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Olaparib (Lynparza®) as first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer

Ludwig Boltzmann Institut
Health Technology Assessment

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Authors: Dr. Eleen Rothschedl

Internal review: Priv.-Doz. Dr. phil. Claudia Wild; Nicole Grössmann, MSc

External review: Univ.-Prof. Dr. Alexander Reinthaller
Klinische Abteilung für Allgemeine Gynäkologie und Gynäkologische Onkologie, Universitätsklinik für Frauenheilkunde, Medizinische Universität Wien

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CONTACT INFORMATION

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Responsible for Contents:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

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Abstract

Introduction

In December 2018, the US Food and Drug Administration approved olaparib, a poly polymerase (PARP) inhibitor, for the first-line maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete response (CR) or partial response (PR) to first-line platinum-based chemotherapy. To date, olaparib has not yet been approved by the European Medicines Agency for the assessed indication.

Methodology

Published and grey literature were identified by searching the Cochrane Library, CRD database, Embase, Ovid Medline, PubMed, Internet sites and contacting the manufacturer, resulting in 153 references overall. A quality assessment was conducted to assess the risk of bias at the study level based on the EUnetHTA internal validity for randomised controlled trials. The Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology was not applicable due to lack of median progression-free survival (PFS) – and overall survival (OS) data.

Results from the SOLO1 trial

The SOLO1 trial evaluated the efficacy and safety of olaparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer, primary peritoneal cancer or fallopian tube cancer and a BRCA1/2 mutation, who had a CR or PR after platinum-based chemotherapy. Investigator-assessed analysis showed that the Kaplan-Meier estimate of the rate of freedom from disease progression and from death at three years was 60% in the olaparib group versus 27% in the placebo group. According to the analysis assessed by blinded independent central review, the Kaplan-Meier estimate of the rate of freedom from disease progression and from death at three years was 69% in the olaparib group versus 35% in the placebo group. A sensitivity analysis of investigator-assessed PFS showed that the median PFS was 36.1 months longer in patients of the olaparib group than in patients of the placebo group. An interim analysis of OS data showed a Kaplan-Meier estimate of the rate of freedom from death at three years of 84% (olaparib group) vs 80% (placebo group). The median time to the first subsequent therapy or death was longer in olaparib group patients (51.8 months) than in placebo group patients (15.1 months). Serious adverse events (AEs) occurred in 21% of patients receiving olaparib and 12% of patients who received placebo. No AEs that occurred during the study intervention led to death.

Conclusion

SOLO1 trial results showed a benefit with olaparib first-line maintenance therapy in delay of disease progression in patients with newly diagnosed ovarian cancer and BRCA1/2 mutation. However, the trial is currently ongoing, the presented data are the primary analysis data, and interim OS data are immature. HRQoL data also derives from primary analysis and the detected between-group difference was not considered to be clinically meaningful. Final analysis data from the SOLO1 trial is pending and may confirm the clinical benefit of olaparib first-line maintenance therapy. Further investigation of olaparib first-line maintenance therapy in phase III trials, long-term data, as well as a direct comparison of olaparib with different PARP inhibitors are warranted to determine the optimal treatment for this patient population.

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1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used to structure this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

EUnetHTA HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is olaparib?
A0022	Who manufactures olaparib?
A0007	What is the target population in this assessment?
A0020	For which indications has olaparib received marketing authorisation?
Health problem and current use	
A0002	What is ovarian cancer?
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A0006	What are the consequences of ovarian cancer for the society?
A0023	How many people belong to the target population?
A0005	What are the symptoms and the burden of ovarian cancer?
A0003	What are the known risk factors for ovarian cancer?
A0024	How is ovarian cancer currently diagnosed according to published guidelines and in practice?
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Clinical effectiveness	
D0001	What is the expected beneficial effect of olaparib on mortality?
D0006	How does olaparib affect progression (or recurrence) of ovarian cancer?
D0005	How does olaparib affect symptoms and findings (severity, frequency) of ovarian cancer?
D0011	What is the effect of olaparib on patients' body functions?
D0012	What is the effect of olaparib on generic health-related quality of life?
D0013	What is the effect of olaparib on disease-specific quality of life?
Safety	
C0008	How safe is olaparib in relation to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying olaparib?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of olaparib?
A0021	What is the reimbursement status of olaparib?

2 Drug description

Generic/Brand name/ATC code:

Olaparib/Lynparza®/L01XX46

B0001: What is olaparib?

olaparib is a PARP inhibitor

Olaparib (Lynparza®) is a small molecule inhibitor of the human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2 and PARP-3) with potential chemosensitising, radiosensitising and antineoplastic activities. It has been shown to inhibit tumour growth in vivo (as well as the growth of selected tumour cell lines in vitro) either by single-use or in combination with established chemotherapies. Olaparib selectively binds and inhibits PARPs, which are required for the efficient repair of deoxyribonucleic acid (DNA) single-strand breaks. By the inhibition of PARP, the cytotoxicity of DNA-damaging agents may be enhanced and tumour cell chemoresistance and radioresistance may be reversed [2, 3].

PARP are required for the efficient repair of DNA single-strand breaks

BRCA mutation status needs to be determined prior to treatment start

Prior to the initiation of olaparib treatment, the patients' breast cancer susceptibility gene (BRCA) mutation status should be determined by using an appropriately validated test. If the patients have a confirmed deleterious or suspected deleterious BRCA mutation in either the germline or the tumour, they are eligible for olaparib therapy [2].

300 mg olaparib orally twice daily

The recommended dose of olaparib is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg [2]. In Austria, Lynparza® is available as tablets (100 and 150 mg) and capsules (50 mg) [4].

CAVE: dosing differences between tablets and capsules!

There are important differences in posology between olaparib capsules and tablets; olaparib capsules should not be substituted for olaparib tablets due to differences regarding the dosing and bioavailability of each formulation. The specific dose recommendations for each formulation should be followed. Olaparib is for oral use; the tablets should be swallowed whole and not be chewed, crushed, dissolved or divided. Lynparza® tablets may be taken without regard to meals [2].

olaparib initiation within 8 weeks after completion of chemotherapy

Olaparib treatment should be started no later than eight weeks after completion of the final dose of the platinum-containing chemotherapy; it is recommended that the treatment should be continued until disease progression. In case of the occurrence of adverse reactions (e.g., nausea, vomiting, diarrhoea and anaemia), olaparib treatment may be interrupted and dose reduction can be considered. The concomitant use of strong or moderate Cytochrome(CYP)3A inhibitors is not recommended and the use of alternative agents should be considered [2].

contraindications: hypersensitivity, breast-feeding

Olaparib is contraindicated in case of hypersensitivity to the active substance or to any of the excipients (see Table 4), and breast-feeding during treatment and one month after the last dose [2].

A0022: Who manufactures olaparib?

AstraZeneca. Olaparib is being co-developed by AstraZeneca and Merck [5].

3 Indication

A0007: What is the target population in this assessment?

Olaparib (Lynparza®) is indicated as first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer, primary peritoneal cancer or fallopian tube cancer (or a combination thereof) with a germline or somatic mutation in BRCA1, BRCA2, or both (BRCA1/2) who had a complete response (CR) or partial response (PR) after platinum-based chemotherapy [5].

women with newly diagnosed ovarian cancer and a BRCA1/2 mutation with CR or PR after platinum-based chemotherapy

4 Current regulatory status

A0020: For which indications has olaparib received marketing authorisation?

To date, olaparib (Lynparza®) has not been approved by the European Medicines Agency (EMA) for the assessed indication. The EMA granted marketing authorisation for Lynparza® as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in response (CR or PR) to platinum-based chemotherapy [6].

not approved by the EMA for the assessed indication

In December 2018, the U.S. Food and Drug Administration (FDA) approved olaparib (Lynparza®) for the first-line maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in CR or PR to first-line platinum-based chemotherapy. Patients with gBRCAm advanced epithelial ovarian, fallopian tube or primary peritoneal cancer should be selected for therapy based on an FDA-approved companion diagnostic [7].

FDA-approved for first-line maintenance treatment since 12/2018

The FDA additionally granted marketing authorisation for the following indications [8]:

further FDA-approved indications

- As maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in CR or PR to platinum-based chemotherapy
- For the treatment of adult patients with deleterious or suspected deleterious gBRCAm advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Patients should be selected for therapy based on an FDA-approved companion diagnostic.
- For the treatment of patients with deleterious or suspected deleterious gBRCAm, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be con-

sidered inappropriate for endocrine therapy. Patients should be selected for therapy based on an FDA-approved companion diagnostic.

5 Burden of disease

A0002: What is ovarian cancer?

7th most common cancer in Austria

In Austria, ovarian cancer is the seventh most common cancer in women; 3% of cancer cases in women are ovarian cancers [9]. Ovarian cancer develops in the fallopian tubes (70%), ovaries (30%) and, in rare cases, derives from the peritoneum (primary peritoneal cancer).

most ovarian cancers are of epithelial origin

The majority of tumours (approximately 90%) are of epithelial origin. The following subtypes can be distinguished: serous-papillary (which is the most common histological type), endometrioid, clear cell, mucinous, Brenner (transitional cell), mixed epithelial tumours, undifferentiated and unclassified [10, 11].

