STUDY REPORT SYNOPSIS

HRDx-Ovarian

A Cross-sectional, Noninterventional, Multicentre Study to Determine the Prevalence of Homologous Recombination Deficiency Among Women with Newly Diagnosed, High-grade, Serous or Endometrioid Ova1ian, Primary Peritoneal, and/or Fallopian Tube Cancer

The role of homologous recombination deficiency (HRD)-associated mutations has been well-characterized in several cancer types including ovarian and breast cancers. A majority of ovarian cancers are malignant epithelial tumours, histopathologically differentiated as high-grade serous ovarian cancer (HGSOC), endometrioid, clear-cell, mucinous, and low-grade serous carcinoma. HGSOC is an aggressive disease often diagnosed at an advanced stage with a poor prognosis. Around 50% of patients with HGSOC exhibit HRD. HRD impairs the repair of normal DNA damage in tumour cells, resulting in loss or duplication of chromosomal regions, known as genomic loss of heterozygosity.

This observational study was canied out to understand the region and cotmtly-specific prevalence of HRD in women with stage III or IV high-grade serous or endometi'ioid ovarian, prima1y peritoneal, ancVor fallopian tube cancer and associated factors with clinical characteristics in Asia-Pacific cOlmtries, Russia, and Middle East and African cotmtries. The findings of this study will assist the oncologist in the selection of patients and to take the clinical decision for first-line maintenance of ovarian cancer patients.

Milestones:

Milestone	Date
Study Protocol approved.	September 2020
First subject/patient in	02May2021
Last subject/patient in	15 August 2021
Last subject/patient last visit	15 August 2022
Final database lock	25 May2023
Clinical study report approved	Ongoing

Phase of development: IV or Retrospective Study

Sponsor: AstraZeneca

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Background/rationale: The role of homologous recombination deficiency (HRD) associated mutations has been well-characterized in several types of cancer, such as ovarian and breast cancers. A majority of ovarian cancers are malignant epithelial hlillours, histopathologically differentiated as high-grade serous ovarian cancer (HGSOC), endometrioid, clear-cell, mucinous, and low-grade serous carcinoma. HGSOC is an aggressive disease often diagnosed at an advanced stage with a poor prognosis. Arotmd 50% of patients with HGSOC exhibit HRD. HRD impairs the repair of n01mal DNA damage in tllillour cells, which results in loss or duplication of chromosomal regions, termed genomic loss ofheterozygosity.
PARP inhibitors make use of synthetic lethality where the loss of 1 ftmction is compatible with cell viability, but the concmTent loss of 2 critical ftmctions in cell replication results in cell death. Thus, patients with HRD are appropriate candidates for PARP inhibitor therapy. Also, PAOLA-I and PRIMA trials have demonstrated better progression-free survival with PARP inhibitors in patients with HRD positive HGSOC, endometrioid ovarian, prima1y peritoneal, or fallopian t1.1be cancer.

To maximize the accessibility and benefit of PARP inhibitors to eligible patients, it is essential to know the prevalence of HRD in women with advanced high-grade serous or endometrioid ovarian cancer. Presently, the prevalence data for HRD are available from selected geographies only and ranges from 31% to 50%. Fmthermore, the risk factors associated with HRD and the clinical characteristics of patients with HRD need exploration for region-specific differences. This study aims to collect region and cotmtly-specific prevalence ofHRD in women with stage III or IV high-grade serous or endometifoid ovarian, prima1y peritoneal, and/or fallopian h1be cancer and associated factors with clinical characteristics in Asia Pacific cotmti·ies, Latin America, Russia, Australia, and Middle East and African cotmtries. The st1.1dy's results will help the oncologists select the patient and take clinical decisions for first line maintenance of high-grade serous ovarian cancer patients.

Objectives:

Primary Objectives

- To estimate the overall prevalence ofHRD in patients with newly diagnosed stage III or IV high-grade serous or endometrioid ovarian, primary peritoneal, and/or fallopian t1.1be cancer

Secondary Objectives

- To determine the region-specific prevalence ofHRD in the patient population from different geographies
- To determine the prevalence ofhlillour BRCAl mutation (tBRCAlm)/ttlillour BRCA2 mutation (tBRCA2m) in the patient population from different geographies
- To determine the prevalence of genomic instability (GI high excluding tBRCAm) in the patient population from different geographies
- To identify the factors associated with HRD positive stah1s and tBRCAlm/tBRCA2m (tBRCAl/2m)

Exploratory Objectives

To describe the clinical characteristics of the patient population with HRD (overall and from different geographies)

Study design: Cross-sectional, noninte1vention al, multicentre, epidemiological, obse1vational sh1dy

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Data source: The data source for this study was history repo1ted by the patients and available medical records. The HRD status repo1t received from the routine reference lab defined by each country was the source for primaiy and secondary outcome variables from index date until end of follow up.

