EU RMP	
Drug Substance	Olaparib
Version Number	30
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EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR OLAPARIB

The content of this RMP has been reviewed and approved by the Deputy EU QPPV

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the Marketing Authorisation Holder's Deputy QPPV in the EU, as delegated by QPPV in the EU

Anne Lappereau-Gallot

Administrative Information

Other RMP version under evaluation	**Not Applicable**
Details of currently approved RMP	**Version Number:** 29 **Approved with procedure:** EMEA/H/C/003726/IB/0067 **Date of approval**: 05 January 2024

Rationale for Submitting an Updated RMP

To extend the indication to include olaparib in combination with durvalumab for the maintenance treatment of endometrial cancer.

Summary of Significant Changes in this RMP

Part I: Product Overview	To include the indication for olaparib in combination with durvalumab for the maintenance treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair proficient (pMMR) whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel
Part II Safety Specification	
Module SI: Epidemiology of the Indication And Target Population	Epidemiology of endometrial cancer added
Module SIII: Clinical Trial Exposure	Exposure data updated for the monotherapy all dose pool and combination therapy (olaparib + bevacizumab and olaparib + abiraterone) and added for the olaparib + durvalumab combination (DUO-E)
Module SIV: Populations not Studied in Clinical Trials	Exposure data updated for patients with renal impairment, ethnic origin, and subpopulations carrying relevant genetic polymorphisms for the monotherapy all dose pool and the olaparib + abiraterone combination, and added for the olaparib + durvalumab combination (DUO-E)
Module SV: Post-authorisation Experience	Cumulative global and EU post-marketing patient exposure for capsules and tablets updated
Module SVII: Identified and Potential Risks	**Section 7.3** Updated incidence data

Part IV Plans for Post-authorisation Efficacy Studies	DUO-E added as a post-authorisation efficacy study (PAES) to Table IV-1
Part VI Summary of the Risk Management Plan for Olaparib	
VI: 1 The Medicine and What it is Used For	Addition of the indication for olaparib in combination with durvalumab for the maintenance treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair proficient (pMMR) whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel
VI:2.3 Post-authorisation Development Plan	Addition of DUO-E as a post-authorisation commitment.
Part VII - ANNEXES	Annex 5 and 8 updated

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PART VII. ANNEXES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
5-FU	5 fluorouracil
ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
AE	Adverse event
AML	Acute myeloid leukaemia
ATM	Ataxia telangiectasia mutated
BCRP	Breast Cancer Resistance Protein
bd	Twice daily
BRCA	Breast cancer susceptibility gene (*BRCA1* and *BRCA2*)
BRCAm	*BRCA*-mutated
CA-125	Cancer Antigen-125
CHMP	Committee for Medicinal Products for Human Use
CNS	Central nervous system
CR	Complete response
CRPC	Castrate-resistant prostate cancer
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCO	Data cut-off
DHPC	Direct Healthcare Professional Communication
DNA	Deoxyribonucleic acid
ECIS	European Cancer Information System
ECOG	Eastern Co-operative Oncology Group
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	Oestrogen receptor
ESMO	European Society for Medical Oncology
ESR	Externally Sponsored Studies
EU	European Union
FIGO	The International Federation of Gynecology and Obstetrics

Abbreviation/ Special term	**Definition/Explanation**
gBRCA	Germline *BRCA*
gBRCAm	Germline *BRCA*-mutated
GFR	Glomerular filtration rate
HDI	Human Development Index
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
HRD	Homologous recombination deficient
HRR	Homologous recombination repair
HSPC	Hormone-sensitive prostate cancer
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
MAP	Managed Access Programme
mCRPC	Metastatic castrate-resistant prostate cancer
MDS	Myelodysplastic syndrome
NCCN	National Comprehensive Cancer Network
NHA	New hormonal agent
NICE	National Institute for Health and Care Excellence
NPM	New primary malignancy
od	Once daily
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose polymerase
PBRER	Periodic Benefit-Risk Evaluation Report
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression-free survival
PFS2	Time from start of randomisation to second progression or death
PgR	Progesterone receptor
PK	Pharmacokinetics
pMMR	Mismatch repair proficient
PL	Package leaflet
PR	Partial response
PSR	Platinum-Sensitive Relapsed
PT	Preferred term

