# SYNOPSIS

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| **Name of Sponsor/Company:** Astra Zeneca KK | |
| **Name of Finished Product**: Not Applicable | |
| **Name of Active Ingredient**: Not Applicable | |
| **Title of Study**: CHaRacterIzing the croSs-secTional approach to invEstigate the prevaLence of tissue *BRCA1/2* mutations in newLy diagnosEd advanced ovarian cancer patients (CHRISTELLE study) | |
| **Investigator sites**: 20 Investigator sites in Japan. | |
| **Background/rationale:**<br>In Japan, the prevalence of g*BRCA*m in patients with newly diagnosed OC with stage I - IV according to the International Federation of Gynecology and Obstetrics (FIGO) was shown to be 14.7% while in patients with stage III- IV the prevalence was 24.1%. However, there are no data regarding the prevalence of t*BRCA*m and s*BRCA*m among these patients. According to global data, s*BRCA*m are present in up to 7% of OC in the first line or platinum-sensitive relapsed clinical setting. Based on these data, we estimate that the prevalence of t*BRCA*m, namely s*BRCA*m plus g*BRCA*m, would be 30-40% in Japan for newly diagnosed OC patients (FIGO stage III- IV). As these patients cannot be detected by germline *BRCA* testing from blood samples alone, effective treatment with PARP inhibitors might be withheld from these patients. In addition, HRD which shows the tumor's genomic instability status, may be another biomarker beyond *BRCA* status for predicting the effectiveness of PARP inhibitors. Therefore, this study was therefore designed to investigate the prevalence of t*BRCA*m, s*BRCA*m as well as HRD score / genomic instability score (GIS) in tumor specimens. | |
| **Study Dates**: 19 Mar 2020 (first patient enrolled) to 13 Nov 2020 (last patient last visit) | **Phase of Development**: Post-marketing observational |
| **Objectives**:<br>The objective of this study was to investigate *BRCA* mutations and homologous recombination deficiency (HRD) score in patients with newly diagnosed advanced (at the first diagnosis of) ovarian cancer (OC).<br>**Primary Objectives:**<br>To investigate the prevalence of t*BRCA*m in the subjects.<br>**Secondary Objectives:**<br>1. To investigate the prevalence of g*BRCA*m in the subjects.<br>2. To investigate the prevalence of s*BRCA*m in the subjects. | |

3. To investigate the ratio of s*BRCA*m out of t*BRCA*m.

**Exploratory Objectives:**

1. To assess t*BRCA* variant description.
2. To assess prevalence of HRD status.
3. To evaluate prevalence of t*BRCA*m and HRD status in each subgroups as below:
   Age, Menopausal status, Cancer type, Histological classification (central pathologist reviewing), FIGO stage, Nuclear grade, History of cancer, Family history of cancer, History of smoking.

**Study design and Data source**:

This was a Japanese, multi-center, observational study. Patients with FIGO stage III - IV OC newly diagnosed after 01 January 2019 were enrolled sequentially.

Patients who had undergone or were planning to undergo BRACAnalysis for detecting g*BRCA* mutations were eligible for this study. Data was collected at 20 sites in Japan. To reduce regional bias of study sites, the number of enrolled patients per site was capped.

After patients had read the study information and signed and dated the informed consent form (ICF), they could be enrolled in the study. The patient's clinical background information, sample collection information and other data at enrollment were collected and recorded from the medical records and other available sources. Information that could identify an individual, such as name and medical chart number, was not collected. Instead, each patient was assigned an enrollment code and the study site investigator prepared and managed any documents linking the patients to their enrollment codes.

If a patient could not be contacted because they had died or were no longer being managed by the study site, this was recorded in the medical record. It was also checked whether patients or their relatives had chosen to optout of study participation either at the study site or on the hospital website, where information of study participation was posted. Patients who had not chosen to optout were enrolled in the study. The instructions of the Ethical Review Board of each site were followed regarding the handling of cases such as death.

Archived formalin-fixed paraffin-embedded (FFPE) samples from enrolled patients were forwarded to the central laboratories for t*BRCA* testing according to Sample Handling Procedures. Histopathology was assessed by the central pathologists using serial sections of the submitted samples.

The results of t*BRCA* testing and HRD score with tumor specimens as well as histopathological assessment by the central pathologists were not reported to the study sites. These results were not disclosed to study patients, as the tests that were used to collect the information had not been approved in Japan (at the time of study planning) and may not have been sufficiently accurate or reliable to evaluate health status, and disclosure of the information may have been unnecessarily stressful or misleading for the study patients and their relatives.

**Number of patients (planned and analyzed)**:

Planned: 200

Analyzed: 206

**Study population and main criteria for inclusion**:

Japanese women aged 20 years or older with newly diagnosed advanced OC (FIGO stage III - IV) with epithelial ovarian cancer, primary peritoneal cancer or fallopian-tube cancer [or a combination thereof] were included in this study. Patients had archived formalin-fixed paraffin-embedded (FFPE) samples of the primary or peritoneal metastatic tumor collected after 01 January 2019 and had or were planning to have BRACAnalysis. Patients had to give their written informed consent to participate in this study. However, if a patient had died, the inclusion was handled in accordance with the instructions of the Ethical Review Board of each site. Any patient who was not recommended by the participating physician to enroll into this study was not included.

