2. SYNOPSIS

Study centres

The study was conducted at 16 centres in India.

Publications

Ghosh J, Das C, Gogia A, et al. Safety and tolerability of olaparib in Indian patients with ovarian cancer: the prospective, single-arm, phase 4 SOLI trial [abstract]. *Int J Gynecol Cancer.* 2022;32:A137.

Safety and tolerability of olaparib in Indian patients with ovarian cancer: the prospective, single-arm, phase 4 SOLI trial. Poster presented at: International Gynecologic Cancer Society Congress, 2022; 29 September 2022 to 01 October 2022; New York City, USA.

Objectives and criteria for evaluation

Table S1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety of olaparib in Indian patients with: • Platinum-sensitive relapsed ovarian cancer who are in complete or partial response following platinum-based chemotherapy, and • HER-2 negative metastatic breast cancer with germline BRCA1/2 mutation.	Number, frequency and proportion of patients with adverse events (AEs) and serious adverse events (SAEs). The safety variables to be analysed include AEs, clinical laboratory tests (haematology and chemistry), physical examination results, vital parameters, World Health Organization (WHO) performance status (PS) and deaths as observed by participating physician.

Abbreviations: BRCA1/2 = breast cancer gene 1/gene 2; HER = human epidermal growth factor receptor.

Study design

This was a prospective, single-arm, multicentre, interventional Phase 4 study to investigate the safety of olaparib in Indian adult patients who received olaparib as per the locally approved prescribing information. Approximately 225 patients (180 with ovarian cancer and 45 with breast cancer) were to be screened to enrol approximately 200 patients (160 with ovarian cancer and 40 with breast cancer). Olaparib was administered orally at a dose of 300 mg (two 150-mg tablets) twice daily.

Patient participation included the following:

- Screening/enrolment phase (Visit 1): Planned up to 7 days prior to Day 1.
- Treatment phase (Visits 2 to 7): Extended from Days 1 to 182 or until study treatment discontinuation due to either disease progression, unacceptable toxicity or other reasons as listed in the drug discontinuation section of the clinical study protocol (CSP), whichever occurred first.

- End-of-treatment (EOT) Visit (Visit 8): An EOT visit was to be scheduled on Day 182 of the study treatment administration. In a case where patient discontinued the study treatment for any reason listed in drug discontinuation section of the CSP before Day 182, the last visit of the patient was considered as EOT visit.
- Follow-up phase (End-of-study [EOS] Visit [Visit 9]): This phase began once a patient discontinued study treatment during treatment phase, and continued until 28 days after last dose, death, lost to follow-up, consent withdrawal for study participation or study end, whichever occurred first. A telephone follow-up was conducted 28 days after the EOT visit. This was considered as EOS visit. Every effort was made to conduct the telephonic EOS visit before the patient started subsequent treatment.
- Post-trial Access to Olaparib: Patients who received clinical benefit from olaparib at EOT phase were allowed post-trial access to olaparib as long as long-term clinical benefit was observed or until the investigator decided it was not in the best interest of the patient to continue olaparib treatment.

Target population and sample size

Female patients aged ≥18 years, who were eligible to receive olaparib for ovarian cancer (for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who were in a complete or partial response to platinum-based chemotherapy); and/or for breast cancer (in patients with deleterious or suspected deleterious germline mutation of BReast CAncer gene 1/2 [gBRCAm], human epidermal growth factor receptor 2-negative metastatic breast cancer who had previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting). Patients with hormone receptor-positive breast cancer who were treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment were eligible for participation in the study.

A total of 200 patients were planned to be evaluated for safety; 202 patients were enrolled and 200 patients were analysed for safety in the study.

Duration of treatment

Olaparib was to be administered from Days 1 to 182 or until study treatment discontinuation due to either disease progression, unacceptable toxicity or other reasons described in the CSP, whichever occurred first.

Statistical methods

Safety analyses were performed on the safety analysis set. Data were summarised using descriptive statistics. Continuous variables were summarised using the number of observations, mean, standard deviation (SD), median and range as appropriate. Categorical values were summarised using the number of observations and percentages as appropriate. All

adverse events (AEs) recorded on the electronic case report form were coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities dictionary (Version 24.1). Assessment of AE severity was based on the National Cancer Institute Common Terminology Criteria for AE (latest version). Treatment-emergent adverse events (TEAEs) are events with a start date on or after the date of first dose of study treatment. Also, AEs that were a consequence of a pre-existing condition that had worsened later during the treatment phase were termed as "Treatment-emergent".

