Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Olaparib

Proprietary Product Name: Lynparza

Sponsor: AstraZeneca Pty Ltd

April 2021

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the plasma concentration time curve
BD	Twice daily (Latin: *bis in die*)
BICR	Blinded independent central review
BRCA	Breast cancer susceptibility protein
BRCA1	Breast cancer susceptibility protein type 1
BRCA2	Breast cancer susceptibility protein type 2
CA-125	Cancer antigen 125
CI	Confidence interval
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CR	Complete response
DSB	Double strand break
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOC	Epithelial ovarian carcinoma
EU	European Union
FDA	Food and Drug Administration (United States)
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynaecology and Obstetrics)
Folfirinox	5-fluorouracil, irinotecan, leucovorin, and oxaliplatin
gBRCAm	Germline breast cancer susceptibility protein mutation
HGSC	High-grade serous carcinoma
HR	Hazard ratio

Abbreviation	Meaning
HRD	Homologous recombination deficiency
HRR	Homologous recombination repair
IDS	Interval debulking surgery
INCa	Institut National du Cancer (French National Cancer Institute)
NED	No evidence of disease
OS	Overall survival
PARP	Poly (adenosine diphosphate-ribose) polymerase
PFI	Platinum-free interval
PFS	Progression-free survival
PFS1	Progression-free survival to first progression or death
PFS2	Time from randomisation to second progression or death
PK	Pharmacokinetic(s)
PR	Partial response
PSUR	Periodic safety update report
RECIST	Response Evaluation Criteria in Solid Tumours
sBRCAm	Somatic breast cancer susceptibility protein mutation
tBRCA	Tumour breast cancer susceptibility protein
tBRCAwt	Tumour breast cancer susceptibility protein wild type
TDT	Time from randomisation to discontinuation of treatment or death
TFST	Time from randomisation to first subsequent therapy or death
TSST	Time from randomisation to second subsequent therapy or death
ULN	Upper limit of normal
US(A)	United States (of America)
VUS	Variant of uncertain significance

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Product name:	Lynparza
Active ingredient:	Olaparib
Decision:	Approved
Date of decision:	4 March 2021
Date of entry onto ARTG:	10 March 2021
ARTG number:	288613, 288614
, *Black Triangle Scheme:*[1]	No
Sponsor's name and address:	AstraZeneca Pty Ltd 66 Talavera Road Macquarie Park NSW 2113
Dose form:	Film coated tablet
Strengths:	100 mg, 150 mg
Container:	Blister pack
Pack size:	56 tablets
Approved therapeutic use:	*Lynparza in combination with bevacizumab is indicated for the:* • *maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:* – *a deleterious or suspected deleterious BRCA mutation (germline or somatic), and/or* – *genomic instability* *HRD status should be determined by an experienced laboratory using a validated test method.*

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Adenocarcinoma of the pancreas

Lynparza is indicated as monotherapy for the:

- *maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Germline BRCA mutation (gBRCAm) status should be determined by an experienced laboratory using a validated test method.*

Route of administration:	Oral
Dosage:	Treatment with Lynparza should be initiated and supervised by a physician experienced in the use of anticancer medicinal products. The recommended dose of Lynparza is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. The 100 mg tablet is available for dose reductions only. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by AstraZeneca Pty Ltd (the sponsor) to register Lynparza (olaparib) 100 mg and 150 mg film coated tablets for the following proposed extension of indications:

Ovarian cancer

Lynparza in combination with bevacizumab is indicated for the:

- *maintenance treatment of adult patients with advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy with bevacizumab.*

Adenocarcinoma of the pancreas

Lynparza is indicated as monotherapy for the:

- *maintenance treatment of adult patients with germline BRCA-mutated metastatic adenocarcinoma of the pancreas whose disease has not progressed on first-line platinum-based chemotherapy.*

Olaparib is an orally active inhibitor of human poly (adenosine diphosphate-ribose) polymerase (PARP) enzymes; PARP-1, PARP-2, and PARP-3.

PARP enzymes are required for the efficient repair of DNA single strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair enzymes. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells this leads to DNA double strand breaks (DSBs) when replication forks meet the PARP-DNA adducts.

In normal cells, the homologous recombination repair (HRR) pathway is effective at repairing these DNA DSBs. In cancers that lack functional components of HRR, such as breast cancer susceptibility protein (BRCA) type 1 (BRCA1) or type 2 (BRCA2), DNA DSBs cannot be repaired accurately or effectively. Instead, alternative and error-prone pathways are activated, such as the non-homologous end joining pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells already have a high DNA damage load relative to normal cells. In the absence of *BRCA1* or *BRCA2* mutations, the HRR pathway may be compromised by other mechanisms, although the causative aberrancy and penetrance are not fully elucidated. Absence of a fully functional HRR pathway is one of the key determinants of platinum sensitivity in ovarian and other cancers.

Advanced ovarian cancer

High-grade serous carcinomas (HGSC) including epithelial ovarian carcinoma (EOC), fallopian tubal, and peritoneal carcinomas, are considered a single clinical entity due to their shared clinical behaviour and treatment. There is also accumulating evidence of a common pathogenesis for these carcinomas. All women with a diagnosis of ovarian, fallopian tube, or peritoneal cancer should have genetic risk evaluation. The presence of a germline or somatic *BRCA1* or *BRCA2* mutation may have treatment implications in maintenance therapy and management of recurrent disease.[2] Women with BRCA gene mutations, particularly *BRCA2*, appear to have a somewhat better prognosis than non-carriers.[3]

HGSCs are characterised by chromosomal instability due to homologous recombination deficiency (HRD). Germline *BRCA1/2* mutations, somatic *BRCA1/2* mutations, and BRCA gene promotor methylations are well-known causes of HRD, but other genetic abnormalities of the HRR pathway could also cause HRD, although no consensus has been reached. The presence of HRD results in irreparable DNA damage from platinum-containing drugs, which leads to cell death. Moreover, an underlying HRD in tumour cells makes the cells sensitive to PARP inhibitors. PARP inhibitors bind to and trap PARP1 and PARP2 on DNA at the sites of single-strand breaks, which results in the generation of double-strand breaks. In cancer cells with HRD, double-strand DNA breaks are repaired by

[2] Chen, L-M and Berek, JS. Epithelial carcinoma of the ovary, fallopian tube and peritoneum: Clinical features and diagnosis, UpToDate. UpToDate accessed 13 August 2020.
[3] Chen, L-M and Berek, JS. Overview of epithelial carcinoma of the ovary, fallopian tube, and peritoneum, UpToDate. UpToDate accessed 13 August 2020.

error-prone pathways (that is, non-homologous end joining), ultimately leading to cell death.[4]

For women with advanced EOC, the chemotherapy options depend on the surgical outcomes but include platinum-based treatment (either carboplatin or cisplatin), plus paclitaxel. Despite initial therapy, the majority of women with advanced-stage ovarian cancer will relapse and require additional treatment.