A0004: What is the natural course of ovarian cancer?

diagnosis in approx. 50% of cases when the tumour has already metastasised

5-year relative survival rate: 44.3%

In Austria, 650 women were affected by ovarian cancer in 2016; 519 women died from the disease. Approximately 50% of the women were diagnosed with ovarian cancer when the tumour had already metastasised: 25% at regional tumour stage, 21% at disseminated tumour stage (one-third of the tumours could not be assigned). The relative survival rate following diagnosis in patients with ovarian cancer (2009–2013) is 75.5% at one year, 55.5% at three years and 44.3% at five years. In 2016, the age-standardised mortality rate (European Standard Population, 2013) was 10.7 per 100,000 women per year [9].

high rate of relapse within 3 years following optimal front-line treatment

Despite the performance of an optimal upfront surgery and the administration of front-line chemotherapy with a paclitaxel- and carboplatin-containing regimen, approximately 70% of patients have a relapse within the first three years [10].

A0006: What are the consequences of ovarian cancer for the society?

A0023: How many people belong to the target population?

incidence rate in Austria: 13.8/100,000 women/year

The age-standardised incidence rate (European Standard Population, 2013) of ovarian cancer in Austria is 13.8 per 100,000 women per year [9]. In 2016, 650 women were newly diagnosed with the disease.

median age at diagnosis: 63 years

In the US, the number of new cases of ovarian cancer was 11.6 per 100,000 women per year; approximately 1.3% of women will be diagnosed with ovarian cancer at some point during their lifetime (based on data from 2013–2015). The median age at diagnoses of ovarian cancer is 63 years; the disease is most frequently diagnosed among women aged between 55 and 64 years. The percentage of ovarian cancer deaths is highest among patients aged 65 to 74 years, with a median age at death of 70 years. The number of deaths was 7.2 per 100,000 women per year [12].

A0005: What are the symptoms and the burden of ovarian cancer?

acute or subacute presentation

The clinical presentation of patients with epithelial ovarian carcinoma, fallopian tube carcinoma and peritoneal carcinoma could be either acute or subacute. In some cases, the disease is discovered incidentally in the course of a surgery performed for another indication.

symptoms are nonspecific

The symptoms associated with ovarian carcinoma, fallopian tube carcinoma and peritoneal carcinoma are nonspecific and may also be caused by urologic, gastrointestinal or other conditions. If symptoms are of new onset, coexist with other symptoms, occur almost daily, and are more severe than expected, further evaluation is warranted. Patients with an acute presentation are typically affected by advanced disease and present with conditions that require urgent care, including pleural effusion (causing shortness of breath), bowel obstruction (severe nausea and vomiting) or, infrequently, venous thromboembolism [13].

acute presentation requires urgent care

symptoms of subacute presentation

Most commonly, affected women present in a clinically subacute manner, including the following symptoms:

- An adnexal mass, discovered on pelvic examination or imaging performed due to symptoms of pelvic pain or pressure or found on routine pelvic examination. In patients with advanced disease, the pelvic mass may extend beyond the adnexa.
- Pelvic and abdominal symptoms such as bloating, urinary urgency or frequency, difficulty eating or feeling full quickly, and pelvic or abdominal pain
- Pelvic pain and pelvic mass
- Abdominal distension due to ascites or bulky abdominal disease
- Atypical glandular cells on cervical cytology (infrequent)
- Paraneoplastic symptoms: cerebellar degeneration, polyneuritis, dermatomyositis, hemolytic anemia, disseminated intravascular coagulation, acanthosis, or nephrotic syndrome) (occurring rarely)
- Palpable inguinal or cervical lymphadenopathy (uncommon)[13].

A0003: What are the known risk factors for ovarian cancer?

risk factors

The risk for ovarian cancer is increased by early menarche and late menopause, infertility, increasing age, endometriosis and polycystic ovarian syndrome, obesity, cigarette smoking (mucinous carcinoma) and, possibly, the use of talcum powder. Furthermore, women who use an intrauterine device, who receive postmenopausal hormone therapy or who are affected by hereditary ovarian cancer syndromes (BRCA gene mutations, Lynch syndrome) have a higher risk of developing ovarian cancer [10, 13, 14].

protective factors

Factors that are protective or decrease the risk for ovarian cancer, respectively, include the use of oral contraceptives, tubal ligation, breastfeeding, suppression of ovulation and previous pregnancy [10, 13, 14].

A0024: How is ovarian cancer currently diagnosed according to published guidelines and in practice?

full clinical assessment, CA-125 level measurement

After conducting a full clinical assessment, serum CA-125 levels are measured. Although CA-125 is not specific for ovarian cancer (levels may also be raised in non-gynaecological malignancies and benign disease), it is elevated in about 85% of patients with advanced ovarian cancer.

ultrasonography

For women with suspected ovarian cancer, ultrasonography of the abdomen and the pelvis is recommended, and transvaginal ultrasonography improves the differentiation between malignant and benign conditions. Based on clinical factors, ultrasound examination and the measurement of the CA-125 level, a "risk of malignancy index" can be calculated. To determine the extent of the disease, a computed tomography (CT) should be conducted, as well as an CT or X-ray of the chest to verify the presence of pleural effusions and the extension of the disease above the diaphragm [10].

CT of abdomen, CT/x-ray of the chest

staging according to FIGO system (2017)

Ovarian cancer, fallopian tube cancer and peritoneum cancer are surgically staged according to the 2017 International Federation of Gynecology and Obstetrics (FIGO) system, representing the most powerful indicator of prognosis. The system includes the following stages [15]:

- Stage I: Tumour limited to ovaries (one or both) or fallopian tube(s)
  - IA: Tumour limited to one ovary (capsule intact) or fallopian tube; no tumour on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
  - IB: Tumour limited to both ovaries (capsules intact) or fallopian tubes; no tumour on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
  - IC: Tumour limited to one or both ovaries or fallopian tubes, with any of the following:
    - IC1: Surgical spill
    - IC2: Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface
    - IC3: Malignant cells in ascites or peritoneal washings
- Stage II: Tumour involves one or both ovaries or fallopian tubes with pelvic extension below pelvic brim or primary peritoneal cancer
  - IIA: Extension and/or implants on the uterus and/or fallopian tube(s) and/or ovaries
  - IIB: Extension to and/or implants on other pelvic tissues
- Stage III: Tumour involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with microscopically confirmed peritoneal metastasis outside the pelvis and/or metastasis to the retroperitoneal (pelvic and/or para-aortic) lymph nodes
  - IIIA1: Positive retroperitoneal lymph nodes only (histologically confirmed)
  - IIIA1i: Metastasis up to and including 10 mm in greatest dimension
  - IIIA1ii: Metastasis more than 10 mm in greatest dimension
  - IIIA2: Microscopic extrapelvic (above the pelvic brim)

peritoneal involvement with or without positive retroperitoneal lymph nodes

IIIB: Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension with or without metastasis to the retroperitoneal lymph nodes

IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumour to capsule of liver and spleen with out parenchymal involvement of either organ)

- Stage IV: Distant metastasis, including pleural effusion with positive cytology; liver or splenic parenchymal metastsis; metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cav ity); and transmural involvement of intestine

IVA: Pleural effusion with positive cytology

IVB: Liver or splenic parenchymal metastases; metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); transmural involvement of intestine.

differential diagnosis varies with the clinical presentation

Since many of the symptoms associated with ovarian cancer, fallopian tube cancer and peritoneal cancer are nonspecific, the differential diagnosis of the diseases varies with the clinical presentation. If an adnexal mass is present, the first step is to confirm the presence and location of the mass by using pelvic imaging, usually ultrasound. Benign, malignant or borderline conditions can be distinguished in regard to the differential diagnosis of adnexal mass. In patients who present with abdominal distension or ascites in the absence of an adnexal mass, evaluation for other conditions should be performed. If women present with symptoms associated with ovarian cancer and/or abdominal distension or ascites, and elevated tumour markers (which are associated with ovarian cancer), a diagnostic laparoscopy should be considered as a part of the diagnostic evaluation [13].

6 Current treatment

A0025: How is newly diagnosed ovarian cancer currently managed according to published guidelines and in practice?