Study population: Women with high-grade (stage III or IV ofFIGO classification 2014) ovarian cancer who are eligible for inclusion into the study if they met all of the inclusion criteria and none of the exclusion criteria.

Inclusion criteria:
1. Patients 2:18 years of age or adults according to age of majority as defined by the local regulations
2. Willing and able to provide written informed consent for paiticipation in the study

3. Patients with histologicaUy confirmed new diagnosis (within past 120 days of enrolment) of high-grade (stage III or IV ofFIGO classification 2014) serious or endometrioid ovarian, primary peritoneal, and/or fallopian tube cancer.

4. Patients having availability ofhistopathology repo1t and FFPE ai·chival tumour tissue block(s) collected within the past 120 days of enrolment.

Exclusion criteria:
1. Patients with mucinous, clear-cell, undifferentiated carcinoma, or malignant Brenner's tumour.
2. Patients diagnosed with any severe acute or chronic medical or psychiatric conditions that may increase the risk associated withsh1dy pa1ticipation or may interfere with the interpretation of the study results, and those in the judgment of the investigator are not appropriate for enrolment in this study.

Statistical methods:

All analyses were performed using Full Analysis Set (FAS) that comprised of all patients who fulfil all the eligibility criteria and were enrolled into the study. All tabulations, figures, and listings were produced using the SAS System (Version 9.2 or higher). Statistical analyses were primarily explorative and descriptive in nature. All the statistical analyses were performed on FAS. Whenever reasonable, the analyses were presented countiy-wise or region-wise. No statistical hypothesis testing was planned for this sh1dy. All relevant parameters were analyzed descriptively with appropriate statistical methods: categorical variables using frequencies, percentages, and conesponding 95% confidence interval (CI) (using n01mal approximation to binomial propo1tions method) and continuous variables using number of observations, ai·ithmetic mean, standard deviation (SD), 95% CI of the mean, median, minimum, and maximum. Logistic regression analysis was used to identify the potential factors associated with HRD positive status and tBRCAl/2m. The paitial dates for parameters (e.g., age) was imputed. No other missing data was input. The analyses were performed using the available data only method. The handling of missing data was detailed in the statistical analysis plan.

Results:

- A total of 812 patients were enrolled in the sh1dy of which 734 patients completed and 78 patients were discontinued due to violation of eligibility criteria. A total of 734 patients were

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included in the FAS population. Among these, HRD testing results were available for 662 and this constituted the FAS test population.

- The study evaluated the overall and region wise (Asia, Russia, Middle East and Africa) prevalence ofHRD, tBRCAl/2m and GI high excluding tBRCAm.
- Overall prevalence of HRD positive status was 56.04% (371/662), of which patients with tBRCAl/2m (comprising pathogenic and likely pathogenic, deleterious, and likely deleterious mutations) accotmted for 25.23% (167/662), while those with GI high excluding tBRCAm (encompassing VUS and likely non-pathogenic variants, along with cases of no mutation detected and non-deleterious variations) accotmted for 30.82% (204/662).
- Region and cotmtly specific data showed that the highest prevalence of HRD positive status was repo1ted in Russia at 58.48% (238/407), followed by the Middle East and Africa at 52.22% (94/180), and Asia at 52.00% (39/75).
- Overall prevalence of tBRCAlm, tBRCA2m, tBRCAlm and tBRCA2m, and tBRCAl/2m total was 16.47% (109/662), 7.40% (49/662), 1.36% (9/662) and 25.23% (167/662) respectively.
    - In Asia, the prevalence of tBRCAlm and tBRCA2m positive patients was 5.33% (4/75) for each, while none of the patients had both tBRCAlm and tBRCA2m. Overall, the prevalence oftBRCAl/2m total in Asia was 10.67% (8/75).
    - In the MEA region, prevalence of tBRCAlm, tBRCA2m, tBRCAlm and tBRCA2m was 16.11% (29/180), 8.33% (15/180), and 3.89% (7/180), respectively. Overall, the prevalence of tBRCAl/2m total in MEA region was 28.33% (51/180).
    - In Russia, the prevalence of tBRCAlm, tBRCA2m, tBRCAlm and tBRCA2m was 18.67% (76/407), 7.37% (30/407), 0.49% (2/407). Overall, the prevalence of tBRCAl/2m total in Russia was 26.54% (108/407).
- Overall, the prevalence of GI high excluding tBRCAm status was 30.82% (204/662).
    - The prevalence of GI high excluding tBRCAm was 31.94% (130/407) in Russia, 41.33% (31/75) in Asia, and 23.89% (43/180) in Middle East and Africa.
- Factors associated with HRD positive status
    - Univariate analysis showed that obese patients (Odds Ratio [OR]: 0.650; p=0.0353), patients who attained menarche before the age of 13 (OR: 0.477; p=0.0407), patients with Stage IV cancer (OR: 0.654; p=0.0192), or those who had a histo1y ofhigh-grade serous peritoneum cancer (OR: 0.347; p=0.0227) are associated with lower odds ofHRD positive stahIS. On the contra1y, patients with a fainily histo1y of genetic-related cancer (OR: 2.638; p<0.0001), one comorbidity (OR: 1.537; p=0.0333), history ofinjectables or oral contraceptives (OR: 2.036; p=0.0123) showed higher odds of HRD positive stah1s .
    - Multivariate analysis showed that patients with fainily histo1y of genetic related cancer (OR: 2.614; p=0.0002), or patients with histo1y of injectables and oral contraceptives (OR: 2.347; p=0.0087) showed higher odds ofHRD positive stah1s while patients with a histo1y of post-menopa11Sal ho1mone replacement therapy (OR: 0.096; p=0.0067) showed lower odds ofHRD positive stah1s.
- Factors associated with tBRCAl/2m
    - Univariate analysis revealed lower odds of tBRCAl/2m in patients aged 2::65 years (OR: 0.654; p=0.0405), individuals in Asia (OR: 0.346; p=0.0067), patients with the primaiy h1mour located in the peritoneum (OR 0.208; p=0.0335), or those with Stage