The approach to treatment at relapse depends upon the amount of time that has elapsed between the completion of platinum-based treatment and the detection of relapse, known as the platinum-free interval (PFI). This is because the PFI correlates with progression-free survival (PFS), overall survival (OS), and response to subsequent treatment (both with platinum and non-platinum agents as well as cytoreduction). Patients with a PFI of six months or longer are considered to have chemotherapy-sensitive disease. Women with platinum-sensitive recurrent EOC should be considered for both secondary cytoreduction and second-line chemotherapy regimen that contains a platinum agent, with or without bevacizumab. Maintenance treatment with bevacizumab, olaparib or niraparib have been used, although all of these agents have demonstrated improvements in PFS when used as maintenance, only bevacizumab has shown an OS benefit.

Adenocarcinoma of the pancreas

Cancer of the exocrine pancreas is a highly lethal malignancy. The commonly used term 'pancreatic cancer' usually refers to a ductal adenocarcinoma of the pancreas (including its subtypes), which represents approximately 85% of all pancreatic neoplasms. The five-year survival rate for pancreatic cancer is 10.7%.[5]

Surgical resection is the only potentially curative treatment. Unfortunately, because of the late presentation, only 15 to 20% of patients are candidates for pancreatectomy. Furthermore, prognosis is poor, even after a complete resection. Five-year survival after margin-negative pancreaticoduodenectomy is approximately 30% for node-negative and 10% for node-positive disease. Signs of metastatic disease may occur at presentation. Metastatic disease most commonly affects the liver, peritoneum, lungs, and less frequently, bone. For patients with metastatic cancer, palliative systemic chemotherapy can improve disease-related symptoms and prolong survival.[6]

The two preferred regimens for initial treatment of metastatic disease include the combination of fluorouracil, irinotecan, leucovorin, and oxaliplatin (Folfirinox);[7] or gemcitabine in combination with nab-paclitaxel.[8,9] Gemcitabine alone or in combination with either capecitabine or erlotinib may also be used in the first-line treatment setting.[10] These chemotherapy regimens have modest, at best, impact on PFS and OS.

[4] Takaya, H. et al. Homologous recombination deficiency status-based classification of high-grade serous ovarian carcinoma. *Sci Rep*, 2020; 10.
[5] Cancer Council, Types of cancer: Pancreatic cancer. Accessed 3 November 2020 from the Cancer Council website.
[6] Carlos Fernandex-del Castillo. Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer in UpToDate. Up to date accessed 3 November 2020.
[7] Folfirinox is the name of a combination of cancer drugs that includes: FOL, folinic acid (also called leucovorin, or calcium folinate); F, fluorouracil (also called 5FU); IRIN, irinotecan; and OX, oxaliplatin.
[8] Ducreux M, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 2015; 26(Suppl 5): v56-68.
[9] National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology: pancreatic adenocarcinoma. Version 1.2019. Available from the NCCN website.
[10] Sohal DPS, et al. Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol* 2018; 36(24): 2545-2556.

Regulatory status

The 100 mg and 150 mg products received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 23 May 2018 for the following indications:

> *Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum- sensitive relapsed high grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.*

On 1 August 2018, the following extension of indications was approved:

> *Lynparza is indicated as monotherapy for the treatment of adult patients with germline BRCA mutated HER2-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Germline BRCA mutation (gBRCAm) status should be determined by an experienced laboratory using a validated test method.*

On the 18 June 2019, the following extension of indications was approved:

> *Ovarian cancer*
>
> *Lynparza is indicated as monotherapy for the:*
>
> *maintenance treatment of adult patients with advanced BRCA-mutated (germline or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy. BRCA mutation status should be determined by an experienced laboratory using a validated test method.*

Advanced ovarian cancer indication

At the time the TGA considered this application, similar applications had been approved in the European Union (EU; approved on 17 September 2020), United States (US; approved on 8 May 2020) and Switzerland (approved on 26 November 2020). Similar applications were also under consideration in Singapore (submitted January 2020) and New Zealand (submitted on 1 April 2020).

See Table 1 for the approved indications in the EU and US.

Table 1: International regulatory status (advanced ovarian cancer indication) as of January 2021, European Union and United States only

Region	Submission date	Status	Approved indications
EU (via Centralised Procedure)	21 November 2019	Approved on 17 September 2020	*Lynparza in combination with bevacizumab is indicated for the:* *maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability.*
US	13 November 2019	Approved on 8 May 2020	*In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:* • *a deleterious or suspected deleterious BRCA mutation, and/or* • *genomic instability.* *Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.*

FDA = Food and Drug Administration, FIGO = Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynaecology and Obstetrics).

Adenocarcinoma of the pancreas indication

At the time the TGA considered this application, similar applications had been approved the EU (approved on 3 July 2020), US (approved on 27 December 2019), Canada (approved on 14 February 2020), Singapore (approved on 14 August 2020) and Switzerland (approved on 14 May 2020), and an application was under consideration in New Zealand (submitted on 1 April 2020).

See Table 2 for the approved indications in the EU and US.

Table 2: International regulatory status (adenocarcinoma of the pancreas indication) as of January 2021, European Union and United States only

Region	Submission date	Status	Approved indications
EU (via Centralised Procedure)	2 July 2019	Approved on 3 July 2020	*Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen.*
US	28 June 2019	Approved on 27 December 2019	*For the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.* *Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.*

gBRCAm = germline BRCA-mutated; FDA = Food and Drug Administration.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 3: Timeline for Submission PM-2020-00161-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	2 March 2020
First round evaluation completed	26 August 2020
Sponsor provides responses on questions raised in first round evaluation	29 September 2020
Second round evaluation completed	6 November 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	17 December 2020
Sponsor's pre-Advisory Committee response	21 January 2021
Advisory Committee meeting	4 and 5 February 2021
Registration decision (Outcome)	4 March 2021
Completion of administrative activities and registration on the ARTG	10 March 2021
Number of working days from submission dossier acceptance to registration decision*	225

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The two new studies to support the request for the new indications were the PAOLA-1 and POLO trials; these were provided in the dossier.

- Study D0817C00003 (the PAOLA-1 trial) was a Phase III, randomised, double blind study in patients newly diagnosed advanced FIGO Stage III to IV high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who were in response following first line treatment with platinum-taxane chemotherapy and bevacizumab.
- Study D081FC00001 (the POLO trial) was a Phase III, randomised, double blind, placebo controlled, multicentre study of olaparib maintenance treatment (300 mg, as 2 x 150 mg tablets, twice daily (BD)) in patients with metastatic adenocarcinoma of the pancreas with gBRCAm that were loss of function mutations, whose tumours had not progressed following at least 16 weeks of first-line platinum-based chemotherapy.

Additional studies were provided for safety analysis, including the ovarian cancer study, the SOLO3 trial.

- Study D0816c00010 (the SOLO3 trial): a Phase III, open label, randomised, controlled, multicentre study to assess the efficacy and safety of olaparib monotherapy versus physician's choice single agent chemotherapy in the treatment of platinum sensitive relapsed ovarian cancer in patients carrying germline *BRCA1/2* mutations.
- Study D0810c00022 provided safety and pharmacokinetic (PK) data.
  Study D0810c00022 was a Phase I, open label, dual centre study to assess the safety and tolerability of olaparib in combination with bevacizumab (Avastin) in patients with advanced solid tumours.

Pharmacokinetics

No PK data was collected from the pivotal study for the proposed ovarian cancer.