ESMO recommendations

According to the European Society for Medical Oncology (ESMO) [10], the aim for patients with advanced epithelial ovarian cancer is the complete cytoreduction of all macroscopic visible disease, which is associated with a significant increase in overall survival (OS) and progression-free survival (PFS). Optimal cytoreduction is defined as total macroscopic tumour clearance with no residual visible disease. For patients with poor performance status at the time of presentation and those with very extensive tumour dissemination, the use of neoadjuvant chemotherapy with interval surgery is offered.

optimal cytoreduction

chemotherapy for front-line treatment of patients with epithelial ovarian cancer and FIGO stage II-IV post surgery recommended

Since the risks of recurrence of disease spread beyond the ovary are substantial, the ESMO recommends chemotherapy for front-line treatment of patients with epithelial ovarian cancer and FIGO stage II-IV post surgery. The standard chemotherapeutical regimen is a combination of paclitaxel (175 mg/m2) and carboplatin AUC 6–5 administered intravenously (IV) every three weeks for usually six cycles. For patients who develop an allergy to paclitaxel or who do not tolerate paclitaxel, a combination therapy of docetaxel-carboplatin or pegylated liposomal doxorubicin-carboplatin can be considered alternatively.

recommendations of the SGO and ASCO

The Society of Gynecologic Oncology (SGO) and the American Society of Clinical Oncology (ASCO) recommend the following approach for patients with newly diagnosed or suspected stage IIIC or IV epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer [16]:

assessment of extent of disease

- Prior to therapy initiation, it should be evaluated whether patients with suspected stage IIIC or IV invasive epithelial ovarian cancer are eligible for primary cytoreductive surgery (PCS).
- To assess the extent of the disease and the feasibility of surgical resection, a CT of the abdomen and pelvis (including the use of an oral and IV contrast) and chest imaging should be performed.
- Patients with a high perioperative risk profile or a low likelihood of achieving cytoreduction to <1 cm should receive neoadjuvant chemotherapy (NACT).

PCS or NACT

- NACT or PCS may be offered to patients who are eligible for PCS. However, according to the external reviewer, PCS is the preferred approach in patients who are eligible for this treatment option. NACT is associated with less peri- and postoperative morbidity and mortality, and shorter hospitalisation; PCS, if successful, seems to offer superior survival.
- In women who have a high likelihood of achieving cytoreduction to <1 cm with acceptable morbidity, PCS is recommended over NACT.
- For women who are eligible for PCS, but who are deemed unlikely to achieve cytoreduction <1 cm, NACT is recommended over PCS.
- Histologic confirmation, preferably by core biopsy, should be conducted in all patients prior to NACT.

NACT: platinum/taxane doublet

- A platinum/taxane doublet therapy is recommended for NACT; different regimens (containing a platinum agent) may be selected based on individual patient factors.
- After ≤4 cycles of NACT, interval cytoreductive surgery should be performed in patients who had a response to NACT or stable disease.

7 Evidence

A literature search was conducted on 15 January 2019 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were “olaparib”, “lynparza”, “ovarian cancer”, “ovarian neoplasm”, “ovarian tumour”, “advanced”, “maintenance”, “newly diagnosed”, “first line” and “initial”. The manufacturer was also contacted and submitted two references that both had already been identified by systematic literature search. A manual search identified 28 additional references (web documents and journal articles).

systematic literature search in 5 databases: 125 hits
manual search: 28 additional references

Overall, 149 references were identified. Included in this reported is:

overall: 153 references

- Primary analysis data from SOLO1, a multi-centre, randomised, double-blind, phase III trial assessing the efficacy and safety of olaparib maintenance therapy in patients with newly diagnosed advanced high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer or fallopian tube cancer (or a combination thereof) with a BRCA1/2 mutation, who had a CR or PR after platinum-based chemotherapy.

included: 1 study

To assess the risk of bias at the study level, the assessment of the methodological quality of the evidence was conducted based on the EUnetHTA internal validity for randomised controlled trials (RCTs) [17]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patient and treating physician, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 6 (see Appendix).

study level risk of bias assessed based on EUnetHTA internal validity for RCTs

The external validity of the included trial was assessed using the EUnetHTA guideline on the applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals, considering the following elements: population, intervention, comparator, outcomes and setting (see Table 5) [18].

applicability of study results

To evaluate the magnitude of “clinically meaningful benefit” that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the ESMO (ESMO-MCBS) was used [19]. In addition, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [20]. Details of the magnitude of the clinically meaningful benefit assessment are reported in Table 3.

magnitude of clinical benefit assessed based on ESMO-MCBS

7.1 Quality assurance

This report has been reviewed by an internal reviewer and an external reviewer. The latter was asked for the assessment of the following quality criteria:

internal and external review

- How do you rate the overall quality of the report?
- Are the therapy options in the current treatment section used in clinical practice and are the presented standard therapies correct?
- Is the data regarding the prevalence, incidence and amount of eligible patients correct?

- Are the investigated studies correctly analysed and presented (data extraction was double-checked by a second scientist)?
- Was the existing evidence from the present studies correctly interpreted?
- Does the current evidence support the final conclusion?
- Were all important points mentioned in the report?

quality assurance method

The LBI-HTA considers the external assessment by scientific experts from different disciplines a method of quality assurance of scientific work. The final version and the policy recommendations are under full responsibility of the LBI-HTA.

7.2 Clinical efficacy and safety – phase III studies

SOLO1: double-blind, placebo-controlled phase III trial

The SOLO1 trial [5, 21, 22] is a multi-centre, randomised, double-blind, phase III trial conducted to evaluate the efficacy and safety of maintenance therapy with olaparib, a PARP inhibitor, in patients with newly diagnosed advanced ovarian cancer with a germline or somatic mutation in BRCA1, BRCA2, or both (BRCA1/2), who had a CR or PR after platinum-based chemotherapy. Between September 2013 and March 2015, a total of 391 patients from 15 countries underwent randomisation. After completion of platinum-based chemotherapy, the patients were assigned in a 2:1 ratio to either the olaparib group (n=260) or to the placebo group (n=130, one patient withdrew before receiving the intervention). Patients who were eligible for the SOLO1 trial had to have newly diagnosed, histologically confirmed advanced FIGO stage III or IV high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian tube cancer (or a combination thereof) and a deleterious or suspected deleterious germline or somatic BRCA1/2 mutation. Eligible patients had to have received platinum-based chemotherapy without bevacizumab and were having a clinical CR (no evidence of disease on imaging after chemotherapy and a normal CA-125 level) or a clinical PR (a ≥30% decrease in tumour volume from the start to the end of chemotherapy or no evidence of disease on imaging after chemotherapy, but a CA-125 level above the upper limit of the normal range). Since the SOLO1 trial is ongoing, primary and interim analysis data were presented.

trial is ongoing; primary/interim analysis data were presented

patient characteristics

Patients of both groups had a median age of 53 years; 76.9% of patients in the olaparib group and 80.2% of placebo group patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0. In 84.6% of the olaparib group patients and in 86.3% of the placebo group patients, the primary tumour was located in the ovary. 73.5% of patients in the olaparib group had a BRCA1 mutation, as had 69.5% of placebo group patients. The majority of patients (81.9% in the olaparib group and 81.7% in the placebo group) showed a clinical CR after platinum-based chemotherapy. 76.2% of patients in the olaparib group and 80.9% of placebo group patients received six cycles of platinum-based chemotherapy. Detailed patient characteristics including inclusion and exclusion criteria can be found in Table 5.

olaparib tablets: 300 mg twice daily vs. matching placebo tablets

Patients of the olaparib group received olaparib at a dose of 300 mg twice daily; patients of the placebo group received green film-coated tablets matching the olaparib tablets, administered in the same manner as olaparib. Study drug administration was continued until investigator-assessed objective disease progression on imaging, according to Response Evaluation Criteria in Solid Tumours (RECIST, version 1.0). In patients who had no evidence of disease at two years, the trial intervention was stopped, whereas patients who had a PR at two years were permitted to receive the study drug in a blinded manner.

primary endpoint: PFS

The primary endpoint of the SOLO1 trial was PFS, which was defined as the time from randomisation to objective disease progression on imaging or death from any cause. Secondary endpoints were second PFS (defined as the time from randomisation to second disease progression or death), OS, the time from randomisation to the first/second subsequent therapy or death, and health-related quality of life (HRQoL).

median duration of treatment (months): 24.6 (olaparib) vs. 13.9 (placebo)

The median duration of olaparib treatment among SOLO1 trial patients was 24.6 months (ranging from 0.0–52.0 months), compared to 13.9 months (ranging from 0.2–45.6 months) in placebo group patients. The median duration of follow-up was 40.7 months (olaparib group) and 41.2 months (placebo group). 47% of olaparib group patients and 27% of placebo group patients completed the trial intervention at two years (in accordance with the protocol). 10% (olaparib group) and 2% (placebo group) of patients continued to receive study treatment beyond two years. Of these, 13 patients still received olaparib and one patient received placebo at the time of data-cutoff for the primary analysis on 17 May, 2018. Clinical efficacy data of the SOLO1 trial is presented in Table 1, and adverse events (AEs) are listed in Table 2.

SOLO1 is ongoing until 06/2023

The SOLO1 trial is currently ongoing; the estimated study completion date is 6 June 2023 [23]. Due to the ongoing status of the SOLO1 trial, primary analysis data and interim analysis data (OS) was presented.

7.2.1 Clinical efficacy

D0001: What is the expected beneficial effect of olaparib on mortality?

OS interim analysis data

Data from an interim analysis of OS (data maturity, 21%[1]) showed that the Kaplan-Meier estimate of the rate of freedom from death at three years was 84% in olaparib group patients, compared to 80% in placebo group patients; the hazard ratio (HR) was 0.95; 95% confidence interval (CI), 0.60–1.53, p-value not reported [5].