Abbreviation/ Special term	**Definition/Explanation**
Q	Quarter
QTc	Corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumours
RMP	Risk Management Plan
rPFS	Radiological progression-free survival
SAE	Serious adverse event
sBRCA	Somatic *BRCA*
sBRCAm	Somatic *BRCA*-mutated
SEER	Surveillance, Epidemiology, and End Results programme
SmPC	Summary of Product Characteristics
tds	Three times daily
TNBC	Triple-negative breast cancer
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
VTE	Venous thromboembolism
WHO	World Health Organisation

I: PART I: PRODUCT OVERVIEW

Table I-1 Product Overview

Active substance(s) (INN or common name)	Olaparib
Pharmacotherapeutic group(s) (ATC Code)	L01XK01
Marketing authorisation holder	AstraZeneca
Medicinal products to which this RMP refers	Olaparib
Invented name(s) in the European Economic Area (EEA)	LYNPARZA
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Polyadenosine 5' diphosphoribose polymerase (PARP) inhibitor
	Summary of mode of action: Oral PARP inhibitor (PARP-1, PARP-2, PARP-3), a targeted anticancer agent that exploits deficiencies in DNA repair mechanisms present in cancer cells
	Important information about its composition: Not applicable
Hyperlink to the Product Information	LYNPARZA, Summary of Product Characteristics
Indication(s) in the EEA	**Current** **Indication 1:** 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 or partial) to platinum-based chemotherapy. **Indication 2:** Monotherapy for the treatment of adult patients with germline *BRCA1/2*-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy. **Indication 3:** Monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) *BRCA1/2*-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial) following completion of first-line platinum-based chemotherapy. **Indication 4**: Monotherapy for the maintenance treatment of adult patients with germline breast cancer susceptibility gene (*gBRCAm*) mutated metastatic adenocarcinoma of the

Table I-1 Product Overview

	pancreas whose disease has not progressed on first line platinum-based chemotherapy. **Indication 5** Monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and *BRCA* 1/2 mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent. **Indication 6:** Combination with bevacizumab 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 *BRCA* 1/2 mutation and/or genomic instability. **Indication 7:** Monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline *BRCA1/2* mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy. **Indication 8:** Combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated. **Proposed** **Indication 9:** Combination with durvalumab for the maintenance treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair proficient (pMMR) whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel.
Dosage in the EEA	**Current (tablets):** Lynparza is available as 100 mg and 150 mg tablets. 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 reduction.
Pharmaceutical form(s) and strengths	**Current (film-coated tablets):** 100 mg: yellow to dark yellow, oval, bi convex, film-coated tablet debossed with 'OP100'on one side and plain on the other side. 150 mg: Green to green/grey, oval, bi-convex film-coated tablet debossed with 'OP150'on one side and plain on the other side.
Is the product subject to additional monitoring in the EU?	No

II: PART II: SAFETY SPECIFICATION

II: 1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

II: 1.1 Ovarian Cancer

Incidence

Globally, there were around 295,414 new cases of ovarian cancer in 2018, with 67,771 occurring in Europe, 24,469 in the US, and 10,672 in Japan (Globocan 2018a). A higher incidence is seen in Europe, and particularly Northern, Central and Eastern Europe, where rates are over 9 per 100,000 woman years, Age Standardised to the World population. In Europe in 2018, ovarian cancer was estimated to be the fifth most common cause of cancer death (44,576 deaths) and the sixth most common newly diagnosed cancer (67,771 new cases) in females in Europe (Globocan 2018a).