Study D0810C00022 assessed the safety and tolerability of olaparib in combination with bevacizumab in patients with advanced solid tumours. This study had not previously been submitted though it was conducted from June 2008 to March 2009. Successive cohorts of 4 to 6 patients received increasing doses of olaparib (100, 200 and 400 mg BD) continuously in combination with intravenous bevacizumab at a fixed dose of 10 mg/kg given every 14 days (1 cycle). To be evaluable for PK assessment and potential dose escalation, patients had to complete at least 1 cycle of bevacizumab, and have a full PK profile for olaparib taken both in the monotherapy setting (on Day 4) and on the day of first administration of bevacizumab.

Twelve patients (four in each treatment group) with a mean age of 49.7 years (age range 22 to 71 years) were enrolled and received study treatment (olaparib and bevacizumab). This study had very small sample sizes for each olaparib dose group. No gross PK effect on olaparib from the addition of bevacizumab was apparent however, the clinical evaluator has noted that one patient showed approximately an apparent 40% decrease in maximum plasma concentration (C_{max}) and differences also in area under the plasma concentration time curve (AUC) and minimum plasma concentration (C_{min}) compared with olaparib as monotherapy.

Efficacy

Advanced ovarian cancer indication: Study D0817C00003 (PAOLA-1 trial)

The PAOLA-1 trial was a Phase III, randomised, double blind, placebo controlled trial of olaparib versus placebo added to bevacizumab (vascular endothelial growth factor inhibitor) for the maintenance treatment of newly diagnosed advanced ovarian cancer

patients who were in response following first line platinum-based chemotherapy and bevacizumab. It was conducted in 11 countries with the first subject enrolled in July 2015 and the last subjects in August 2017. The report included in this submission had a data cut-off date of 22 March 2019. The estimated date for the last follow-up is in the third quarter of 2022.

Objectives and endpoints

The primary objective is to determine the efficacy by progression free survival to first progression or death (PFS1),[11] investigator based according to modified Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, of olaparib maintenance compared to placebo in high grade epithelial ovarian, fallopian tube, or peritoneal cancer that are in clinical complete response (CR) or partial response (PR) following first line platinum-taxane based chemotherapy plus bevacizumab, and planned to pursue bevacizumab in the maintenance phase up to a total of 15 months.

Secondary efficacy objectives included: The time from randomisation to the earlier date of modified RECIST 1.1 or cancer antigen 125 (CA-125) progression or death by any cause; time from randomisation to first subsequent therapy or death (TFST); time from randomisation to second progression (PFS2);[12] time from randomisation to second subsequent therapy or death (TSST); and OS.

Inclusion and exclusion criteria

Key inclusion criteria were:

- Female patients with newly diagnosed advanced (FIGO Stage IIIB to IV)[13] ovarian cancer, primary peritoneal cancer and/or fallopian tube cancer that is histologically confirmed as high-grade serous, or high-grade endometrioid, or other epithelial non-mucinous ovarian cancer.
- Eligible patients were those with no evidence of disease (NED) or in clinical CR or in PR, following completion of first line platinum-taxane based chemotherapy plus bevacizumab and for whom bevacizumab maintenance was planned.
- Patients who had completed first line platinum-taxane chemotherapy prior to randomisation. The platinum-taxane based regimen must have consisted of a minimum of six and a maximum of nine treatment cycles; however, if platinum-based therapy was discontinued early as a result of non-haematological toxicity specifically related to the platinum regimen, (for example, neurotoxicity, hypersensitivity), patients must have received a minimum of four cycles of the platinum-based regimen.

[11] **PFS1** = progression-free survival (defined as the time from randomisation until the date of objective radiological disease progression according to modified RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the patient discontinued randomised therapy or received another anticancer therapy prior to progression).
[12] **PFS2** = Time from randomisation to second progression or death (defined as time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death)
[13] Ovarian cancer/high grade serous carcinoma, including endometrial ovarian carcinoma, fallopian tube and peritoneal carcinoma is staged according to the Fédération Internationale de Gynécologie et d'Obstétrique (**FIGO**) **staging system.**
Stage IIIB: The cancer has visibly spread past the pelvis to the abdomen and is 2 cm or smaller, with or without spread to the retroperitoneal lymph nodes.
Stage IIIC: The cancer has visibly spread past the pelvis to the abdomen and is larger than 2 cm, with or without spread to the retroperitoneal lymph nodes.
Stage IV: The cancer has spread to organs outside of the abdominal area.
Stage IVA: The cancer has spread to fluid around the lungs.
Stage IVB: The cancer has spread to the liver or spleen or to organs beyond the abdomen, including lymph nodes in the groin outside of the abdominal cavity.

Key exclusion criteria were:

- Patients whose tumours were of non-epithelial origin of the ovary, the fallopian tube or the peritoneum (that is, germ cell tumours), ovarian tumours of low malignant potential (for example, borderline tumours) or mucinous carcinoma or synchronous primary endometrial cancer, unless both of the following criteria were met:
  - Eastern Cooperative Oncology Group (ECOG) Stage < II.[14]
  - Less than 60 years old at the time of diagnosis of endometrial cancer with Stage IA or Stage IB (Grade 1 or 2), or Stage IA (Grade 3) endometrial carcinoma;[15] or ≥ 60 years old at the time of diagnosis of endometrial cancer with Stage IA (Grade 1 or 2) endometrioid adenocarcinoma. Patients with serous or clear cell adenocarcinoma or carcinosarcoma of the endometrium were not eligible.

Randomisation

Randomisation was stratified as follows:

- First line treatment outcome at screening:
  - NED with complete macroscopic resection at initial debulking surgery.
  - NED/CR with complete macroscopic resection at interval debulking surgery (IDS).
  - NED/CR at screening, in patients who had either incomplete resection (at initial or IDS) or no debulking surgery (debulking surgery considered as not feasible).
  - PR.
- Tumour *BRCA* (tBRCA) status as determined by *BRCA* testing on tumour tissue:
  - Deleterious mutation.
  - Absence of deleterious mutation (tumour *BRCA* wild type (tBRCAwt)/variant of uncertain significance (VUS)/unknown).

Patients were randomised in a 2:1 ratio to olaparib 300 mg BD (tablet) or matching placebo. All patients received bevacizumab 15 mg/kg every 3 weeks for up to 15 months as per label indication including the period of pre-randomisation given with chemotherapy and post-randomisation given with olaparib or placebo. Olaparib was continued for 2 years or until disease progression, as assessed by the investigator. Patients

[14] **ECOG Performance Status**: The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

[15] In the **FIGO staging system,** Stage IA and IB, and Grades I to III are defined as:
Stage IA: The cancer is only inside one ovary or fallopian tube. No cancer is found on the ovarian or fallopian tube surface or in the abdomen.
Stage IB: The cancer is in both ovaries or fallopian tubes. No cancer is found on the surface of the ovary or fallopian tube or in the peritoneal fluid.
Grade 1: The tissue is well differentiated. This means the cells look and are organised within the tumour like normal cells. These tumours tend to grow more slowly.
Grade 2: The tissue is moderately differentiated. It shares features between well and poorly differentiated.
Grade 3: The tissue is poorly differentiated or undifferentiated. All or most cells appear very abnormal and do not have any normal tissue structure. These tumours tend to grow fast and can spread rapidly.

who in the opinion of the treating physician could derive further benefit from continuous treatment, could be treated beyond 2 years. Patients in both treatment arms had tumour assessments according to modified RECIST v1.1 at Baseline and every 24 weeks.