[1] According to the study protocol, an interim analysis for OS and second PFS will be performed at the time of the PFS analysis (approx. 100 OS events). A further analysis of these two endpoints will be performed when the OS data are approx. 60% mature (approx. 206 events), which is anticipated to occur approx. 80 months after the first patient is enrolled in the study.

D0006: How does olaparib affect progression (or recurrence) of ovarian cancer?

PFS prolonged in patients of olaparib group

PFS, as assessed by the investigators, was the primary endpoint of the SOLO1 trial; analysis was performed after 198 of the 391 patients had disease progression or had died; data maturity was 51%[2]. The Kaplan-Meier estimate of the rate of freedom from disease progression and from death at three years (primary analysis data) was 60% in olaparib group patients, compared to 27% in placebo group patients (HR for disease progression or death was 0.30, 95% CI 0.23–0.41, p<0.001). In patients of the placebo group, the median PFS from the end of chemotherapy was 13.8 months. The analysis of PFS as assessed by blinded independent central review (data maturity, 38%) showed a Kaplan-Meier estimate of the rate of freedom from disease progression and from death at three years of 69% in olaparib group patients versus 35% in placebo group patients (HR for disease progression or death was 0.28, 95% CI 0.20–0.39, p<0.001). To evaluate possible attrition bias, a sensitivity analysis of investigator-assessed PFS was performed, showing that the median PFS was 36.1 months longer in patients of the olaparib group than in patients of the placebo group (HR was 0.31, 95% CI 0.23–0.41, p<0.001) [5, 22].

70% lower risk of disease progression or death with olaparib than with placebo

sensitivity analysis performed

higher rate of 2nd PFS in olaparib group patients than in placebo group patients

Analysis of the second PFS (data maturity, 31%) showed a Kaplan-Meier estimate of the rate of freedom from second disease progression and from death at three years of 75% in olaparib group patients versus 60% in placebo group patients (HR for second disease progression or death was 0.50, 95% CI 0.35–0.72, p<0.001). Among patients receiving placebo, the median second PFS was 41.9 months [5].

D0005: How does olaparib affect symptoms and findings (severity, frequency) of ovarian cancer?

time to 1st and 2nd subsequent therapy and death at 3 years prolonged with olaparib

In patients of the olaparib group, the median time to the first subsequent therapy or death was 51.8 months, compared to 15.1 months in patients of the placebo group (HR 0.30; 95% CI 0.22–0.40). The Kaplan-Meier estimate of the rate of freedom from the use of a second subsequent therapy and from death at three years was 74% in olaparib group patients versus 56% in placebo group patients: HR for the use of a second subsequent therapy or death was 0.45; 95% CI 0.32–0.63. The median time to the second subsequent therapy or death was 40.7 months in patients of the placebo group. Based on Kaplan-Meier estimates, the rate of freedom from disease progression and death among patients receiving olaparib compared to patient receiving placebo was 88% and 51% at one years, 74% and 35% at two years, 60% and 27% at three years, and 53% and 11% at four years, respectively [5].

[2] It was determined that 206 primary end-point events (disease progression or death) would provide the trial with 90% power, at a two-sided significance level of 0.05, to show a significant difference in PFS between the olaparib group and the placebo group, with a corresponding HR for disease progression or death of 0.62 (assuming a median PFS of 13 months in the placebo group). Due to the fact that the rate of primary end-point events was lower than projected, the protocol was amended such that the primary analysis of PFS was to be performed when approx. 196 events had occurred (data maturity, approximately 50%) or when the last patient to undergo randomisation had done so at least 3 years earlier, whichever came first.

D0011: What is the effect of olaparib on patients'body functions?

Patients of the SOLO1 trial who received olaparib had a higher rate of dyspnoea of any grade (15%), as compared to patients of the placebo group (5%). There was no grade 3/4 dyspnoea reported in either group. Pneumonitis or interstitial lung disease occurred in 2% of olaparib group patients and in none of the placebo group patients [5].

higher rate of dyspnoea, pneumonitis/interstitial lung disease with olaparib

D0012: What is the effect of olaparib on generic health-related quality of life?

D0013: What is the effect of olaparib on disease-specific quality of life?

In patients of the SOLO1 trial, the HRQoL was evaluated by the use of the Trial Outcome Index (TOI) score on the Functional Assessment of Cancer Therapy-Ovarian Cancer (FACT-O) questionnaire. TOI scores ranged from 0 to 100; higher scores indicate better HRQoL, and a difference of 10 points indicates a clinically meaningful difference [5, 22].

HRQoL evaluated by TOI on FACT-O

At baseline, the mean TOI score was 73.6 in patients of the olaparib group and 75.0 in patients of the placebo group. In the olaparib group, the score remained stable from baseline to two years (adjusted mean change of 0.30 points, 95% CI, -0.72–1.32). Among patients of the placebo group, a change of 3.30 points (95% CI, 1.84–4.76) could have been observed from baseline to two years. The estimated between-group difference in change was -3.00 points (95% CI, -4.78 to -1.22), and not considered to be clinically meaningful [5].

between-group difference in change of TOI score: not clinically meaningful

Table 1: Efficacy results of SOLO1 trial [5, 22]

Descriptive statistics and estimate variability	Treatment group	Olaparib	Placebo
	Number of patients	260	130
	Rate of freedom from disease progression and death at 3 years (investigator-assessed), %	60	27
	Median PFS from the end of chemotherapy, months	-	13.8
	Rate of freedom from disease progression and death at 3 years (assessed by blinded independent review), %	69	35
	Rate of freedom from disease progression and death (investigator-assessed), % at 1 year at 2 years at 3 years at 4 years	 88 74 60 53	 51 35 27 11
	Rate of freedom from second disease progression and death at 3 years, %	75	60
	Median second PFS, months	-	41.9
	Rate of freedom from death (OS) at 3 years, %	84	80
	Median time to first subsequent therapy or death, months	51.8	15.1
	Rate of freedom from the use of a second subsequent therapy and death at 3 years, %	74	56
	Median time to second subsequent therapy or death, months	-	40.7
	TOI score change from baseline to 2 years, points	0.30	3.30
Effect estimate per comparison	Comparison groups		Olaparib vs. placebo
	Rate of freedom from disease progression and death at 3 years (investigator-assessed)	HR for disease progression or death	0.30
		95% CI	0.23–0.41
		p-value	<0.001
	Rate of freedom from disease progression and death at 3 years (assessed by blinded independent review)	HR for disease progression or death	0.28
		95% CI	0.20–0.39
		p-value	<0.001
	Rate of freedom from second disease progression and death at 3 years	HR for second disease progression or death	0.50
		95% CI	0.35–0.72
		p-value	<0.001
	Rate of the freedom from death (OS) at 3 years	HR for death	0.95
		95% CI	0.60–1.53
		p-value	NR
	Median time to first subsequent therapy or death	HR	0.30
		95% CI	0.22–0.40
		p-value	NR
	Use of a second subsequent therapy or death	HR	0.45
		95% CI	0.32–0.63
		p-value	NR
	Between-group difference of TOI score from baseline to 2 years	HR	NR
		95% CI	-4.78 to -1.22
		p-value	NR

Abbreviations: CI = confidence interval, HR = hazard ratio, NR =not reported, OS = overall survival, PFS = progression-free survival, TOI = Trial Outcome Index

7.2.2 Safety

C0008: How safe is olaparib in relation to the comparator(s)?

Adverse events (AEs) of any grade that occurred during the trial intervention or up to 30 days after discontinuation of the intervention were reported in 98% of olaparib group patients and 92% of placebo group patients. Most common AEs of any grade among olaparib group patients were nausea, fatigue or asthenia, vomiting, anaemia and diarrhoea. Among placebo group patients, nausea, fatigue or asthenia occurred most frequently.

most common AEs of any grade in olaparib group: nausea, fatigue, asthenia, vomiting, anaemia, diarrhoea

AEs of grade 3 or 4 occurred in 39% of olaparib group patients and 18% of placebo group patients; the most common were anaemia (22%) and neutropenia (9%) in patients receiving olaparib, and neutropenia (5%) in patients receiving placebo.

AEs grade 3/4: in 39% (olaparib) vs. 18% (placebo)

Serious AEs occurred in 21% of patients receiving olaparib and 12% of patients who received placebo. The most common serious, treatment-emergent AEs in the olaparib group were anaemia (6.5%) and urinary tract infection (1.2%), which occurred in no patients of the placebo group. No AEs that occurred during the study intervention (or up to 30 days after discontinuation) led to death.

serious AEs in 21% (olaparib) vs. 12% (placebo)

Among patients of the olaparib group, AEs led to discontinuation of the intervention in 12% of patients, to dose reduction in 28% of patients, and to dose interruption in 52% of patients. In the placebo group, AEs led to discontinuation of the intervention in 2% of patients, to dose reduction in 3% of patients, and to dose interruption in 17% of patients. The most common AEs leading to discontinuation in patients receiving olaparib were nausea and anaemia (2.3% each). Three patients (1%) of the olaparib group were affected by acute myeloid leukaemia (AML), occurring more than 30 days after the end of study treatment, and in none of patients of the placebo group. New primary cancers were reported in 2% of patients in either group. In patients receiving olaparib, pneumonitis and interstitial lung disease were reported in 2% of them [5, 22].