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IV cancer (OR 0.620; p=0.0326). Conversely, white patients (OR 3.532; p=0.0022), and south-east Asians (OR 5.314; p=0.0447), ex-smokers (OR 2.537; p=0.0031), those with a family history of genetic-related cancer (OR 4.961; p=0.0001) or a histo1y of injectables or oral contraceptives (OR: 1.919; p=0.0163) were linked to higher odds of tBRCAl/2m.

- Multivariate analysis showed that patients with family histo1y of genetic related cancer (OR: 4.538; p<.0001) or histo1y of injectables and oral contraceptives (OR:1.871; p= 0.0456) showed higher odds oftBRCAl/2m.

- Factors associated with GI high excluding tBRCAm
  - Univariate analysis showed that patients aged 2::65 years (OR 1.468; p= 0.0336) or individuals with a single comorbidity (0 R: 1.642, p=0.0146) demonstrated higher odds of a GI high excluding tBRCAm. Conversely, white patients (OR 0.558; p=0.0269), patients with a family histo1y of genetic-related cancer (OR 0.512; p=0.0098), individuals who attained menarche before the age of 13 (OR: 0.469; p=0.0278) exhibited lower odds of a GI high excluding tBRCAm
  - Multivariate analysis showed patients with one comorbidity showed higher odds of GI high excluding tBRCAm(OR: 1.714; p=0.0182) compared to those without any comorbidity. On the other hand, patients with fainily histo1y of genetic related cancer (OR: 0.535; p=0.0263) were found to have lower odds of GI high excluding tBRCAm.

- Demographic and clinical characteristics of the study coho1t
  - Patients with HRD positive status had a median age of 59 years and a median BMI of 25.7 Kg/m^2. The majority of the patients had hypertension (74.21%). Other prevalent medical conditions in the study patients were diabetes mellihIS (24.21%) and coronary hea1t disease (16.04%). Majority of patients were classified as never smokers (88.15%).
  - Majority of patients were either fully active and could carry out all pre-disease performance without restriction (48.77%; ECOG grade 0) or were restricted in physically strenuous activity but ambulatory and capable of canying out work of a light or sedenta1y nah1re (44.01%; ECOG grade 1). The primary hlillour location in the sh1dy cohort was ovaiy (92.92%), predominantly high-grade serotIS (87.87%).
  - Majority of patients with HRD had FIGO stage III carcinoma (74.80%) and without family histo1y of cancer (65.94%).
  - In terms ofreproductive histo1y, majority of patients with HRD had attained menarche at the age of 13-15 years (67.17%), were multiparotIS (78.75%), and reached menopause (83.92%).
  - Majority had no histo1y of injectable or oral contraceptives consumption (89.24%) or postmenopausal ho1mone replacement therapy (98.37%).

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