Gene testing

The Myriad myChoice HRD Plus assay was used to assess HRD status in a subset of patients. A positive HRD status means that there are mutations in *BRAC1* and *BRCA2* genes or a high Genomic Instability Score in patients with ovarian cancer. With a positive HRD status, a patient's DNA is unable to repair. HRD status is based on a Myriad HRD score and *BRCA* mutation (BRCAm) status. A positive HRD status is determined either by presence of a *BRCA1/2* mutation or by a Myriad score at or above a pre-specified cut-off in the absence of a *BRCA1/2* mutation. The Myriad myChoice HRD Plus test consists of gene sequencing of a panel of 108 genes, including the HRR genes, performed by Myriad Genetics, Inc.

Patients may be classified as having Myriad HRD positive or Myriad HRD negative tumours using a combination of *BRCA* status and Myriad HRD score. BRCAm tumours are automatically defined as Myriad HRD positive irrespective of their Myriad HRD score. Myriad HRD status is only ever derived from tumour. The Myriad positive HRD status cut off 42 or cut off 33 are defined by the presence of BRCAm or an HRD score ≥ 42 or 33, respectively.

Where reference is made to a subset of the tBRCA population, specifically those patients tested with the myChoice HRD Plus test the abbreviation 'Myriad tBRCA' is used. The subset of patients confirmed with a tBRCA mutation using this test should be referred to using the abbreviation 'Myriad tBRCAm'. Germline BRCA (gBRCA) testing was not mandatory in the study, and gBRCA status was available for half of the patients (404 out of 806 (50.1%)). Of these, 12 out of 404 (29.7%) patients were gBRCAm.

Statistical methods

PFS1 according to investigator assessment based on modified RECIST 1.1 was the primary efficacy endpoint. PFS was analysed using a log-rank test stratified by first line treatment outcome and tBRCA status with the hazard ratio (HR) and associated confidence interval (CI) estimated from a stratified Cox Proportional Hazards model. A sensitivity analysis to assess ascertainment bias based on blinded independent central review (BICR). RECIST data was also performed.

Key secondary endpoints were: time to earliest progression or death; TFST; PFS2; TSST and OS. To control for multiplicity hierarchical testing strategy was used where PFS1 is tested first and key secondary endpoints of PFS2 and OS will then be tested using a multiple testing procedure with a recycling strategy (that is, the multiple testing procedure will recycle the test mass to the endpoint not yet rejected in the hierarchy.

There were multiple exploratory analyses which included pre planned subgroup analyses of efficacy (including PFS1 and OS) based on relevant potential prognostic factors, including, but not limited to stratification factors, clinical characteristics and tumour HR deficiency status (BRCAm, mutations in other HR genes and Myriad HRD scar status). No adjustments to the significance level for testing were made since all these subgroup analyses were considered exploratory and may only be supportive of the analysis of PFS1.

A total of 806 patients were randomised and the data cut-off for the analysis of PFS (22 March 2019) took place when 474 progression events had occurred (58.8% maturity), approximately 45 months after the first patient was randomised. It was estimated that 458 PFS events would have approximately > 80% power to show PFS at a 2 sided 5% level if the assumed true treatment effect was HR 0.75; this translates to an improvement in median PFS from 15.8 months (placebo/bevacizumab arm) to 21.1 months (olaparib/bevacizumab arm). In addition to the planned analyses, PFS1, PFS2, OS, TFST,

TSST and time from randomisation to discontinuation of treatment or death (TDT) were tested at a 2 sided significance level of 5% to control the type I error at 2.5% (1 sided).

The final PFS2 analysis is planned when the PFS2 data are approximately 53% mature or after a maximum duration of 1 year following the PFS analysis, whichever occurs first. If PFS2 is statistically significant then OS will also be tested. If the final PFS2 analysis is not statistically significant, a final OS summary will be performed when the OS data are approximately 60% mature or after a 3 year duration from the main PFS analysis, whichever occurred first.

Results

A total of 806 patients were randomised; 537 to olaparib/bevacizumab and 269 to placebo/bevacizumab. The median age was 61 years. Patients were stratified based on their first line treatment outcome at screening and their screening laboratory tBRCAm result. Stratification factors were well balanced between treatment arms. Approximately 30% of patients had tBRCAm tumours and approximately 70% of patients were non-tBRCAm based on screening laboratory data. The majority of patients in both arms had either NED due to complete macroscopic resection at initial debulking surgery or interval debulking surgery or had CR to chemotherapy at randomisation. Disease characteristics at Baseline are shown below in Table 4.

Table 4: Study D0817C00003 (PAOLA-1 trial) Baseline characteristics of the full analysis set population

	Olaparib/ bevacizumab (N = 537) Number (%) of patients	**Placebo/ bevacizumab (N = 269)** Number (%) of patients	**Total (N = 806)** Number (%) of patients
ECOG performance status			
(0) Normal activity	378 (70.4)	189 (70.3)	567 (70.3)
(1) Restricted activity	153 (28.5)	76 (28.3)	229 (28.4)
Missing	6 (1.1)	4 (1.5)	10 (1.2)
Tumour characteristics			
Primary tumour location			
Ovary	456 (84.9)	238 (88.5)	694 (86.1)
Fallopian tube	39 (7.3)	11 (4.1)	50 (6.2)
Peritoneal	42 (7.8)	20 (7.4)	62 (7.7)
Histological grade			
High-grade	537 (100)	268 (99.6)	805 (99.9)
Low grade	0	1 (0.4)	1 (0.1)
FIGO Staging			
IIIB	43 (8.0)	17 (6.3)	60 (7.4)
IIIC	335 (62.4)	169 (62.8)	504 (62.5)
IV	159 (29.6)	83 (30.9)	242 (30.0)
CA-125 status at Baseline			
CA-125 levels ≤ ULN	463 (86.2)	234 (87.0)	697 (86.5)
CA-125 levels > ULN	74 (13.8)	34 (12.6)	108 (13.4)
Missing	0	1 (0.4)	1 (0.1)
Histology type			
Serous	519 (96.6)	253 (94.1)	772 (95.8)
Endometrioid	12 (2.2)	8 (3.0)	20 (2.5)
Clear cell	2 (0.4)	0	2 (0.2)
Undifferentiated	1 (0.2)	6 (2.2)	7 (0.9)
Other	3 (0.6)	2 (0.7)	5 (0.6)