AEs led to discontinuation in 12% (olaparib) vs. 2% (placebo) of patients

1% of olaparib group patients affected by AML

C0002: Are the harms related to dosage or frequency of applying olaparib?

The mode of administration and dosing of olaparib used in the SOLO1 trial is consistent with the FDA-approved license [8]. AEs occurring in SOLO1 trial participants were usually managed by dose interruption or dose reduction [5]. According to the FDA label information, the recommended dose reduction is 250 mg (one 150 mg tablet and one 100 mg tablet) taken twice daily, for a total daily dose of 500 mg [8].

SOLO1: AEs usually managed by dose interruption/dose reduction rather than discontinuation

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of olaparib?

According to FDA label information, the following warnings and precautions are listed [8]:

- Myelodysplastic syndrome (MDS)/AML: The incidence of MDS and AML in patients who received olaparib monotherapy in clinical trials (including long-term follow-up)

warnings and precautions: MDS, AML, pneumonitis, embryo-foetal toxicity

was <1.5% with a predominantly fatal outcome, and additional cases were reported in patients treated with olaparib in combination studies and post-marketing reports. All of these patients had received previous chemotherapy. Olaparib should not be administered until patients have recovered from haematological toxicity caused by previous chemotherapy. Complete blood count should be monitored for cytopenia. In the case of prolonged haematological toxicities, olaparib treatment should be interrupted and blood counts should be monitored weekly until recovery. If the levels have not recovered (to grade ≤1) after four weeks, further investigation should be performed; if MDS or AML is confirmed, olaparib should be discontinued.

- Pneumonitis: If new or worsening respiratory symptoms (e.g., dyspnoea, cough, fever or radiological abnormality) occur in patients treated with olaparib, the intervention should be interrupted for further investigation. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient needs to be treated appropriately.
- Embryo-foetal toxicity: Since olaparib can cause foetal harm, patients should be advised to use effective contraception during treatment and for six months following the last dose of olaparib.

Table 2: Most frequent adverse events [5]

Adverse event (according to NCI-CTCAE version 4.0)	**Olaparib** (n = 260)		**Placebo** (n = 130)	
	Any grade n (%)	Grade 3 or 4 n (%)	Any grade n (%)	Grade 3 or 4 n (%)
Any	256 (98)	102 (39)	120 (92)	24 (18)
Nausea	201 (77)	2 (1)	49 (38)	0 (0)
Fatigue or asthenia	165 (63)	10 (4)	54 (42)	2 (2)
Vomiting	104 (40)	1 (<1)	19 (15)	1 (1)
Anaemia	101 (39)	56 (22)	13 (10)	2 (2)
Diarrhoea	89 (34)	8 (3)	32 (25)	0 (0)
Constipation	72 (28)	0 (0)	25 (19)	0 (0)
Dysgeusia	68 (26)	0 (0)	5 (4)	0 (0)
Arthralgia	66 (25)	0 (0)	35 (27)	0 (0)
Abdominal pain	64 (25)	4 (2)	25 (19)	1 (1)
Neutropenia	60 (23)	22 (9)	15 (12)	6 (5)
Headache	59 (23)	1 (<1)	31 (24)	3 (2)
Dizziness	51 (20)	0 (0)	20 (15)	1 (<1)
Decreased appetite	51 (20)	0 (0)	13 (10)	0 (0)
Upper abdominal pain	46 (18)	0 (0)	17 (13)	0 (0)
Dyspepsia	43 (17)	0 (0)	16 (12)	0 (0)
Cough	42 (16)	0 (0)	28 (22)	0 (0)
Back pain	40 (15)	0 (0)	16 (12)	0 (0)
Dyspnoea	39 (15)	0 (0)	7 (5)	0 (0)
Thrombocytopenia	29 (11)	2 (1)	5 (4)	2 (2)
Led to discontinuation of intervention	30 (12)	NA	3 (2)	NA
Led to dose reduction	74 (28)	NA	4 (3)	NA
Led to dose interruption	135 (52)	NA	22 (17)	NA

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events, n = Number, NA = not available, NCI = National Cancer Institute

7.3 Clinical effectiveness and safety – further studies

Currently, the SOLO1 trial is the only trial investigating the role of olaparib in patients with newly diagnosed advanced ovarian cancer and a BRCA1/2 mutation, who had a CR or PR after platinum-based chemotherapy. Ongoing trials assessing olaparib in different settings/combinations are listed in Chapter 9.

currently SOLO1 is the only trial assessing olaparib in newly diagnosed ovarian cancer patients

8 Estimated costs

A0021: What is the reimbursement status of olaparib?

112 Lynparza® tablets = € 5,059.29

In Austria, Lynparza® is available as tablets (100 and 150 mg) and capsules (50 mg). The costs for 112 Lynparza® tablets (150 mg) are € 5,059.29 (ex-factory price [4].

€ 5,059.29 for 1 month of olaparib treatment
€ 124,458.53 for 2 years

Patients of the SOLO-1 trial, who were assigned to the olaparib group, received 300 mg of olaparib twice daily. Based on this dosing regimen, 28 days of olaparib treatment would cost € 5,059.29. The median duration of the trial intervention among patients of the olaparib group was 24.6 months, resulting in costs of € 124,458.53.

plus costs for platinum-based chemotherapy and BRCA testing

In addition, costs are incurred for the BRCA mutation status test and the platinum-based chemotherapy, which is administered prior to olaparib maintenance treatment.

9 Ongoing research

SOLO-1 is ongoing until 06/2023

In January 2019, a search in the databases www.clinicaltrials.gov and www.clinicaltrialsregister was conducted. The SOLO1 trial (NCT01844986) is currently ongoing with an estimated study completion date in June 2023.

2 further phase III trials identified

Two trials evaluating the efficacy and safety of olaparib administered in patients with newly diagnosed advanced ovarian cancer were identified:

PAOLA-1: olaparib vs. placebo

- NCT02477644 (EudraCT Number: 2014-004027-52): PAOLA-1 is a randomised, double-blind, phase III trial of olaparib versus placebo in patients with advanced FIGO stage IIIB-IV high grade serous or endometrioid ovarian, fallopian tube or peritoneal cancer treated with standard first-line treatment, combining platinum-taxane chemotherapy and bevacizumab concurrent with chemotherapy and maintenance. Estimated study completion date is June 2022.

DUO-O: patients of one treatment arm receive olaparib

- NCT03737643 (EudraCT Number: 2017-004632-11): DUO-O is a randomised, double-blind, multi-centre study to evaluate the efficacy and safety of durvalumab in combination with standard of care platinum-based chemotherapy and bevacizumab followed by maintenance durvalumab and bevacizumab or durvalumab, bevacizumab and olaparib in patients with newly diagnosed advanced ovarian cancer. Estimated study completion date is July 2025.

study of long-term responders on olaparib in solid tumours

The OLALA study (NCT02489058, EudraCT Number: 2017-002808-28) is an observational and sample collecting study of long-term responders on olaparib in solid tumours, aiming to elucidate how olaparib works and to better identify patients who may benefit from this therapy.

several trials assessing olaparib in patients with relapsed disease

There are several trials assessing olaparib in patients with previously treated and relapsed disease, such as the ICON9 trial (NCT03278717), the OPINION trial (NCT03402841) or the OReO trial (NCT03106987). Further trials are aiming to investigate the efficacy and safety of olaparib in different dis-

eases, including breast cancer, pancreatic cancer, castration-resistant prostate cancer or advanced gastric cancer.

10 Discussion

approved for the assessed indication by the FDA, not yet by the EMA

In December 2018, the FDA approved olaparib (Lynparza®) for the first-line maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm or sBRCAm advanced epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in CR or PR to first-line platinum-based chemotherapy [7]. To date, olaparib has not yet been approved by the EMA for the assessed indication [6].

risk of disease progression or death was 70% lower with olaparib than with placebo

higher rate of freedom from second progression and death at 3 years with olaparib

interim analysis of OS data: no difference

time to 1st subsequent therapy/death prolonged with olaparib

The SOLO1 trial [5, 21, 22] evaluated the efficacy and safety of olaparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer, primary peritoneal cancer or fallopian tube cancer and a BRCA1/2 mutation, who had a CR or PR after platinum-based chemotherapy. Investigator-assessed analysis showed that the Kaplan-Meier estimate of the rate of freedom from disease progression and from death at three years was 60% in the olaparib group versus 27% in the placebo group (HR for disease progression or death was 0.30). According to the analysis assessed by blinded independent central review, the Kaplan-Meier estimate of the rate of freedom from disease progression and from death at three years was 69% in the olaparib group versus 35% in the placebo group. A sensitivity analysis of investigator-assessed PFS showed that the median PFS was 36.1 months longer in patients of the olaparib group than in patients of the placebo group (HR was 0.31). The Kaplan-Meier estimate of the rate of freedom from second disease progression and from death at three years was higher among patients of the olaparib group (75%) than among patients of the placebo group (60%). An interim analysis of OS data showed a Kaplan-Meier estimate of the rate of freedom from death at three years of 84% (olaparib group) versus 80% (placebo group); HR for death was 0.95. The median time to the first subsequent therapy or death was longer in olaparib group patients (51.8 months) than in placebo group patients (15.1 months). The estimated between-group difference in change of TOI score was -3.00 points, and thus considered not to be clinically meaningful.

