Study Report Synopsis	
Drug Substance	Not applicable
Study Code	D0816R00012
Edition Number	1.0
Date	14 December 2018
NCT Number	NCT03078036

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. [redacted] 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.

Study dates: First subject enrolled: 13 March 2017
Last subject last visit: 20 June 2018

Phase of development: Not applicable, observational study

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

[redacted]

Study centre(s)

Patients were enrolled from 102 sites and 14 countries.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective		Outcome Variable
Priority	**Description**	**Description**
Primary	To estimate the prevalence of germline breast cancer susceptibility (g*BRCA)* gene mutations among the metastatic human epidermal growth factor receptor 2 negative (HER2-ve) breast cancer patient population.	g*BRCA* gene mutation status
Secondary	To describe the standard of care treatments by line of therapy for g*BRCA* mutated (g*BRCA*m) metastatic HER2-ve breast cancer.	Number of agents (unique) Agent name Regimen (per patient) Duration of therapy (months)
Secondary	To estimate the progression-free survival (PFS) of g*BRCA*m metastatic HER2-ve breast cancer by line of therapy.	Not addressed*
Secondary	To estimate the overall survival (OS) of g*BRCA*m metastatic HER2-ve breast cancer by line of therapy.	Not addressed*
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Objective		Outcome Variable
Priority	**Description**	**Description**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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

[redacted]

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, [redacted] 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.

Target patient population and sample size

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.

Inclusion criteria:

- Provision of, written, signed and dated informed consent.
- Adult females.
- Histologically or cytologically confirmed HER2-ve breast cancer with evidence of metastatic disease.
- 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]).

Exclusion criteria:

- Previous enrollment in this study.
- Involvement in the planning and/or conduct of this study.
- Current participation in a clinical study with an investigational oncology product.

- Previous or current PARPi therapy, including, but not limited to, participation in a previous clinical study that included PARPi therapy.
- Current commencement of PARPi treatment.

The prevalence objectives of the study were planned to be achieved from a cross-sectional sample of 2,000 patients. The Full Analysis Set (FAS) included 341 patients.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Not applicable.

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

[redacted]

Due to early termination of the study, some of the planned secondary [redacted] analyses were not performed because of [redacted] the absence of follow-up data for the description of treatment patterns and associated clinical outcomes. As a result, the secondary [redacted] analyses related to PFS and OS assessments were not performed. The standard of care treatments were presented for 1st line therapy only, [redacted] The Eastern Cooperative Oncology Group (ECOG) performance status, the site and number of metastases were summarized at initiation of the 1st line therapy.

Summary of 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 FAS included 341 patients from 102 sites and 14 countries. [redacted]

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).

Eastern Cooperative Oncology Group (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).

Summary of safety results

Not applicable.

Conclusions

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.

Study report	
Study code	BREAKOUT: D0816R00012; PRAEGNANT: SEN-01/14
Version	01
Date	15 May 2020

BREAKOUT: **International Breast Cancer Biomarker, Standard of Care and Real World Outcomes Study (Germany data)**

Germany – A subproject of the Prospective academic translational research network for the optimization of the oncological Health Care quality in the Adjuvant and advanced/ metastatic setting: health care research, Pharmacogenomics, Biomarkers, Health economics (**PRAEGNANT**) breast cancer registry

Sponsor of BREAKOUT Study	**Astrazeneca UK limited** **1 Francis Crick Avenue** **Cambridge CB2 0AA** England UK
Sponsor of PRAEGNANT Registry	**Universitätsklinikum Tuebingen** **Forschungsinstitut für Frauengesundheit Baden-Württemberg** **Calwerstraße 7** **72076 Tübingen**
Author:	[redacted] Erlangen University Hospital, Universitaetsstrasse 21-23, 91054 Erlangen, Germany Phone: +49 (0) 9131 85 33508 Fax: +49 (0) 9131 85 33938 [redacted]