	Olaparib/ bevacizumab (N = 537) Number (%) of patients	**Placebo/ bevacizumab (N = 269)** Number (%) of patients	**Total (N = 806)** Number (%) of patients
Type of prior surgery and outcome			
Patients with debulking surgery	499 (92.9)	248 (92.2)	747 (92.7)
Residual macroscopic disease	176/499 (35.3)	88/248 (35.5)	264/747 (35.3)
No residual macroscopic disease	323/499 (64.7)	160/248 (64.5)	483/747 (64.7)
Patients with initial debulking surgery	271 (50.5)	138 (51.3)	409 (50.7)
Residual macroscopic disease	111/271 (41.0)	53/138 (38.4)	164/409 (40.1)
No residual macroscopic disease	160/271 (59.0)	85/138 (61.6)	245/409 (59.9)
Patients with IDS	228 (42.5)	110 (40.9)	338 (41.9)
Residual macroscopic disease	65/228 (28.5)	35/110 (31.8)	100/338 (29.6)
No residual macroscopic disease	163/228 (71.5)	75/110 (68.2)	238/338 (70.4)
Patients with no debulking surgery, n (%)	38 (7.1)	21 (7.8)	59 (7.3)
Screening laboratory *tBRCA* status (obtained from the randomisation schedule)			
Deleterious mutation	161 (30.0)	80 (29.7)	241 (29.9)
Absence of deleterious mutation[a]	376 (70.0)	189 (70.3)	565 (70.1)
Screening laboratory *tBRCA* status on tumour tissue (obtained from the eCRF)			
tBRCAm	157 (29.2)	80 (29.7)	237 (29.4)
Non-*tBRCAm*[a]	380 (70.8)	189 (70.3)	569 (70.6)
First line treatment outcome at screening (obtained from the randomisation schedule)			
NED with complete macroscopic resection at initial debulking surgery	170 (31.7)	86 (32.0)	256 (31.8)
NED/CR with complete macroscopic resection at IDS	166 (30.9)	84 (31.2)	250 (31.0)
NED/CR at screening, in patient who had either incomplete resection (at initial or IDS) or no debulking surgery	82 (15.3)	40 (14.9)	122 (15.1)
PR	119 (22.2)	59 (21.9)	178 (22.1)
First line treatment outcome at screening (obtained from the eCRF)			
NED with complete macroscopic resection at initial debulking surgery	158 (29.4)	83 (30.9)	241 (29.9)
NED/CR with complete macroscopic resection at IDS	158 (29.4)	75 (27.9)	233 (28.9)
NED/CR at screening, in patient who had either incomplete resection (at initial debulking surgery or IDS) or no debulking surgery	80 (14.9)	36 (13.4)	116 (14.4)
PR	134 (25.0)	73 (27.1)	207 (25.7)
Not applicable as per eCRF[b]	7 (1.3)	2 (0.7)	9 (1.1)

a: Includes test cancelled/failed patients (that is, inconclusive and unknown *tBRCA* status): 26 patients in the olaparib/bevacizumab arm and 7 patients in the placebo/bevacizumab arm. b: Not applicable as unable to assign to 1 of detailed categories.

CA-125 = cancer antigen 125; CR = complete response; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; = FIGO Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynaecology and Obstetrics); IDS = interval debulking surgery; NED = no evidence of disease; PR = partial response; tBRCA = tumour BRCA; tBRCAm = tumour BRCA mutated; ULN = upper limit of normal.

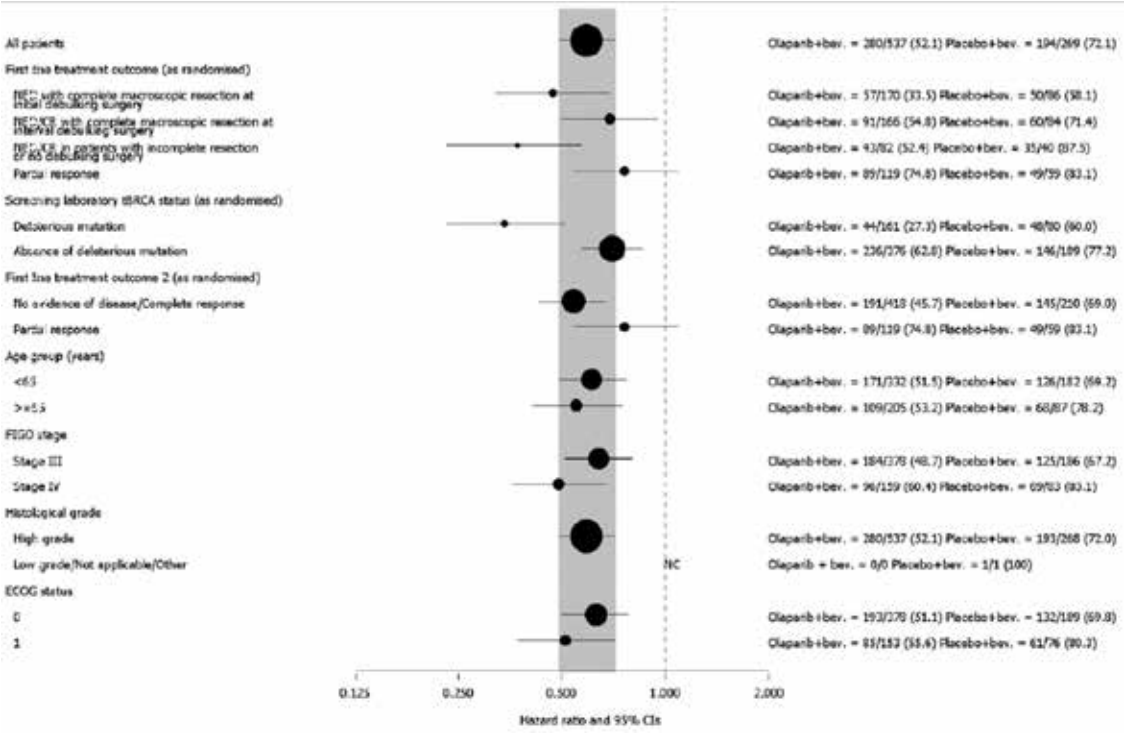
Median follow up was 22.7 months in the olaparib arm versus 24.0 months in the placebo arm. PFS assessment was at 58.8% maturity. There were 280 (52.1%) and 194 (72.1%) PFS events in the olaparib/bevacizumab and placebo/bevacizumab arms, respectively, of which 6 events in the olaparib/bevacizumab arm and 6 events in the placebo/bevacizumab arm were death in the absence of disease progression. The HR for

PFS for olaparib/bevacizumab versus placebo/bevacizumab-treated patients was HR 0.59; 95% CI 0.49 to 0.72; median PFS 22.1 versus 16.6 months; p < 0.0001). The BICR of PFS was HR 0.63; 95% CI 0.51 to 0.77; p < 0.0001). A discrepancy rate of 18% observed between investigator and BICR in assessment of PFS.

Results for secondary endpoints were either supportive of the addition of olaparib or were immature.

Exploratory analyses of PFS by subgroup stratification factors and clinical characteristics were performed, with results summarised in the Forest plot below (see Figure 1).

Figure 1: Study D0817C00003 (the PAOLA-1 trial) Progression free survival as a Forest plot, by subgroup stratification factors and clinical characteristics for the full analysis set population



Of particular note, patients with and without tBRCA mutations as randomised derived a PFS benefit from treatment with olaparib (tBRCAm: HR 0.34, 95% CI 0.23 to 0.51, median PFS 37.2 months olaparib/bevacizumab versus 22.0 months placebo/bevacizumab; non-tBRCAm: HR 0.70, 95% CI 0.57 to 0.86, median PFS 18.9 months olaparib/bevacizumab versus 16.0 months placebo/bevacizumab).

PFS results by Myriad myChoice HRD Plus test are shown below (see Table 5).