primary analysis data

OS data are currently immature

benefit in PFS, PFS2, and time to 1st and 2nd subsequent therapy

final OS data + long-term benefit data needed

Since the SOLO1 trial is ongoing until June 2023, no final data analysis is available; the presented results are primary and interim analysis results. Due to the fact that the OS data are currently immature and the estimated between-group difference in change of HRQoL was not clinically meaningful, the clinical benefit of olaparib maintenance could not be confirmed. This is especially important, since the confidence intervals of the hazard ratio of death (HR 0.95, 95% CI, 0.60–1.53) indicate that olaparib offers no survival improvement. However, among SOLO1 trial patients, olaparib maintenance therapy provided a benefit in PFS, second PFS, and the median time to the first (and second) subsequent therapy or death. This is relevant with regard to the fact that the majority of patients—despite optimal upfront surgery and administration of paclitaxel/carboplatin chemotherapy—have a relapse within the first three years [10]. Nevertheless, since newly diagnosed advanced ovarian cancer can potentially be cured [24], the final analysis of OS data and the assessment of the long-term benefit of olaparib

maintenance therapy are substantial. It should be noted that patients who had a PR at two years were permitted to receive olaparib in a blinded manner; hence, the validity of SOLO1 long-term data may be affected by this cross-over approach.

HRQoL data: no clinically meaningful difference between olaparib group and placebo group

As mentioned above, the primary analysis of HRQoL data showed no clinically meaningful between-group difference between patients of the olaparib group and patients of the placebo group [5]. Since HRQoL is a clinically important aspect for patients, final analysis data are of major importance. Data from SOLO2 trial [25], a phase 3 trial evaluating olaparib maintenance therapy in platinum-sensitive, relapsed ovarian cancer patients with a BRCA1/2 mutation, who received at least two lines of previous chemotherapy, showed that olaparib led to a significant improvement in PFS without significant detrimental effect on HRQoL. Furthermore, the delay of progression was associated with a longer duration of "good quality of life". Ledermann et al. [26] assessed that maintenance treatment with olaparib was well-tolerated and had no adverse impact on HRQoL in a phase II study of patients with platinum-sensitive relapsed serous ovarian cancer who had responded (CR or PR) to their most recent platinum-based therapy. Final analysis of SOLO1 HRQoL data might confirm these findings.

more phase III data for patients with newly diagnosed ovarian cancer required

comparison with different PARP inhibitors: rucaparib, niraparib

To date, the SOLO1 trial is the only trial investigating the role of olaparib in patients with newly diagnosed advanced ovarian cancer and a BRCA1/2 mutation, who had a CR or PR after platinum-based chemotherapy. Available data from different trials refer to olaparib maintenance therapy in patients with relapsed disease, e.g., the SOLO2 trial [27]. In the ARIEL3 trial [28], rucaparib, a different PARP inhibitor, versus placebo was assessed in patients with high-grade, platinum-sensitive, recurrent ovarian carcinoma after response to second-line or later platinum-based chemotherapy. Further investigation may give information about the role of rucaparib as maintenance therapy in patients with newly diagnosed ovarian cancer. Furthermore, a direct comparison of rucaparib and olaparib may help find the optimal treatment for this patient population. The same applies to niraparib, a PARP inhibitor investigated versus placebo as maintenance treatment for patients with platinum-sensitive, recurrent ovarian cancer who had received at least two platinum-based therapies in the course of the phase III ENGOT-OV16/NOVA trial [29]. In this regard, the results of OVARIO [30], a phase II, single-arm, open-label study to assess the safety and efficacy of niraparib combined with bevacizumab as maintenance treatment in patients with newly diagnosed advanced ovarian cancer, fallopian tube cancer, or primary peritoneal cancer following front-line platinum-based chemotherapy with bevacizumab, will be of interest.

AEs grade3/4: in 39% (olaparib) vs. 18% (placebo)

serious AEs in 21% (olaparib) vs. 12% (placebo)

1% of olaparib group patients affected by AML

AEs of grade 3 or 4 occurred in 39% of olaparib group patients and 18% of placebo group patients; serious AEs occurred in 21% of patients receiving olaparib and 12% of patients who received placebo. No AEs that occurred during the study intervention (or up to 30 days after discontinuation) led to death. AEs led to discontinuation of the intervention in 12% (olaparib group) and 2% (placebo group) of patients. Three patients (1%) of the olaparib group were affected by acute myeloid leukaemia (AML), occurring more than 30 days after the end of study treatment. Pneumonitis and interstitial lung disease were reported in 2% of patients of the olaparib group and in none of placebo group patients. It can be noted that most AEs in olaparib group patients could have been managed by dose reduction (28%) and dose interruption (52%), rather than study drug discontinuation (12%) [5].

Given the non-curative setting of olaparib and the statistically significant primary endpoint PFS, we applied form 2b of the ESMO-MCBS in order to assess whether olaparib satisfies the criteria for a "meaningful clinical benefit" (score 4 or 5) [19]. However, since the median PFS and OS were not available for the olaparib group, no score calculations could be applied.

ESMO-MCBS evaluations were not applicable due to lack of median PFS and OS data

The SOLO1 trial was conducted as a double-blind study. Adequate generation of the randomisation sequence and adequate allocation concealment were described in the protocol; the reasons for treatment discontinuation were reported. However, no median PFS data were available and, additionally, some other aspects that may affect the risk of bias were identified: the trial was designed by the first and last authors in collaboration with the manufacturer and the Gynecologic Oncology Group. The manufacturer was responsible for overseeing the collection, analysis, and interpretation of the data. Hence, the risk of bias is considered to be high. Regarding the applicability of evidence, it is notable that the trial population was highly selected and the median age of participants was approximately ten years lower than the median age at diagnosis of ovarian cancer usually is. Moreover, almost 80% of the olaparib group patients had an ECOG performance status of 0, meaning that the women were able to carry on normal activity. Due to the fact that final analysis data are lacking and OS data at the time of interim analysis were immature, the applicability of results is limited.

high risk of bias

The costs for 28 days of olaparib treatment are € 5,059.29 (ex-factory price [4]. The median duration of olaparib administration among patients of the SOLO1 trial was 24.6 months, resulting in costs of € 124,458.53. In addition, costs are incurred for the BRCA mutation status test and the platinum-based chemotherapy which is administered prior to olaparib maintenance treatment.

€ 5,059.29 for 28 days, more than € 125,000 for approx. 2 years of olaparib treatment

SOLO1 trial results showed a benefit with olaparib first-line maintenance therapy in the delay of disease progression in patients with newly diagnosed ovarian cancer and BRCA1/2 mutation. However, the trial is currently ongoing, the presented data are the primary analysis data, and interim OS data are immature. HRQoL data also derive from the primary analysis and the detected between-group difference was not considered to be clinically meaningful. Final analysis data from the SOLO1 trial are pending and may confirm the clinical benefit of first-line olaparib maintenance therapy. Further investigation of olaparib first-line maintenance therapy in phase III trials, long-term data, as well as a direct comparison of olaparib with different PARP inhibitors, are warranted to determine the optimal treatment for this patient population.

benefit in delay of disease progression, but clinical benefit needs to be proven

final analysis data, more phase III data and comparison with different PARP inhibitors is required

Table 3: Benefit assessment based on original ESMO-MCBS and adapted benefit assessment based on adapted ESMO-MCBS [19, 20]

ESMO-MCBS	Active substance	Indication	Intention	PE	Form	MG standard treatment	Efficacy				Safety		AJ	FM
							MG months	*HR (95% CI)*	*Score calculation*	*PM*	*Toxicity*	*QoL*		
Adapt-ed ESMO-MCBS	Olaparib	Ovarian cancer	NC	PFS	-	-	-	-	-	-	-	-	-	**NA**[3]
Original ESMO-MCBS	Olaparib	Ovarian cancer	NC	PFS	-	-	-	-	-	-	-	-	-	**NA**3

Abbreviations: AJ = Adjustments, CI = confidence interval, FM = final adjusted magnitude of clinical benefit grade, HR = hazard ratio, m = months, MG = median gain, NA = not applicable, PE = primary endpoint, PFS = progression-free survival, PM = preliminary magnitude of clinical benefit grade, QoL = quality of life

DISCLAIMER

The scores achieved with the ESMO Magnitude of Clinical Benefit Scale are influenced by several factors: By the specific evaluation form used, by the confidence interval (CI) of the endpoint of interest, and by score adjustments due to safety issues. Ad form: Every individual form measures a different outcome. The meaning of a score generated by form 2a is not comparable to the exact same score resulting from the use of form 2c. To ensure comparability, we report the form that was used for the assessment. Ad CI: The use of the lower limit of the CI systematically favours drugs with a higher degree of uncertainty (broad CI).We thus decided to avoid this systematic bias and use the mean estimate of effect. Ad score adjustments: Cut-off values and outcomes that lead to an up- or downgrading seem to be arbitrary. In addition, they are independent of the primary outcome and, therefore, a reason for confounding. Hence, we report the adjustments separately.