Prevalence

The IARC estimated 762,663 five-year prevalent cases at the year 2018 in the world, including around 188,069 cases in Europe, 80,446 in Northern America, and 31,658 in Japan (Globocan 2018a). In the US, the complete prevalence of ovarian cancer cases is estimated at approximately 190,000 cases (Howlader et al 2014).

Prevalence of s*BRCAm*

From literature data and AstraZeneca unpublished data on file, the proportion of *BRCAm* patients carrying an *sBRCA* mutation is between 6.4% and 10% (Cancer Genome Atlas Research Network 2011, Pennington et al 2014, Norquist et al 2016, Callens et al 2017, Mirza et al 2016, Coleman et al 2017, Dougherty et al 2017).

Germline mutations are prevalent in around 5 to 25%, with *gBRCA1* mutations in 4 to 18% and *gBRCA2* mutations in 4 to 7% (Eccles et al 2016). A recent study conducted in ovarian cancer patients in Germany (n=523) found a *gBRCA1* prevalence of 15.5% and a *gBRCA2* prevalence of 5.5% (Harter et al 2017). Other global variations are likely, due to ethnic associations with carrier mutations.

Demographics of the Population in the Approved Indication and Risk Factors for the Disease

Ovarian cancer occurs only in females, and the incidence is notably higher in Europe, the US and worldwide in patients aged 65 and older (Lowe et al 2013), though *gBRCA* mutated ovarian cancer is associated with an earlier age of onset (around 53 years and 58 years with *BRCA1* and *BRCA2* mutation respectively (Hirsch-Yechezkel et al 2003). Germline *BRCA* mutation is also associated with certain ethnic lineages, such as Ashkenazi Jews. Large

variations in incidence of ovarian cancer between different regions are partly associated with lifestyle (particularly null parity or delayed childbearing), age, ethnicity, socio-economic status and access to high-quality care. Ovarian cancers also tend to be more prevalent in developed societies where expected life spans are longer.

Several risk factors have been identified, including family history, low parity, infertility, early age of menarche, and late age of menopause (Coleman et al 2015). Other risk factors are oestrogen hormone replacement therapy and tobacco smoking, and (limited evidence) perineal use of talc-based body powder and exposure to X-radiation and gamma (γ)-radiation (for medical purposes) (Weiderpass and Labreche 2012).

The Main Existing Treatment Options

Newly Diagnosed Ovarian Cancer

The current standard of care for newly diagnosed advanced ovarian cancer, including those patients with *BRCAm* high-risk ovarian cancer, consists of radical debulking surgery followed by post-operative platinum-based first line chemotherapy (NCCN Ovarian 2018). For patients for whom upfront surgery is unlikely to achieve a complete resection, treatment consists of neoadjuvant chemotherapy followed by interval debulking surgery and adjuvant chemotherapy (NCCN Ovarian 2018). Platinum containing chemotherapy is considered the treatment of choice for patients with newly diagnosed advanced ovarian cancer, including those patients with *BRCAm* high risk advanced ovarian cancer.

Olaparib tablet formulation in combination with bevacizumab is now available in the US, the EU and Brazil, as well as in other markets, 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.

Relapsed Ovarian Cancer

Platinum-based chemotherapy remains the treatment of choice for PSR ovarian cancer patients. Despite responding to treatment, most patients subsequently relapse and experience disease progression within a year of starting chemotherapy and require further chemotherapy with attendant morbidity (Colombo et al 2010). Subsequent to disease progression, treatment for all patients with PSR ovarian cancer is another platinum-based chemotherapy regimen, eg, a doublet combining carboplatin with paclitaxel, gemcitabine, or pegylated liposomal doxorubicin (Colombo et al 2010). Each of the successive lines of therapy is limited in duration even in responding patients due to the cumulative toxicity burden from cytotoxic chemotherapy. In between lines of treatment, patients wait and are watched for the next progression.