Table 5: Study D0817C00003 (PAOLA-1) trial progression free survival subgroup analyses (full analysis set population), tumour characteristics as assessed by Myriad myChoice HRD Plus test (data cut-off 22 March 2019)

Subgroup	Olaparib/ bevacizumab (n = 537)	Placebo/ bevacizumab (n = 269)
Myriad tumour *BRCA* mutation status		
tBRCAm		
Number of events/total number of patients (%)	44/158 (27.8)	52/77 (67.5)
Median PFS (months)	37.2	18.8
HR (95% CI)	0.28 (0.19 to 0.42)	
Non-*tBRCAm*[a]		
Number of events/total number of patients (%)	223/346 (64.5)	130/174 (74.7)
Median PFS (months)	18.2	16.4
HR (95% CI)	0.77 (0.62 to 0.96)	
Myriad HRD status (*tBRCAm* or ≥ 42 cut-off)		
HRD Positive		
Number of events/total number of patients (%)	87/255 (34.1)	92/132 (69.7)
Median PFS (months)	37.2	17.7
HR (95% CI)	0.33 (0.25 to 0.45)	
HRD Negative		
Number of events/total number of patients (%)	145/192 (75.5)	66/85 (77.6)
Median PFS (months)	16.6	16.2
HR (95% CI)	1.00 (0.75 to 1.35)	
Myriad HRD status excluding Myriad *tBRCAm* (42 cut-off)		
HRD Positive		
Number of events/total number of patients (%)	43/97 (44.3)	40/55 (72.7)
Median PFS (months)	28.1	16.6
HR (95% CI)	0.43 (0.28 to 0.66)	
Post-hoc analysis: Myriad HRD status cut-off 42[a]		
Cancelled/failed/missing		
Number of events/total number of patients (%)	48/90 (53.3)	36/52 (69.2)
Median PFS (months)	22.1	14.6
HR (95% CI)	0.71 (0.46 to 1.10)	

a: Non-tBRCAm = tBRCAwt/VUS, b: HR and associated CI derived using an interaction term accounting for all patients: HRD positive, HRD negative and HRD test cancelled/failed/missing

BRCA = breast cancer susceptibility gene; BRCAm = BRCA mutated; CI = confidence interval; HR = hazard ratio; HRD = homologous recombination deficiency; PFS = time from randomisation to first progression or death; tBRCAm = tumour BRCA mutated.

The above results in Table 5 show that for the 664 patients in whom Myriad HRD status was determined (section highlighted in green), those with tumours which were tBRCAm negative or Myriad HRD < 42 had no increase in median PFS from the addition of olaparib with HR 1 (95%CI 0.75; 1.35). That group comprised 277 out of 664 (42%) of patients in whom Myriad HRD testing was performed.

The biological biomarkers analysis to determine the frequency of somatic *BRCA* mutations (sBRCAm) in tumour samples and to compare this with gBRCAm status was performed in a subgroup of patients. For the 372 out of 806 (46.2%) patients who had an available

Myriad tBRCA test and a local germline test (by eCRF), sBRCA status (that is, *BRCA* variant found in the tumour but not in the germline) was derived. Of these, 32 out of 372 (8.6%) were deduced to be sBRCAm.

PFS was analysed using a log-rank test stratified by first line treatment outcome at screening (the timing and outcome of surgery, and the response to chemotherapy) and screening laboratory tBRCA status on tumour tissue for generation of the p-value and using the Breslow approach for handling ties. Stratification factors, as randomised or per eCRF, were well balanced between treatment arms. Approximately 30% of patients had tBRCAm tumours and approximately 70% of patients were non-tBRCAm based on screening laboratory data.

gBRCA testing was not mandatory in the study; however, information regarding gBRCA status was requested for all randomised patients. Central gBRCA testing at one of the Institut National Du Cancer (INCa; French National Cancer Institute)-recommended institutions was performed only for patients at study sites in France. In the eCRF, gBRCA status was available for half of the patients (404 out of 806 (50.1%)). Of these, 120 out of 404 (29.7%) patients were gBRCA.

Adenocarcinoma of the pancreas indication: Study D081FC00001 (POLO trial)

One study was submitted to support the proposed pancreatic cancer indication. The POLO trial (Study D081FC00001) was a Phase III, randomised, double blind, placebo controlled, multi-centre study to investigate olaparib maintenance treatment in gBRCAm patients with metastatic pancreatic adenocarcinoma whose disease had not progressed after receiving a minimum of 16 weeks of first line platinum-based chemotherapy. There was no upper limit to the duration of chemotherapy that a patient had received.

This was a multicentre study conducted in 59 centres in 12 countries including Australia. The study commenced in January 2015 and the last patient visit was in January 2019. A total of 3315 patients were screened and 154 were randomised. Study patients were randomised 3:2 to receive either olaparib (300 mg (2 x 150 mg tablets) BD, tablet formulation) or matched placebo. No stratification factors were used for randomisation. Treatment was to continue until disease progression or intolerable toxicities.

The primary endpoint was PFS as determined by BICR. OS was a key secondary endpoint which was controlled for multiplicity however patients could switch out of the study to a PARP inhibitor so this endpoint is potentially confounded. PFS and OS were tested at a 1 sided significance level of 2.5%. In addition, OS was tested only after statistical significance was shown for PFS. Additional secondary endpoints, not controlled for multiplicity, in the POLO trial were delay in PFS2, TDT, the delay in TFST, and the delay in TSST. Quality of life endpoints were exploratory.

All patients had to have documented evidence of a loss of function (deleterious or suspected deleterious) gBRCA mutation (either gBRCA1 or gBRCA2) at study entry. Loss of function gBRCA1 or gBRCA2 mutation was determined prior to study entry from an existing local gBRCA test or from prospective testing using either the Myriad BRACAnalysis test or the Myriad BRACAnalysis CDx test. A subgroup analysis of patients with gBRCAm confirmed by Myriad BRACAnalysis or BRACAnalysis CDx tests was performed.

Patients also had histologically or cytologically confirmed pancreatic adenocarcinoma, were receiving initial chemotherapy for metastatic disease and whose disease had not progressed after receiving a minimum of 16 weeks of treatment with a first line platinum-based chemotherapy. The platinum could subsequently be discontinued at any time for toxicity and the other agents continued; the patients would remain eligible for randomisation as long as there was no evidence of progression at any time during chemotherapy treatment. Patients continued to receive study treatment until objective