Study population

A total of 214 patients were screened for the study. Of these, 202 patients were enrolled in the study and 200 patients (161 ovarian cancer, 38 breast cancer and 1 with ovarian cancer and breast cancer) received at least 1 dose of the study treatment and were included in the safety analysis set.

Overall, 123 (61.5%) patients completed the study; 104 (64.6%) with ovarian cancer, 18 (47.4%) with breast cancer and 1 (100%) with both ovarian and breast cancer. Seventy-seven (38.5%) patients discontinued the study; 57 (35.4%) with ovarian cancer and 20 (52.6%) with breast cancer. Of the patients who discontinued the study, primary reasons for discontinuation reported for ≥10% of patients overall were disease progression (62.3%), other reasons (13.0%) and investigator decision (10.4%).

Overall, patients had a mean (SD) age of 51.5 (10.01) years and the mean (SD) body mass index was 25.9 (4.60) kg/m^2. International Federation of Gynaecology and Obstetrics stage of cancer at screening reported for ≥10% of patients overall were stage IIIC (34.2%), stage IVA (26.2%) and stage IVB (17.3%). Most patients (93.6%) were not of child-bearing potential. Of the 201 (99.5%) patients overall who received previous cancer therapy, 125 (61.9%) received >2 cancer therapy regimens and 66 (32.7%) received 2 cancer therapy regimens. At baseline, most patients (97.0%) overall had World Health Organization (WHO) performance status of normal activity.

Summary of safety results

Extent of exposure: The mean (SD) duration of exposure to study treatment for patients in the safety analysis set was 146.7 (54.93) days.

Adverse events by SOC and PT: Overall, TEAEs were reported for 179 (89.5%) patients (963 events). The TEAEs by SOC reported for ≥10% of patients were Blood and lymphatic system disorders (59.5%), Gastrointestinal disorders (45.0%), General disorders and administration site conditions (33.0%), Nervous system disorders (17.0%), Musculoskeletal and connective tissue disorders (16.5%), Investigations (15.5%), Infections and infestations (14.5%) and Metabolism and nutrition disorders (13.0%). Treatment-emergent

AEs by PT reported for ≥10% of patients were anaemia (55.0%), thrombocytopenia (21.0%), nausea (18.5%), vomiting (16.0%), fatigue (14.0%), decreased appetite (11.5%), leukopenia (10.5%) and diarrhoea and back pain (10.0% each).

Adverse events by severity: Overall, Grade ≥3 TEAEs were reported for 89 (44.5%) patients (209 events); those reported for ≥10% of patients by SOC and PT were Blood and lymphatic system disorders (37.0%) and anaemia (33.0%), respectively. Overall, Grade ≥3 treatment-related TEAEs were reported for 71 (35.5%) patients (156 events); those reported for ≥10% of patients by SOC and PT were Blood and lymphatic system disorders (32.5%) and anaemia (29.5%), respectively.

Adverse events by relationship to study treatment: Overall, treatment-related TEAEs were reported for 120 (60.0%) patients (503 events). Treatment-related TEAEs reported for ≥10% of patients overall by SOC were Blood and lymphatic system disorders (47.5%), Gastrointestinal disorders (21.5%) and General disorders and administration site conditions (15.0%). Treatment-related TEAEs reported for ≥10% of patients overall by PT were anaemia (44.5%), thrombocytopenia (15.5%) and nausea (10.5%).

Death: Overall, 6 (3.0%) patients died during the study. The fatal TEAEs by PT were death (2 patients); coronavirus disease 2019 (COVID-19) (3 patients) and abdominal distension, abdominal pain, asthenia, coagulopathy, dyspnea, hepatic enzyme increased, hepatic function abnormal, hypophagia, increased tendency to bruise, metastases to liver and thrombocytopenia (all TEAEs in 1 patient). One (0.5%) patient (breast cancer) had a fatal treatment-related TEAE (abdominal distension).

Serious adverse events (SAEs): Overall, treatment-emergent SAEs were reported for 32 (16.0%) patients (55 events). The SAEs reported for ≥5% of patients overall by SOC and PT were Blood and lymphatic system disorders (8.0%) and anaemia (7.0%), respectively.