In addition, in the EU, treatment options include the VEGF inhibitor bevacizumab (Avastin®), either in combination with carboplatin and gemcitabine, followed by bevacizumab alone. Trabectedin (Yondelis®), an antineoplastic agent, is approved in combination with pegylated liposomal doxorubicin for the treatment of patients with relapsed platinum-sensitive ovarian cancer. Finally, there are currently a number of PARP inhibitors (including olaparib, niraparib, and rucaparib) approved as anticancer agents for a range of indications in relapsed ovarian cancer.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

The 5-year relative survival of ovarian cancer patients in Europe is estimated to be 38% (Sung et al 2021). The age-adjusted mortality rate (according to the World standard population) for ovarian cancer is 5.1/100,000 in Europe, 4.1/100,000 in the US, and 3.3/100,000 in Japan (Globocan 2018a). Mortality rates reflect the age at diagnosis and the peak of mortality lies in older women aged between 75 to 84 years contributing 28.8% of mortality cases (Horner et al 2009). Most patients (>70%) present with advanced disease, in whom overall 5-year survival is around 29% (Siegel et al 2018). Breast cancer susceptibility gene mutated ovarian cancer presents characteristics that differ from wild type and between specific mutation type (*BRCA1* and *BRCA2*) (Hennessy et al 2010). Breast cancer susceptibility gene mutated ovarian cancer is more likely to have serous histology, and is often diagnosed at a later stage and at a younger age than ovarian cancer without *BRCA* mutation.

Important Co-morbidities

Important co-morbidities, based on existing literature and the Swedish Cancer and Co-morbidity database have been reported as anaemia, neutropenia, thrombocytopenia, bowel obstruction, renal failure, and secondary MDS/AML and other secondary cancers. Some comorbidities may be due to prior treatment.

An increased risk of primary breast, ovarian and prostate cancer in addition to secondary cancers has been reported among *gBRCA* mutation carriers (Bergfeldt et al 1995).

II: 1.2 Breast Cancer

Incidence

Female breast cancer (ICD-10 code: C50) surpassed lung cancer as the global leading cancer in 2020 with an estimated incidence of 2.3 million newly diagnosed cases, representing 11.7% of all cancer cases. In 2020, a total of 684,996 women died of breast cancer, representing 6.9% of all cancer deaths (Sung et al 2021, WHO Cancer today 2020). In the European Community in 2020, the number of cases of breast cancer in women and men was 355,457 and the number of deaths was 91,826 (ECIS 2020). Metastatic breast cancer remains an incurable disease with an estimated 5-year OS of 25.0% (ESMO 2019).

More breast cancer patients are diagnosed at an early stage (79.0% to 87.0% are diagnosed at Stage I or II), than a late stage (13.0% to 21.0% are diagnosed at Stage III or IV). Between 6.0% and 7.0% of people have metastases at diagnosis (Stage IV) (Cancer Research UK). Stage at diagnosis has been associated with a degree of deprivation, age, and ethnicity (Lyratzopoulos et al 2013, Public Health England 2020). The incidence data presented here represents the majority of the patient population, diagnosed at an early stage, and also represented in the OlympiA study.

Prevalence

At the end of 2020, there were 7.8 million women who had been diagnosed with breast cancer within the past 5 years, making it the world's most prevalent cancer (WHO Breast cancer 2021).

Tumour *BRCA* mutations (*tBRCAm*) can be of germline or somatic origin. Published analysis conducted at AstraZeneca, including tumours from patients coming from the US, Canada and Europe, indicate that 6.6% to 9.5% of breast cancers have loss of function *BRCA* mutations detectable in tumours, with around 3% to 5% of germline origin and at least 2% of somatic origin (Polak et al 2017, Sokol et al 2020). Moreover, studies examining the prevalence of *gBRCA* mutations in unselected European primary breast cancer patient populations report a range of 1.7% to 7.3% (Cortesi et al 2021, Høberg-Vetti et al 2016, Nilsson et al 2018, Winter et al 2016, van den Broek et al 2015); a single European study on patients diagnosed with primary breast cancer (Winter et al 2016) reports a *sBRCAm* prevalence of 3%. Mutation carriers are mostly younger and have a family history of breast and/or ovarian cancer.