STUDY REPORT SYNOPSIS

BREAKOUT Germany –

A subproject of the PRAEGNANT breast cancer registry

Milestones:	Q2 2014	Final PRAEGNANT CSP
	Q3 2014	FPI PRAEGNANT Registry
	Q3 2014	FPI PRAEGNANT Registry (date of consent of first patient data used in BREAKOUT substudy analysis)
	Q2 2015	Final PRAEGNANT CSP Amendment 1
	Q4 2016	Final BREAKOUT CSP
	Q3 2018	Last Patient In
	Q1 2019	Final PRAEGNANT CSP Amendment 2
	Q2 2019	Last data from FMI
	Q2 2019	Data Cut Off
	Q2 2020	Clinical Study Report
Sponsor of BREAKOUT Study	**Astrazeneca UK limited** **1 Francis Crick Avenue** **Cambridge CB2 0AA** **England UK**	
Sponsor of PRAEGNANT Registry	**Universitätsklinikum Tuebingen** **Forschungsinstitut für Frauengesundheit Baden-Württemberg** **Calwerstraße 7** **72076 Tübingen**	

Author: [redacted]

Erlangen University Hospital,

Universitaetsstrasse 21-23, 91054 Erlangen, Germany

Phone: +49 (0) 9131 85 33508

Fax: +49 (0) 9131 85 33938

[redacted]

The study was performed according to Good Clinical Practice (GCP) requirements where applicable.

Background/rationale

Limited epidemiological data exist within the setting of metastatic human epidermal growth factor receptor 2 negative (HER2-ve) breast cancer (BC) on the prevalence of pathogenic mutations of BC susceptibility gene (BRCA) and other homologous recombination repair (HRR) genes. It is well known that the prevalence varies significantly between ethnic groups, geographical areas and BC subtypes. However, existing studies mainly focused on small cohorts and do not allow for stratification by stage and HER2 status. Especially for metastatic HER2-ve patients there are only limited data on the treatment and clinical outcomes of patients with such germline and somatic gene profiles. Furthermore, little is known about the prevalence of germline and somatic HRR (gHRR and sHRR, respectively) mutations. Within the current epidemiologic study we assessed the prevalence of germline BRCA (gBRCA), somatic BRCA (sBRCA) mutations and mutations within other HRR genes. HER2-ve patients who have initiated 1st line systemic cytotoxic chemotherapy at that time were regarded as patients who received all possible hormone therapy options (if hormone receptor positive [HR+ve]) by the investigator's opinion were included in the study.

Study design

The BREAKOUT study was both a cross-sectional and a prospective cohort study. The prevalence objectives of the study were to be achieved from a cross-sectional sample of 2,000 patients with metastatic HER2-ve breast cancer.

The main study includes patients enrolled from outside of Germany and was reported separately.

The BREAKOUT study permitted the use of data from existing registries. This report includes data from patients in Germany from the PRAEGNANT registry, therefore the sample is just 529 patients included in this separate report.

Patients who tested positive for a gBRCA gene mutation were followed prospectively for description of treatment patterns and associated clinical outcomes.

Tumor material from 167 patients was sent for testing for somatic mutations, only the tumour material from 111 patients was evaluable for this analysis, this was optional testing for those patients who test negative for gBRCA gene mutations. There were 28 patient tumour samples with insufficient quality / quantity of DNA for extraction and a further 28 paitent turmour samples that had a qualified result but were excluded from the analysis because it was not possible to be certain of mutation status.

Those patients who tested positive for sBRCA or other HRR gene mutations were followed for evaluation of treatment patterns and associated clinical outcomes.

Study population

Approximately 529 women with HER2-ve metastatic breast cancer who have initiated 1st line systemic cytotoxic chemotherapy (up to 90 days prior to enrolment) and, at that time, are considered to have exhausted hormone therapy options (if HR+ve) per investigator's opinion.

For the analysis three patient populations have been defined, which are each total subsets of the hierarchical higher populations.

Population-1 - "germline genotyped population"

529 patients from the PRAEGNANT registry met the inclusion and exclusion criteria of BREAKOUT (metastatic HER2-ve BC, initiated 1st line systemic cytotoxic chemotherapy for metastatic BC in the last 90 days and at that time are considered to have exhausted hormone therapy options, and tested for gBRCA mutations) and genotype results from germline genotyping were available. This population will be referred to as the *germline genotyped population.*

Population-2 – "germline BRCA1/2 negative population"

The patients, who do not have a mutation in either BRCA1 or BRCA2 is referred to as the *germline BRCA1/2 negative population*, which is the patient population from which patients are selected to collect tumor material as formalin-fixed, paraffin embedded (FFPE) tumors for somatic genotyping.

Population 3 – "somatic genotyping population"

The patients for whom results of the somatic genotyping was available is referred to as *somatic genotyping population*.

Objectives

Primary objectives

(**P_01**) Prevalence of gBRCA gene mutations (gBRCAm) among metastatic HER2-ve BC patients in Population-1.