[3] An ESMO-MCBS score cannot be assessed, since none of the available study endpoints was applicable to evaluate the MCBS.

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12 Appendix

Table 4: Administration and dosing of olaparib (Lynparza®) [2, 21]

	Technology	Comparator
Administration mode	Lynparza® is for oral use; the tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Lynparza® tablets may be taken without regard to meals.	Placebo will be available as green film-coated tablets matching the olaparib tablets.
Description of packaging	Lynparza® 100 mg tablets are yellow to dark yellow, oval, bi-convex, film-coated tablets, marked with "OP100" on one side and plain on the other. Lynparza® 150 mg tablets are green to green/grey, oval, bi-convex, film-coated tablets, marked with "OP150" on one side and plain on the other.	-
Total volume contained in packaging for sale	Lynparza® is supplied in packs containing 56 film-coated tablets (7 blisters of 8 tablets each), or multipacks containing 112 (2 packs of 56) film-coated tablets.	-
Dosing	The recommended dose of Lynparza® is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg.	Placebo tablets should be taken as per instructions for olaparib tablets.
Median treatment duration	SOLO1 trial: The median duration of the trial intervention in the olaparib group was 24.6 months (ranging from 0.0 to 52.0).	SOLO1 trial: The median duration in the placebo group was 13.9 months (ranging from 0.2 to 45.6).
Contraindications	✪ Hypersensitivity to the active substance or to any of the excipients (tablet core: copovidone, silica, colloidal anhydrous, mannitol, sodium stearyl fumarate/tablet coating: hypromellose, macrogol 400, titanium dioxide [E171], iron oxide yellow [E172], iron oxide black [E172, 150 mg tablets only]) ✪ Breast-feeding during treatment and for 1 month after the last dose. Olaparib should not be used during pregnancy and in women of childbearing potential not using reliable contraception during therapy and for 1 month after receiving the last dose of olaparib.	-
Drug interactions	Clinical studies of olaparib in combination with other anticancer medicinal products, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity. The recommended Lynparza® monotherapy dose is not suitable for combination with myelosuppressive anticancer medicinal products. Combination of olaparib with vaccines or immunosuppressant agents has not been studied. Therefore, caution should be taken if these medicinal products are co-administered with olaparib and patients should be closely monitored. Known strong (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, boceprevir, telaprevir) or moderate (e.g., erythromycin, diltiazem, fluconazole, verapamil) inhibitors of CYP3A are not recommended with olaparib. It is also not recommended to consume grapefruit juice while on olaparib therapy, as it is a CYP3A inhibitor. Known strong inducers of CYP3A (e.g., phenytoin, rifampicin, rifapentine, carbamazepine, nevirapine, phenobarbital, and St John's Wort) are not recommended with olaparib, as it is possible that the efficacy of olaparib could be substantially reduced. The magnitude of the effect of moderate to strong inducers (e.g., efavirenz, rifabutin) on olaparib exposure is not established; therefore, the co-administration of olaparib with these medicinal products is also not recommended. Caution should be exercised when sensitive CYP3A substrates or substrates with a narrow therapeutic margin (e.g., simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine) are combined with olaparib. Appropriate clinical monitoring is recommended for patients receiving CYP3A substrates with a narrow therapeutic margin concomitantly with olaparib. The potential for olaparib to induce CYP2C9, CYP2C19 and P-gp can also not be excluded. Therefore, olaparib upon co-administration	-

	may reduce the exposure to substrates of these metabolic enzymes and transport protein. The efficacy of some hormonal contraceptives may be reduced if co-administered with olaparib. Olaparib may cause clinically relevant drug interactions with substrates of P-gp (e.g., simvastatin, pravastatin, dabigatran, digoxin and colchicine). Appropriate clinical monitoring is recommended. It cannot be excluded that olaparib may increase the exposure to substrates of BCRP (e.g., methotrexate, rosuvastatin), OATP1B1 (e.g., bosentan, glibenclamide, repaglinide, statins and valsartan), OCT1 (e.g., metformin), OCT2 (e.g., serum creatinine), OAT3 (e.g., furosemide and methotrexate), MATE1 (e.g., metformin) and MATE2K (e.g., metformin). In particular, caution should be exercised if olaparib is administered in combination with any statin. Tamoxifen decreased exposure to olaparib by 27%. The clinical relevance of this effect is unknown.	

Table 5: Characteristics of SOLO1 trial

Title: Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer [5, 21, 22]			
Study identifier	NCT01844986, EudraCT Number: 2013-001551-13		
Design	International, randomised, double-blind, placebo-controlled phase III trial		
	Duration of main phase:		Randomisation: from September 3, 2013 to March 6, 2015 Time of data cut-off for the primary analysis: May 17, 2018 Median follow-up:41 months
Hypothesis	Superiority		
Funding	Astra Zeneca and Merck		
Treatments groups	Intervention (n = 260)		Patients received olaparib tablets (300 mg) twice daily until investigator-assessed objective disease progression on imaging (according to modified RECIST, version 1.1), provided that the patient was having a benefit and did not meet any discontinuation criteria. Patients who had no evidence of disease at 2 years stopped receiving the trial intervention, but patients who had a PR at 2 years were permitted to continue receiving the trial intervention in a blinded manner.
	Control (n = 130)		Patients received placebo tablets (matching the olaparib tablets).
Endpoints and definitions	Progression-free survival (primary endpoint)	PFS	Defined as the time from randomisation to objective disease progression on imaging (according to modified RECIST, version 1.1) or death from any cause
	Second progression-free survival	PFS2	The time from randomisation to second disease progression or death
	Overall survival	OS	Defined as the time from the date of randomisation until death due to any cause
	Time from randomisation to the first subsequent therapy or death	-	-
	Time from randomisation to the second subsequent therapy or death	-	-
	Health-related quality of life	HRQoL	Assessed by the TOI of the FACT-O
Database lock	NR		
Results and analysis			

Title: Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer [5, 21, 22]		
Study identifier	NCT01844986, EudraCT Number: 2013-001551-13	
Analysis description	**Primary analysis** It was determined that 206 primary endpoint events (disease progression or death) would provide the trial with 90% power, at a two-sided significance level of 0.05, to show a significant difference in PFS between the olaparib group and the placebo group, with a corresponding HR for disease progression or death of 0.62 (assuming a median PFS of 13 months in the placebo group). Because the rate of primary endpoint events was lower than projected, the protocol was amended such that the primary analysis of PFS was to be performed when approximately 196 events had occurred (data maturity, approximately 50%) or when the last patient to undergo randomisation had done so at least 3 years earlier, whichever came first. Data on efficacy and HRQoL were summarised and analysed in the ITT population (all patients who underwent randomisation, regardless of the intervention that they actually received). Data on safety were summarised in the safety population (all patients who received ≥ 1 dose of the trial intervention). A multiple-testing procedure was used to control the type I error rate, with a test for PFS to be performed first, a test for second PFS to be performed if the null hypothesis for PFS were rejected, and a test for OS to be performed if the results for PFS and PFS2 were significant. The analyses of time to the first subsequent therapy and time to the second subsequent therapy were not adjusted for multiple comparisons. To describe the potential benefit of olaparib, tests for time to the first subsequent therapy, time to the second subsequent therapy, and change from baseline in the TOI score were performed at a two-sided significance level of 0.05. The analysis of PFS was performed with a stratified log-rank test, with calculation of a hazard ratio, an accompanying 95% confidence interval, and a P value. Analyses of PFS2, OS, time to the first subsequent therapy, and time to the second subsequent therapy were performed with a method similar to that used for the analysis of PFS. The analysis of change from baseline in the TOI score was performed with a mixed-effects model for repeated measures.	
Analysis population	Inclusion	✲ Patients must be aged ≥18 years ✲ Female patients with newly diagnosed, histologically confirmed, advanced (FIGO stage III-IV) BRCA mutated high-grade serous or high grade endometrioid (based on local histopathological findings) ovarian cancer, primary peritoneal cancer and/or fallopian tube cancer who have completed first-line, platinum-based chemotherapy (IV or intraperitoneal) ✲ Stage III patients must have had one attempt at optimal debulking surgery; stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery. ✲ Deleterious or suspected deleterious germline or somatic BRCA1/2 mutation, as determined by local or central testing, with the use of the BRACAnalysis test (Myriad) or, in China, with the use of a BRCA1/2 genetic testing assay (BGI) ✲ Patients had received platinum-based chemotherapy without bevacizumab and were having a complete clinical response (no evidence of disease on imaging after chemotherapy and a normal CA-125 level) or a partial clinical response (a ≥30% decrease in tumour volume from the start to the end of chemotherapy or no evidence of disease on imaging after chemotherapy but a CA-125 level above the upper limit of the normal range. ✲ Patients must have normal organ and bone marrow function. ✲ ECOG performance status 0-1 ✲ Life-expectancy of ≥16 weeks ✲ Postmenopausal or evidence of non-childbearing status for women of childbearing potential ✲ Formalin-fixed, paraffin-embedded tumour sample from the primary cancer must be available for central testing.