Demographics of the Population in the Approved Indication and Risk Factors for the Disease

Breast cancer incidence is strongly associated with age, with age-specific incidence rates increasing steadily from age 30 to 34 and more steeply from age 70 to 74 (NICE 2018).

Risk factors for breast cancer include modifiable factors such as weight, physical activity, hormone replacement therapy, nulliparity, breast feeding, ionizing radiation, and alcohol consumption; and non-modifiable factors such as age, sex, family history with or without high-risk germline mutation(s), early menarche, and dense breasts (Kluttig and Schmidt-Pokrzywniak 2009).

The Main Existing Treatment Options

The decision to treat patients with early breast cancer with neoadjuvant or adjuvant chemotherapy in addition to surgery/radiotherapy is driven by the consideration of clinical characteristics, tumour stage and pathology. Randomised clinical trials have found no

significant differences in long-term outcomes when systemic chemotherapy is given before or after surgery (Mauri et al 2005, Rastogi et al 2008).

For TNBC, neoadjuvant/adjuvant chemotherapy has been the main systemic treatment option for patients since hormone therapy and HER2 targeted drugs are not choices for these patients. Adjuvant endocrine therapy is recommended following neo/adjuvant chemotherapy for all ER- and/or PgR-positive HER2-negative patients (ESMO 2019, NCCN Guidelines 2021).

Standard neo/adjuvant chemotherapy for HER2-negative early disease is an anthracycline alkylator, and taxane-containing regimen. The ESMO Guidelines (ESMO 2019) recommend that a sequential anthracycline/taxane-based regimen be standard for the majority of patients. The NCCN and ESMO guidelines consider there is insufficient evidence for the routine use of platinum in neoadjuvant regiments for TNBC patients. Whilst platinum compounds are not routinely recommended, the addition of a platinum compound may be considered in high risk TNBC patients with deleterious *BRCA1/2* mutations (ESMO 2019) and in select patients where better local control is desirable (NCCN Guidelines 2021). In high risk TNBC patients not achieving pathological CR after standard neoadjuvant chemotherapy, the addition of adjuvant capecitabine post-operatively may be considered (ESMO 2019, NCCN Guidelines 2021).

Results from the OlympiA study have been incorporated into the NCCN guidelines as being recommended for high-risk breast cancer patients with HER2-negative disease and *gBRCA* mutation. The preferred regimen is olaparib 300 mg bd for 1 year (NCCN Guidelines 2021). In addition, the St Gallen guidelines recommend adjuvant olaparib for women with Stage II or III, HER2-negative cancers who meet the eligibility criteria for OlympiA. These recommendations are irrespective of ER status or prior platinum chemotherapy treatment. Genetic testing for a confirmed *gBRCA* mutation is recommended (Burstein et al 2021).

Pembrolizumab is also approved in the US and the EU for the treatment of patients with high-risk early stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery (Keytruda USPI 2021).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Breast cancer is the fifth leading cause of cancer mortality worldwide, with 685,000 deaths. Among women, breast cancer represents 1 in 4 cancer cases and 1 in 6 cancer deaths, ranking first for incidence in the vast majority of countries (WHO Breast cancer 2021). Breast cancer incidence in transitioned nations is higher, while relative mortality is greatest in transitioning nations (Grundmann et al 2020). Globally, the mortality rates of breast cancer are lower compared to incidence rates (approximately 17.7 per 100,000 compared to 58.5 per 100,000, crude rate) due to the more favourable survival of breast cancer in transitioned nations. The

EUROCARE-5 study reports the European mean age-standardised 5-year relative survival for breast cancer in women is 81.8% (De Angelis et al 2014). The WHO reported in 2020 that the breast cancer mortality in Europe was 141,765, and the crude rate 15.3 per 100,000 (WHO Cancer today 2020).

Nearly 30% of women with cancer confined to the breast and 75% of women with nodal involvement will ultimately relapse (Rosen et al 1989).