Secondary objectives

Secondary objectives related to germline genotypes (Gene Panel 1 - BRCA1, BRCA2, ATM, RAD51B, RAD51C, RAD51D, RAD54L, BRIP1, FANCL, PALB2, BARD1, CHEK1, CHEK2, CDK12 and PPP2R2A**)**

(O_01) Standard of care treatments by line of therapy for gBRCAm metastatic HER2-ve BC patients in Population-1.

(O_02) PFS of gBRCAm metastatic HER2-ve BC patients by line of therapy in Population-1.

(O_03) OS of gBRCAm metastatic HER2-ve BC patients by line of therapy in Population-1.

[redacted]

Data source

The data in this study report is provided from the PRAEGNANT registry and includes data from approximatley 60 sites across Germany . Patients enrolled were part of the BREAKOUT sub-study of the PRAEGNANT registry.

Inclusion criteria

1. Provision of signed, written and dated informed consent.
2. Adult women aged ≥ 18 years on day of signing informed consent.
3. Histologically or cytologically confirmed, HER2-ve BC with evidence of metastatic disease.
4. Initiated treatment with 1st line systemic cytotoxic chemotherapy (not hormonal therapy) for metastatic BC in the last 90 days and, at that time, are considered to have exhausted hormone therapy options (if HR+ve).

Exclusion criteria

1. Previously enrolled in this study.
2. Involvement in the planning and/or conduct of this study (applies to both AstraZeneca staff and/or staff at the study site) – as far as this was known.
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

Data were summarized using descriptive statistics as appropriate. Continuous variables were summarized by the number of observations (n), mean, standard deviation, median, quartiles, minimum, and maximum. Categorical variables were summarized by frequency counts and percentages for each category. Baseline characteristics (including demographic variables, disease characteristics, comorbidities, etc.) were described in the overall patient population and stratified by BRCA and other HRR gene mutation status. The prevalence of gBRCA gene mutations was evaluated with exact 95% confidence interval (CI) estimated using the Clopper-Pearson method. A detailed statistical analysis plan (SAP) was prepared before database lock.

Results

529 patients were identified from the PRAEGNANT registry, who met the defined inclusion and exclusion criteria and for whom a BRCA1/2 genotyping result was available. Of those 24 patients harbored a germline mutation in BRCA1 or BRCA2 (4.5%) BRCA2 (4.5%; 95% CI 2.9% 6.7%). [redacted]

Patient characteristics revealed gBRCAm patients were younger at study entry (51 years) compared to patients with gBRCA wildtype (58.9 years); Fewer gBRCAm patients were HR+ve when compared to gBRCA wildtype patients, out of all gBRCAm patients 26.1% had TNBC while 73.9% were HR+ve,

whereas out of all gBRCA wildtype patients 15.6% were TNBC while 82.8% were HR+ve. gBRCAm patients (56.5% with grade 3) tended to have a higher tumor grading than gBRCA wildtype (32.8% with grade 3).

In gBRCAm carriers 34.8% of patients received a platinum-based therapy, 26.1% received taxane monotherapy and 17.4% received bevacizumab treatment as 1st line chemotherapy at study entry independent from overall therapy lines. [redacted]

Patients with [redacted] and gBRCAm [redacted] were not associated with a significantly better PFS compared to patients without a mutation. Median PFS time for the gBRCA cohort was 9.9 months (95% CI: 5.1-NA) and median PFS time for the "no mutation" group was 6.9 months (95% CI: 6.1- 8.2).

OS was significantly longer in the gBRCA cohort compared to the patient population with no mutation (adjusted HR=0.38 (0.17, 0.86); *P*=0.02), median OS time of gBRCAm was not reached compared to the median 23.1 (95% CI: 19.5, 27.2) in "no mutation" population.

[redacted]

Conclusion

In summary, our study provides promising data for the prevalence of germline [redacted] BRCA, [redacted] repair gene mutations, which might help to stratify a suitable patient collective for PARPi clinical trials. Due to [redacted] DNA repair gene mutations not being associated with the presence of positive genetic testing criteria, we conclude that if those are taken into account for e.g. PARPi therapy, testing of all metastatic BC patients eligible for PARPi therapy seems to be justified. [redacted]

Publications

- Fasching PA, et al. BRCA1 and BRCA2 mutations in patients with HER2 negative metastatic BC(mBC) treated with first line chemotherapy – Data from the German PRAEGNANT registry. ASCO meeting 2019