Discontinuation of study treatment due to adverse events: Overall, TEAEs leading to dose discontinuation were reported for 22 (11.0%) patients (42 events). The TEAEs leading to dose discontinuation reported for ≥2% of patients overall by SOC were Blood and lymphatic system disorders (4.5%), Gastrointestinal disorders (3.5%) and General disorders and administration site conditions (3.0%). The TEAEs leading to dose discontinuation reported for ≥2% of patients overall by PT were anaemia (3.5%) and thrombocytopenia (2.0%).

Overall, TEAEs that lead to dose reduction were reported for 47 (23.5%) patients (65 events). The TEAEs leading to dose reduction reported for ≥2% of patients overall by SOC were Blood and lymphatic system disorders (19.5%), Gastrointestinal disorders (3.0%) and General disorders and administration site conditions (2.0%). The TEAEs leading to dose reduction reported for ≥2% of patients overall by PT were anaemia (17.0%) and thrombocytopenia (3.0%).

Overall, TEAEs leading to dose interruption were reported for 126 (63.0%) patients (296 events). The TEAEs leading to dose interruption reported for ≥5% of patients overall by SOC were Blood and lymphatic system disorders (45.0%), General disorders and administration site conditions (11.5%), Gastrointestinal disorders (9.0%), Infections and infestations (8.0%) and Investigations (5.0%). The TEAEs leading to dose interruption reported for ≥5% of patients overall by PT were anaemia (38.0%), thrombocytopenia (17.0%), leukopenia (7.0%) and COVID-19 (6.0%).

Adverse events of special interest: Overall, 3 (1.5%) patients, all having ovarian cancer, had AEs of special interest: 1 patient had the event of tetany (mild, nonserious, not related to study treatment) in the SOC of Endocrine disorders; 1 patient had the event of ischemic stroke (life-threatening or disabling AE, serious, not related to study treatment) in the SOC of Nervous system disorders and 1 patient had the event of deep vein thrombosis (moderate, nonserious, not related to study treatment) in the SOC of Vascular disorders.

Clinical laboratory evaluation:

Haematology: A shift from normal level at baseline to below normal levels at EOT visit in haematology results were reported for basophils (18 [9.0%] patients), eosinophils (10 [5.0%] patients), haemoglobin (28 [14.0%] patients), leucocytes (23 [11.5%] patients), lymphocytes (29 [14.5%] patients), monocytes (27 [13.5%] patients), neutrophils (14 [7.0%] patients) and platelets (27 [13.5%] patients).

Clinical chemistry: Overall, no remarkable changes in mean from baseline visit to postbaseline EOT visit were observed for alanine aminotransferase (ALT), albumin, alkaline phosphatase, total bilirubin, blood urea nitrogen and creatinine. The mean (SD) change from baseline to EOT for decrease in aspartate aminotransferase (AST) was -2.24 U/L (21.32 U/L). No patient had ALT ≥3 × upper limit of normal (ULN) or AST ≥3 × ULN and total bilirubin ≥2 × ULN during the study.

Urinalysis: Urinalysis was sporadically positive for albumin or glucose or haemoglobin/erythrocytes/blood or protein for some patients.

Vital signs and electrocardiogram (ECG) results: No remarkable changes in mean from baseline visit to postbaseline EOT visit were observed for vital signs. Overall, no patients had abnormal clinically significant ECG results at baseline. One (0.5%) patient (breast cancer) with normal ECG at baseline had abnormal clinically significant ECG results (prolonged QTc interval) at EOT visit.

Other Observations Related to Safety: No pregnancies were reported during the study. No cases of study treatment overdose were reported during the study. At EOS visit, WHO

performance status overall showed normal activity for 104 (52.0%) patients, restricted activity for 8 (4.0%) patients and ‘in bed ≤50% of the time’ for 1 (0.5%) patient.

Conclusion

Overall, the 300-mg (two 150-mg tablets) oral dose of olaparib administered twice daily was tolerable in Indian patients with platinum sensitive relapsed ovarian cancer who were in complete or partial response following platinum-based chemotherapy and/or metastatic breast cancer with gBRCAm. The safety observations in this study were consistent with the known safety profile of olaparib and no new safety signals were observed.