any g*BRCA* mutation in this subgroup of Japanese patients (n=24) was 25.0% (n=6/24; 95% CI 9.8%, 46.7%).

Since the patient population was HER2-ve, all patients with HR-ve status presented a TNBC. The prevalence of any g*BRCA* mutation was similar regardless of the HR status, it was 9.3% (n=20/215; 95% CI 5.8%, 14.0%) in patients with HR+ve status (non-TNBC patients) and 9.2% (n=11/119; 95% CI 4.7%, 15.9%) in patients with HR-ve status (TNBC patients).

The prevalence of g*BRCA1* mutations was 2.8% (n=6/215; 95% CI 1.0%, 6.0%) in HR+ve (non-TNBC) patients and 7.6% (n=9/119; 95% CI 3.5%, 13.9%) in HR-ve (TNBC) patients. Conversely, the prevalence of g*BRCA2* mutations was 4.7% (n=10/215; 95% CI 2.3%, 8.4%) among HR+ve (non-TNBC) patients and 1.7% (n=2/119; 95% CI 0.2%, 5.9%) in patients with HR-ve status (TNBC patients).

In Japan, among HR+ve (non-TNBC) patients, the prevalence of any g*BRCA* mutation was 14.3% (n=4/28; 95% CI 4.0%, 32.7%), all these patients were g*BRCA2* mutation carriers. The prevalence of any g*BRCA* mutation among HR-ve (TNBC) patients was 20.0% (n=3/15; 95% CI 4.3%, 48.1%), all these patients were g*BRCA1* mutation carriers.

The prevalence of g*BRCA* mutations was higher among patients with a family history of breast or ovarian cancer (n=66). In this subgroup, the prevalence of any g*BRCA* mutation was 22.7% (n=15/66; 95% CI 13.3%, 34.7%), whereas it was 6.6% (n=18/274; 95% CI 3.9%, 10.2%) among the patients without relevant family history (n=274). Both the g*BRCA1* and g*BRCA2* mutations were more prevalent in patients with a family history of cancer, whereas joint g*BRCA1* and g*BRCA2* mutations were present in 1.5% of patients, irrespective of family history.

Compared to the overall FAS population; the prevalence of any g*BRCA* mutation was higher among patients with a family history of breast or ovarian cancer in Asia; it was 40.0% (n=6/15; 95% CI 16.3%, 67.7%) among patients with a family history of breast or ovarian cancer recruited in Japan, South Korea and Taiwan; and it was 62.5% (n=5/8; 95% CI 24.5%, 91.5%) among patients with a family history of breast or ovarian cancer recruited in Japan only.

The prevalence of any g*BRCA* mutation among the 250 patients with at least one risk factor (including a family history of breast or ovarian cancer, age ≤50 years at breast cancer diagnosis, and TNBC) was 10.4% (n=26/250; 95% CI 6.9%, 14.9%), whereas it was 5.8% (n=5/86; 95% CI 1.9%, 13.0%) among patients without any risk factor. This difference was due to the distribution of g*BRCA1* mutations: 6.0% (n=15/250; 95% CI 3.4%, 9.7%) of patients with at least one risk factor and 1.2% (n=1/86; 95% CI 0.0%, 6.3%) of patients without any risk factor had a g*BRCA1* mutation. There was no difference between these subgroups with respect to the frequency of g*BRCA2* mutations and joint g*BRCA1* and g*BRCA2* mutation.

In the subgroup of Japanese patients, no g*BRCA* mutation was found in patients without any risk factor (n=8). In the Japanese patients with at least one risk factor (n=34), 17.6% (n=6/34; 95% CI 6.8%, 34.5%) of patients carried a g*BRCA* mutation, half of them carried a g*BRCA1* mutation, and half carried a g*BRCA2* mutation.