**Test product, dose and mode of administration, batch number**: Not applicable

**Reference therapy, dose and mode of administration, batch number**: Not applicable.

**Duration of treatment**: Not applicable.

**Criteria for evaluation:**

**Outcome measures:**

The following tests were performed with the patients' blood and tumor samples:

1. BRACAnalysis at the study sites: *BRCA1/ BRCA2* classification: deleterious / suspected deleterious / variant of uncertain significance (VUS) or uncertain clinical significance / favor polymorphism or no mutation detected or not specified / other.
2. Myriad myChoice at the central laboratory: *BRCA1/ BRCA2* classification: deleterious mutation / suspected deleterious / VUS / favor polymorphism / no mutation detected, variant information, HRD value.
3. Histological classification by the central pathologist: high-grade serous carcinoma / low-grade serous carcinoma/ endometrioid carcinoma /clear cell carcinoma/ mucinous carcinoma/ other.

**Safety**: Not applicable, as no medication was given

**Statistical Methods:**

Baseline demographics and clinical characteristics were summarized descriptively (by frequency distribution for categorical variables, and by descriptive statistics for continuous variables).

**Analysis Populations:**

The enrollment population consisted of all patients who met eligibility criteria signed informed consent (or met the requirement of optout).

The full analysis set (FAS) consisted of enrolled patients who underwent g*BRCA*m and t*BRCA*m tests and had histological specimens available for central pathologist confirmation.

The per protocol analysis set (PPS) consisted of enrolled patients who had valid *gBRCA* and *tBRCA* results and who underwent histopathological assessment by the central pathologist.

**Primary Analysis:**

For the primary endpoint regarding the prevalence of t*BRCA*m in the newly diagnosed advanced OC patients, the status of tumor *BRCA1*, *BRCA2* and *BRCA1/2* mutation was presented in a table using summary statistics.

**Secondary Analyses:**

1. For the first secondary endpoint regarding the prevalence of g*BRCA*m in the newly diagnosed advanced OC patients, the status of germline *BRCA1*, *BRCA2* and *BRCA1/2* mutations were presented in a table using summary statistics.
2. For the second secondary endpoint regarding the prevalence of s*BRCA*m in the newly diagnosed advanced OC patients, the status of somatic *BRCA1*, *BRCA2* and *BRCA1/2* mutations were presented in a table using summary statistics. The prevalence of s*BRCA*m was calculated by subtracting the figure (deleterious mutation or suspected deleterious) by BRACAnalysis from the figure (deleterious mutation or suspected deleterious) by Myriad myChoice.
3. For the third secondary endpoint regarding s*BRCA*m and t*BRCA*m in the newly diagnosed advanced OC patients, the ratio of s*BRCA*m out of t*BRCA*m, was presented in a table using summary statistics.

**Exploratory Analyses:**

1. For the first exploratory endpoint regarding t*BRCA*, the variant description of t*BRCA* was presented in a table using summary statistics. .
2. For the second exploratory endpoint regarding HRD status, the HRD status (positive, negative, unknown [failed]) was presented in a table using summary statistics.
3. For the third exploratory endpoint regarding t*BRCA*m, the status of tumor *BRCA1*, *BRCA2* and *BRCA1/2* mutation and HRD status (positive / negative / unknown (failed)) in the following subgroups was presented in a table using summary statistics.
    - Age at clinical diagnosis of ovarian cancer
    - Menopausal status
    - Cancer type
    - Histological classification (central pathologist review)

- o FIGO stage
- o Medical history
- o Family history of cancer
- o History of smoking.

**Determination of Sample Size**

It was expected that the number of advanced OC (FIGO stage III - IV) was approximately 50% out of all patients with OC according to epidemiological research. The number of newly diagnosed OC is around 10000 patients per year in Japan. Considering previous studies, assuming a prevalence of t*BRCA*m in 30% of patients with OC in Japan , at least 166 patients were required to have a ≥90% probability of obtaining a point estimate with a 95% confidence interval (CI) of ± 7.5%. Taking into consideration potential issues such as loss of patients due to withdrawal of consent or technical and analytical problems of the t*BRCA* test, the number of targeted patients was set to be 200 in this study.

**Results and Conclusions**:

This study was conducted in 20 study sites in Japan and included patients with newly diagnosed OC of FIGO stage III and IV. From March 2020 to November 2020, 206 patients were entered in the FAS and 205 patients were entered in the PPS. Two patients (1.0%) had died in the PPS (99.0%). The mean (SD) age of the PPS at diagnosis was 59.4 (10.9) years, and 151 patients (73.7%) were post-menopausal.

The patients were diagnosed OC of FIGO stage III in 137 patients (66.8%) and IV in 68 patients (33.2%). OC types were as follows: 171 epithelial ovarian cancer (83.4%), 20 primary peritoneal cancer (9.8%) and 14 fallopian tube cancer(6.8%).

Currently, the main results are under evaluation; thus, the updated study results will be reported by the end of 2022.

**Date of Report**: 30.Sep 2021

**Publication (reference)**: None