Title: Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer [5, 21, 22]		
Study identifier	NCT01844986, EudraCT Number: 2013-001551-13	
	Exclusion	❁ BRCA1 and/or BRCA2 mutations that are considered to be non-detrimental ❁ Patients with early-stage disease (FIGO stage I,IIA, IIB, or IIC) ❁ Stable disease or progressive disease on the post-treatment scan, or clinical evidence of progression at the end of the patient's first-line chemotherapy treatment ❁ Patients where more than 1 debulking surgery has been performed before randomisation to the study. Eligible patients are those who, at the time of diagnosis, are deemed to be unresectable and undergo only a biopsy or oophorectomy, but then go on to receive chemo-therapy and interval debulking surgery. ❁ Patients who have previously been diagnosed and treated for earlier stage ovarian, fallopian tube or primary peritoneal cancer ❁ Patients who have previously received chemotherapy for any ab-dominal or pelvic tumour, including treatment for prior diagnosis at an earlier stage for their ovarian, fallopian tube or primary peritone-al cancer ❁ Patients with synchronous primary endometrial cancer unless both of the following criteria are met: o stage <2 o less than 60 years old at the time of diagnosis of endometrial cancer with stage IA or IB grade 1 or 2, or stage IA grade 3 en-dometrioid adenocarcinoma OR ≥60 years old at the time of diagnosis of endometrial cancer with stage IA grade 1 or 2 en-dometrioid adenocarcinoma. ❁ Patients who have had a drainage of their ascites during the final two cycles of their last chemotherapy regimen prior to enrolment in the study ❁ Any previous treatment with a PARP inhibitor, including olaparib ❁ Other malignancy within the last 5 years (for exceptions, see sup-plementary appendix) ❁ Resting ECG with a corrected QT interval >470 msec on two or more time points within a 24-hour period or family history of long QT syndrome ❁ Patients receiving any systemic chemotherapy or radiotherapy (ex-cept for palliative reasons) within 3 weeks prior to study treatment (or a longer period depending on the defined characteristics of the agents used) ❁ Concomitant use of known potent cytochrome P450 inhibitors ❁ Persistent toxicities (CTCAE grade ≥2) caused by previous cancer therapy, excluding alopecia ❁ Patients with myelodysplastic syndrome/acute myeloid leukaemia ❁ Patients with symptomatic, uncontrolled brain metastases ❁ Major surgery within 2 weeks of starting study treatment, and pa-tients must have recovered from any effects of any major surgery ❁ Patients considered a poor medical risk due to a serious, uncon-trolled medical disorder, non-malignant systemic disease or active, uncontrolled infection ❁ Patients unable to swallow orally administered medication, and pa-tients with gastrointestinal disorders likely to interfere with absorp-tion of the study medication ❁ Breastfeeding women ❁ Immunocompromised patients ❁ Patients with a known hypersensitivity to olaparib or any of the ex-cipients of the product ❁ Patients with known active hepatitis due to risk of transmitting the infection through blood or other body fluids ❁ Previous allogeneic bone marrow transplant ❁ Whole blood transfusions in the last 120 days prior to entry to the study

Title: Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer [5, 21, 22]				
Study identifier	NCT01844986, EudraCT Number: 2013-001551-13			
	Characteristics		Intervention n = 260	Control n = 131
		Median age (range), years	53.0 (29–82)	53.0 (31–84)
		Response after platinum-based chemotherapy, n (%)		
		Clinical CR	213 (81.9)	107 (81.7)
		PR	47 (18.1)	24 (18.3)
		Number of cycles of platinum-based chemotherapy, n (%)		
		4	2 (0.8)	0 (0.0)
		5	2 (0.8)	1 (0.8)
		6	198 (76.2)	106 (80.9)
		7	17 (6.5)	10 (7.6)
		8	18 (6.9)	7 (5.3)
		9	23 (8.8)	7 (5.3)
		ECOG performance status, n (%)		
		0	200 (76.9)	105 (80.2)
		1	60 (23.1)	25 (19.1)
		Missing	0	1 (0.8)
		Primary tumour location, n (%)		
		Ovary	220 (84.6)	113 (86.3)
		Fallopian tubes	22 (8.5)	11 (8.4)
		Primary peritoneal	15 (5.8)	7 (5.3)
		Other	3 (1.2)	0 (0.0)
		FIGO stage, n (%)		
		III	220 (84.6)	105 (80.2)
		IV	40 (15.4)	26 (19.8)
		Baseline CA-125 level, n (%)		
		≤ULN	247 (95.0)	123 (93.9)
		<ULN	13 (5.0)	7 (5.3)
		Missing	0 (0.0)	1 (0.8)
		Histology, n (%)		
		Serous	246 (94.6)	130 (99.2)
		Endometrioid	9 (3.5)	0
		Mixed serous /endometrioid	5 (1.9)	1 (0.8)
		BRCA mutation, n (%)		
		BRCA1	191 (73.5)	91 (69.5)
		BRCA2	66 (25.4)	40 (30.5)
		Both BRCA1 and BRCA2	3 (1.2)	0
		BRCA mutation status, n (%)		
		Myriad/BGI-confirmed germline BRCA-mutation	257 (98.8)	131 (100.0)
		FMI-confirmed somatic BRCA mutation	2 (0.8)	0
		History of cytoreductive surgery, n (%)		
		Upfront surgery	161 (61.9)	85 (64.9)
		Residual macroscopic disease	37 (23.0)	22 (25.9)
		No residual macroscopic disease	123 (76.4)	62 (72.9)
		Unknown	1 (0.6)	1 (1.2)
		Interval cytoreductive surgery	94 (36.2)	43 (32.8)
		Residual macroscopic disease	18 (19.1)	7 (16.3)
		No residual macroscopic disease	76 (80.9)	36 (83.7)
		No surgery	4 (1.5)	3 (2.3)

Title: Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer [5, 21, 22]	
Study identifier	NCT01844986, EudraCT Number: 2013-001551-13
Applicability of evidence	
Population	The SOLO1 trial population included patients with newly diagnosed, advanced ovarian cancer, fallopian tube cancer or primary peritoneal cancer with a BRCA1/2 mutation and a CR or PR after platinum-based chemotherapy, representing a highly selected trial population. The median age of trial patients of 53 years stands in contrast to a median age at diagnosis of 63 years (ovarian cancer is most frequently diagnosed among women aged 55 to 64 years) [12]. Almost 80% of the patients of the olaparib group had an ECOG performance status of 0, meaning that the women were able to carry on normal activity.
Intervention	The mode of administration and dosing of olaparib in SOLO1 trial patients was consistent with the FDA-approved license [8]. The patients received olaparib until investigator-assessed objective disease progression on imaging (according to RECIST, version 1.1) provided that the patients were having a benefit and did not meet any discontinuation criteria. Patients who had no evidence of disease at 2 years stopped the trial intervention; patients who had a PR at 2 years were permitted to continue olaparib in a blinded manner.
Comparators	In the SOLO1 trial, a placebo was selected as comparator. For direct comparison, different PARP inhibitors, including rucaparib and niraparib, may be appropriate.
Outcomes	There is evidence that the risk of disease progression or death was 70% lower in patients who received olaparib as compared to patients who received placebo. The applicability of results is limited due to the fact that final analysis data are lacking, and the presented data are primary/interim analysis data.
Setting	The SOLO1 trial is an international trial including patients from 15 countries. No issue regarding setting applicability was found.

Abbreviations: BRCA = breast cancer susceptibility gene, CR = complete response, ECG =electrocardiogram, ECOG = Eastern Cooperative Oncology Group, FACT-O = Functional Assessment of Cancer Therapy – Ovarian, FDA = U.S. Food and Drug Administration, FIGO = International Federation of Gynecology and Obstetrics, FMI = Foundation Medicine, HR = hazard ratio, HRQoL = Health-related quality of life, ITT = intention-to-treat, IV = intravenous, n = number, NR = not reported, OS = overall survival, PFS = progression-free survival, PFS2 = second progression-free survival, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumours, TOI = trial outcome index, ULN = upper limit of normal

Table 6: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [5, 17]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: Randomisation was performed centrally with a block design, with stratification according to clinical response after platinum-based chemotherapy (complete or partial).		yes
Adequate allocation concealment: Patients were assigned to a trial group through an interactive Web-based or voice-response system.		yes
Blinding: double-blinded	**Patient:** blinded	yes
	Treating physician: blinded	yes
Selective outcome reporting unlikely: Reasons for discontinuations have been reported. No median PFS data were available.		no
No other aspects which increase the risk of bias: The trial was designed by the first and last authors in collaboration with the manufacturer and the Gynecologic Oncology Group. AstraZeneca was responsible for overseeing the collection, analysis, and interpretation of the data. The manuscript was written by the authors, with medical writing assistance funded by AstraZeneca and Merck. Olaparib is being co-developed by AstraZeneca and Merck, and Merck provided input regarding the interpretation of the data.		no
Risk of bias – study level		high