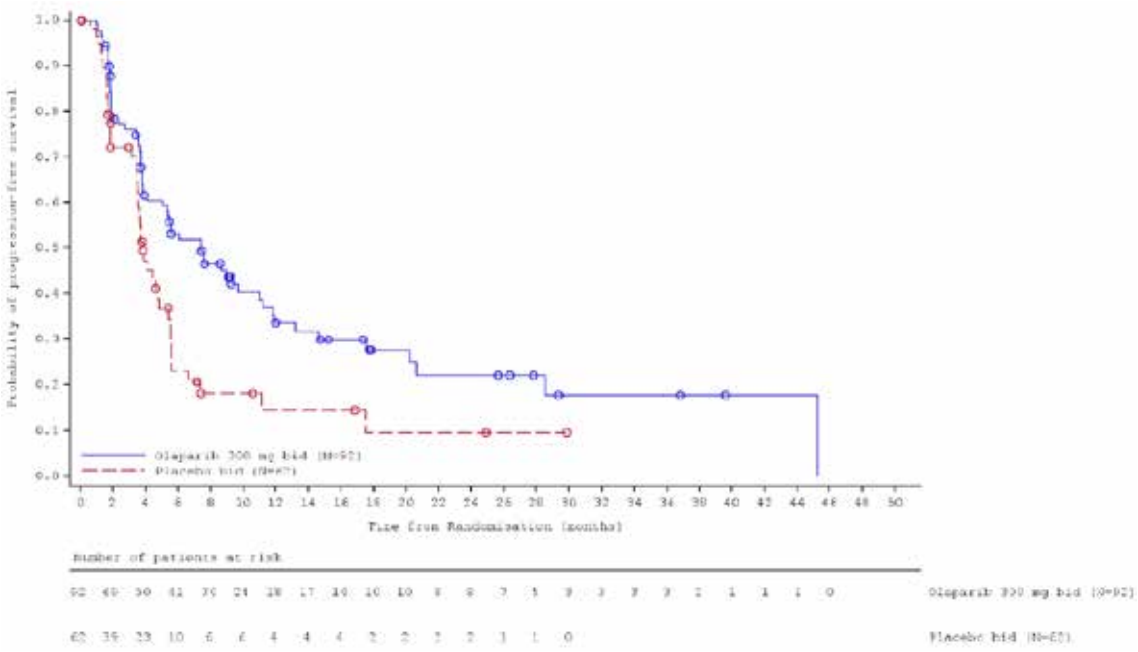
radiological disease progression per modified RECIST v1.1 as assessed by the investigator, unacceptable toxicity, or they did not meet any other discontinuation criteria.

Given the low prevalence of gBRCA mutations in pancreas cancer, and the lack of BRCA screening of pancreas cancer patients as part of standard clinical practice, extensive screening was required to enrol in the POLO trial (a total of 3315 patients were screened, 3175 patients of whom were submitted to Myriad for prospective determination of their gBRCA mutation status). In total, 154 patients were randomised (92 olaparib and 62 placebo): 57.2% in Europe, 22.7% in the US, 3.9% in Asia, and 16.2% in the rest of world.

The majority of patients had an ECOG Performance Status of 0, (70.7% in the olaparib arm and 61.3% in the placebo arm). At Baseline, 48.9% of patients given olaparib and 50.0% given placebo had stable disease at Baseline. At data cut-off date 15 January 2019, 104 PFS events had occurred (67.4% maturity). The median PFS was 7.4 months for olaparib versus 3.8 months for placebo equating to a prolongation of median progression free interval of 3.6 months with olaparib versus placebo. Based on Kaplan-Meier estimates, the percentage of patients who remained alive and progression free in the olaparib arm was 33.7% at 12 months, 27.6% at 18 months and 22.1% at 24 months, compared with 14.5%, 9.6% and 9.6%, respectively, in the placebo arm.

The median duration of response based on BICR data was longer in the olaparib arm (24.9 months) than in the placebo arm (3.7 months), with a longer median time to onset of response (5.4 months for olaparib and 3.6 months for placebo). A total of 53.3% of patients in the olaparib arm and 37.1% of patients in the placebo arm had disease control at 16 weeks.

Figure 2: Study D081FC00001 (POLO trial) Progression-free survival by blinded independent central review, Kaplan-Meier plot (full analysis set)



OS data were 46% mature (71 out of 154 events) and did not show a trend towards prolonged survival with olaparib. The median OS was 18.9 months in the olaparib arm and 18.1 months in the placebo arm (HR of 0.91; 95% CI 0.56, 1.46; p = 0.6833). Other secondary and exploratory events were not controlled for multiplicity and were immature.

Safety

Advanced ovarian cancer indication: Study D0817C00003 (PAOLA-1 trial)

In the PAOLA-1 trial, more patients given olaparib/bevacizumab than placebo/bevacizumab reported adverse events (AEs) of Grade ≥ 3. The proportion of patients who reported AEs leading to discontinuation, dose interruption, or dose reduction of olaparib or placebo treatment was also higher for patients given olaparib/bevacizumab. There were five deaths on study; four in patients given placebo/ bevacizumab and one in a patient given olaparib/ bevacizumab.

The most commonly reported AEs (≥ 20%) in the olaparib/bevacizumab arm were the known adverse drug reactions of olaparib or bevacizumab including nausea, fatigue, hypertension, anaemia, lymphopaenia, vomiting, and arthralgia. The AEs associated with olaparib and bevacizumab were consistent with their known safety profiles.

Adenocarcinoma of the pancreas indication: POLO trial (Study D081FC00001)

The median total duration of exposure in the olaparib arm (182 days (6.0 months)) was approximately 1.6 times longer than the duration of exposure in the placebo arm (113 days (3.7 months)). In the olaparib arm, the most common AEs (reported by ≥ 20% of patients) were fatigue, nausea, abdominal pain, diarrhoea, anaemia, decreased appetite and constipation. In the placebo arm, the most common AEs (reported by ≥ 20% of patients) were fatigue, abdominal pain and nausea.

No new safety concerns associated with olaparib were identified in the POLO trial.

Risk management plan

There was no requirement for a risk management plan evaluation for a submission of this type.[16]

Risk-benefit analysis

Delegate's considerations

Advanced ovarian cancer indication

The major issue with the PAOLA-1 trial is the identification of patients likely to benefit from the addition of olaparib to bevacizumab in the first line maintenance treatment of HGSC in patients who have responded to a platinum-based regimen + bevacizumab. Exploratory analyses suggest there are highly clinically significant differences in the extent of increase in PFS that can be expected based on tumour markers. Patients whose tumours were tBRCAm-positive and negative were both demonstrated to have statistically significant increases in PFS with the addition of olaparib with the greatest benefit accruing to tBRCAm-positive patients. Patients with a negative Myriad HRD status (tBRCAm of < 42 cut-off) were not shown to have any benefit in terms of PFS in the exploratory subgroup analysis. That group comprised 277 patients (192 given olaparib; 85 given placebo) from a total patient population of 664 patients in whom Myriad testing was performed. If approval for all patients regardless of tumour markers were to occur then potentially 277 out of 664 (42%) of patients who are not expected to benefit from the addition of olaparib would be exposed to it.

[16] The sponsor must still comply with routine product vigilance and risk minimisation requirements.

It is clear that patients with tumours with genomic instability that is not due to tBRCAm responded to olaparib + bevacizumab and that the inclusion of these patients in the tBRCAm subgroup was a major factor in the demonstration of efficacy in that subgroup.

Testing of tumours for tBRCAm is not routine in Australia and the Myriad test used in this study is not registered in Australia. The comparison of 372 out of 806 (46.2%) patients who had an available Myriad tBRCA test and a local germline test (by eCRF) was reported as showing that only 32 out of 372 (8.6%) had discordance (that is, BRCA variant found in the tumour but not in the germline). This suggests that patients who are gBRCAm positive do not require testing of their tumours for tBRCAm or for germline instability. Other patients would require assessment of their tumours for tBRCAm and/or genomic instability prior to consideration of the addition of olaparib to their treatment regimen.

The FDA has limited the proposed indication to patients whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:

- a deleterious or suspected deleterious *BRCA* mutation, and/or
- genomic instability.