Patient baseline characteristics by timing of gBRCA test

The assessment of g*BRCA* mutation status was performed either before study entry, at baseline or on both occasions; 311 patients had a g*BRCA* test performed at baseline, 22 only had a g*BRCA* test performed prior to baseline, and eight patients tested at baseline had received a former *BRCA* mutation test, mostly on a tumor sample.

The g*BRCA* mutation prevalence among patients tested at baseline was 7.8% (n=25/319); whereas it was 26.7% (n=8/30) among patients who had been tested prior to baseline.

The mean (SD) age at breast cancer diagnosis among mutation carriers was 43.0 (11.39) years for patients tested at baseline, and 45.9 (15.08) years for patients tested prior to baseline. Family history of hereditary breast or ovarian cancer was present in 17.6% (n=56/318) of patients tested at baseline, but in 43.3% (n=13/30) of patients tested prior to baseline. The frequency of TNBC was higher among the 30 patients tested prior to baseline (n=17/30, 56.7%), than in patients tested at baseline (n=106/312, 34.0%).

Secondary objective: description of 1st line chemotherapy

Among the FAS patients, the most frequent agent used as 1st line chemotherapy in the metastatic setting, regardless of the g*BRCA* mutation status, was paclitaxel (n=127/341, 37.2%), followed by cyclophosphamide (n=60/341, 17.6%), capecitabine (n=57/341, 16.7%), docetaxel (n=48/341, 14.1%), carboplatin (n=31/341, 9.1%), doxorubicin (n=29/341, 8.5%) and gemcitabine (n=28/341, 8.2%). Capecitabine was prescribed slightly more frequently in patients with a g*BRCA* mutation (n=7/33, 21.2%) than in patients without g*BRCA* mutation (n=50/308, 16.2%); a similar finding was observed for docetaxel (n=6/33, 18.2% vs. n=42/308, 13.6%), carboplatin (n=5/33, 15.2% vs. n=26/308, 8.4%), and gemcitabine (n=4/33, 12.1% vs. n=24/308, 7.8%).

For the majority of patients, only baseline data was collected, and 1st line chemotherapy was ongoing at that time. Consequently, information on the duration of 1st line chemotherapy was available for 99 patients only; the median duration was 2.2 months (first and third quartiles 1.1, 3.3) overall (n=99) and 2.6 months (first and third quartiles 2.0, 3.8) in the subgroup of mutation carriers (n=11).

C**onclusion:**

The BREAKOUT study was a global observational study which described the prevalence of g*BRCA* mutations among HER2-ve MBC patients treated with 1st line cytotoxic chemotherapy across different regions and countries and mapped the 1st line standard of care treatments of g*BRCA* mutations carriers. Patients were enrolled from March 2017 to April 2018.

This study was planned to include both a cross-sectional component with a sample of 2,000 patients and a prospective cohort study component. Due to early termination, only the cross-sectional part of the study was conducted, with 341 patients included in the statistical analysis.

The patient and disease characteristics of the participants in the BREAKOUT study correspond to the literature on HER2-ve MBC patients. Overall, 9.7% (95% CI 6.8%, 13.3%) of the patients had g*BRCA1* and/or g*BRCA2* mutations. The prevalence of g*BRCA1* and g*BRCA2* mutations was 4.7% (95% CI 2.7%, 7.5%), and 3.5% (95% CI 1.8%, 6.1%), respectively. Both mutations were present in 1.5% (95% CI 0.5%, 3.4%) of the patients.

In the g*BRCA*m patients (n=33), the most frequent agent used was paclitaxel (36.4%), followed by capecitabine (21.2%), docetaxel (18.2%), cyclophosphamide and carboplatin (15.2% each), bevacizumab and gemcitabine (12.1% each). The slight majority (54.5%) of the g*BRCA*m patients were treated with combination therapy. The treatments administered for these patients were in line with the current treatment guidelines and did not differ substantially compared to sporadic patients.

The study results seem to support the association of g*BRCA* mutations with the traditional risk factors of young age at diagnosis and family history of cancer.