That indication includes gBRCAm positive patients and patients who are either tBRCAm positive or with genomic instability identified on the basis of laboratory testing. The indication in the USA does not specify that Myriad HRD status is required. It is open as to how *BRCA*-positivity and/or genomic instability would be assessed and to what extent such instability would be required.

Adenocarcinoma of the pancreas indication

The POLO trial has demonstrated that patients who have gBRCAm with adenocarcinoma of the pancreas and who have responded to at least 16 weeks of a platinum-based chemotherapy with at least stable disease are likely to have a clinically significant increase in PFS with follow-on monotherapy olaparib. These findings are based on an interim study report and OS data are immature. At this stage, there is no indication that olaparib will extend OS for these patients. Only a small minority of patients with adenocarcinoma of the pancreas would benefit from olaparib due to the relatively low incidence of gBRCAm in the Australian population.

Proposed action

Advanced ovarian cancer indication

While a decision is yet to be made, at this stage the Delegate is inclined to approve an extension of indications with modifications to the proposed indication.

The Delegate does not consider it acceptable to approve the proposed indication as it is likely to expose about 42% of the proposed patient population to a medicine that has not demonstrated any efficacy in them.

It is not clear to the Delegate how the indication can be worded so as to allow access only to patients likely to benefit. The *in vitro* diagnostic device used in the study, Myriad myChoice HRD Plus, is not registered in Australia and is not a product marketed by the sponsor of olaparib in other jurisdictions.

Given the above considerations, at this stage the Delegate proposes the following indication:

> *in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:*

- *a deleterious or suspected deleterious BRCA mutation (germline or somatic), and/or*
- *genomic instability.*

HRD status should be determined by an experienced laboratory using a validated test method.

The Delegate sought advice from the Advisory committee on the advanced ovarian cancer indication (see '*Advisory Committee considerations*' section, below).

Adenocarcinoma of the pancreas indication

The proposed indication should be approved with minor amendments to reflect the patient group in which an increase in PFS was demonstrated. Minor amendments are also recommended to the description of the clinical trial to be included in the PI.

The Delegate did not seek advice from the Advisory Committee regarding the proposed adenocarcinoma of the pancreas indication.

Independent expert advice

The Delegate sought independent expert clinical advice on the advanced ovarian cancer indication, asking the following questions:

- The extent of tumour biomarker testing for serous ovarian carcinoma in Australia.
- Whether gene instability and tBRCA tests are available.
- Is a specific extent and duration of response required to platinum based therapy required?

The Delegate received the following independent expert advice in response to their questions.

- *BRCA* testing for serous ovarian carcinoma is performed in Australia, however, HRD testing is not routinely performed.
- Four cycles of platinum-based therapy is sufficient to determine whether the serous ovarian carcinoma is platinum sensitive.
- It was advised that the indication should reflect the clinical trial evidence that is, it should be limited to patients who responded to first-line platinum-based chemotherapy *and* whose cancer was HRD-positive, defined by either:
  - a deleterious or suspected deleterious *BRCA* mutation, and/or
  - genomic instability.
- The absence of routine testing for HRD status in Australia should not influence the indication.

Advisory Committee considerations[17]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

[17] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market

Specific advice to the delegate

The ACM advised the following in response to the Delegate's specific request for advice.

1. Whether the proposed indication is likely to adequately reflect the available evidence of efficacy and not unduly limit access to patients likely to benefit from Lynparza.

The ACM advised that the proposed indication should reflect the current clinical trial data which demonstrates a clinically and statistically significant benefit in survival for HRD positive and tBRCAm patients.

The ACM commented that while the PAOLA 1 trial did demonstrate an overall treatment arm benefit (22.1 months) for PFS against the placebo (16.6 months), examination of the subgroup data showed the benefit was limited to the tBRCAm (37.2 months) and HRD positive (37.2 months) cohorts. The ACM also commented that the HRD negative and failed/missing/cancelled status cohorts did not have benefit on subgroup analysis.

The ACM noted that the toxicity profile of olaparib, whilst modest, has an impact on treatment and was therefore of the view that Lynparza should be restricted to cohorts where efficacy is clearly demonstrated; tBRCAm-positive or HRD-positive cohorts. Noting this recommendation also aligns with the FDA and European Medicines Agency indications.

The ACM discussed access to genomic instability testing, noting that currently there are limited Australian–based options, and patients can utilise testing available overseas. Although the ACM acknowledged potential challenges if patients were unable to access suitable testing, overall the ACM was of the view that the potential absence of genomic instability testing does not warrant an opening of the indication (removal of HRD status), reiterating the concerns of treatment related toxicity without proven benefit for HRD negative or failed/missing/cancelled status should the indication exclude the HRD status.

Regarding the wording for the ovarian cancer aspect of the indication, the ACM recommended using the terminology 'pathogenic or likely pathogenic' instead of 'deleterious or suspected deleterious' when describing BRCA mutations, and/or genomic instability, stating pathogenic is the more accurate term.

The ACM were also supportive of the inclusion of a statement within the clinical trial section of the PI describing the PAOLO-1 trial, outlining that no benefit was demonstrated in patients whose cancer was not associated with genomic instability.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *In combination with bevacizumab for the maintenance treatment of adult patients with advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either a pathogenic or likely pathogenic BRCA mutation, and/or genomic instability. Homologous recombination deficiency status should be determined by an experienced laboratory using a validated test method.*

advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Lynparza (olaparib) 100 mg and 150 mg film coated tablets blister pack, for the following extension of indications:

Lynparza in combination with bevacizumab is indicated for the:

- *maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:*
  - *a deleterious or suspected deleterious BRCA mutation (germline or somatic), and/or*
  - *genomic instability*

  HRD status should be determined by an experienced laboratory using a validated test method.

Adenocarcinoma of the pancreas

Lynparza is indicated as monotherapy for the:

- *maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Germline BRCA mutation (gBRCAm) status should be determined by an experienced laboratory using a validated test method.*

As such, the full indications at this time were:

Ovarian cancer

Lynparza is indicated as monotherapy for the:

- *maintenance treatment of adult patients with advanced BRCA-mutated (germline or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy. BRCA mutation status should be determined by an experienced laboratory using a validated test method.*
- *maintenance treatment of adult patients with platinum-sensitive relapsed high grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens. Lynparza in combination with bevacizumab is indicated for the:*
- *maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:*
  - *a deleterious or suspected deleterious BRCA mutation (germline or somatic), and/or*
  - *genomic instability*

  HRD status should be determined by an experienced laboratory using a validated test method.

Breast cancer

Lynparza is indicated as monotherapy for the:

- *treatment of adult patients with germline BRCA-mutated HER2-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Germline BRCA mutation (gBRCAm) status should be determined by an experienced laboratory using a validated test method.*

Adenocarcinoma of the pancreas

Lynparza is indicated as monotherapy for the:

- *maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Germline BRCA mutation (gBRCAm) status should be determined by an experienced laboratory using a validated test method.*

Specific conditions of registration applying to these goods

This approval does not impose any requirement for the submission of periodic safety update reports (PSURs). The sponsor should note that it is a requirement that all existing requirements for the submission of PSURs as a consequence of the initial registration or subsequent changes must be completed.

Attachment 1. Product Information

The PI for Lynparza approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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