The known earlier onset of *BRCA1*m and *BRCA2*m related breast cancer, as opposed to sporadic breast cancer, is consistent with the observation that *BRCA* mutations are associated with an aggressive biology and adverse prognostic impact (Atchley et al 2008). This early onset of breast cancer associated with *gBRCA* was also evidenced by the OlympiA trial population where the median age of study participants at the time of randomisation following completion of neo/adjuvant treatment in OlympiA was 42 years (Tutt et al 2021). In the French CANTO registry, women who were *gBRCA1/2* carriers were diagnosed with primary breast cancer at an average age of 43.7 years (Bertaut et al 2021).

BRCA1/2 breast cancer characteristics include high histological grade, continuous pushing margins, TP-53 mutations, loss of RAD51 focus information, extreme genomic instability and sensitivity to DNA crosslinking agents, with *BRCA1* tumours additionally more frequently basal-like and ER-negative (Turner et al 2004). TNBC, which is more frequently associated with *BRCA1*m, generally has a poor prognosis despite high sensitivity to chemotherapy (Metzger-Filho et al 2012) with early recurrence between the first and third year after diagnosis, frequently in association with visceral and/or brain metastases and a shorter period between time of recurrence and death (Dent et al 2007). Within *BRCAm* tumours, the proportions with high-risk features are similar for each gene, regardless of the mutation being germline or somatic (Winter et al 2016).

Breast cancer patients with a *BRCA1* mutation frequently experience metastasis to lung and distant lymph nodes, and *BRCA2* mutation carriers most often to bone and liver; the data also indicate that at least one-half of patients with *BRCA1*-associated or *BRCA2*-associated metastatic breast cancer will develop CNS metastases. Involvement of CNS and other non-CNS distant sites (relative to locoregional recurrence or contralateral disease) as first recurrence events were associated with increased mortality risk (Song et al 2020).

Important Co-morbidities:

It is estimated that the 5 most prevalent co-morbidities among breast cancer survivors are: hypertension (32.8%), arthritis (32.8%), thyroid problem (22.4%) hypercholesterolemia (12.7%), and diabetes (12.0%). Co-morbid hypertension, arthritis, and diabetes were associated with poorer quality of life in multiple domains among breast cancer survivors (Fu et al 2015). In a study published in 2019, the most prevalent baseline comorbidity reported

was cardiovascular conditions (39.0%), followed by pain/pain-inflammation (34.8%) (Ng et al 2019).

II: 1.3 Pancreatic Cancer

Incidence

Pancreatic cancer was the thirteenth most frequent cancer worldwide with an estimated 458,918 new cases diagnosed in 2018 (Globocan 2018). Globally, age-standardised incidence rates (per 100,000 per year) were lowest in Africa (2.2) and highest in Europe (7.7) and North America (7.6) (Globocan 2018). In the US in 2019, pancreatic cancer is estimated to be the ninth most common newly diagnosed cancer (56,770 new cases) (American Cancer Society 2021, Siegel et al 2018). In Europe in 2018, pancreatic cancer was estimated to be the ninth most common newly diagnosed cancer (132,559 new cases) (Globocan 2018). Current trends show increasing incidence in the US and Europe, particularly for younger adults (Wu et al 2018, Rawla et al 2019). At least 50% of newly diagnosed pancreatic tumours are staged as metastatic (SEER Cancer Fact Sheet).

Prevalence

Due to the very poor prognosis of pancreatic cancer with nearly as many deaths as new cases annually, the disease prevalence is low (Bray et al 2018). The estimated 5-year prevalence of pancreatic cancer in 2018 was 282,574 worldwide, with 32,692 prevalent cases in the US and 79,268 cases in Europe (Globocan 2018).

Demographics of the Population in the Approved Indication and Risk Factors for the Disease

Pancreatic cancer incidence is higher for men than women and increases with age; the median age at diagnosis in the US is 70 years (Ferlay et al 2018a, SEER Cancer Fact Sheet). There is some evidence that patients carrying *BRCA* mutations are diagnosed at a younger age; however, results are not consistent (Bannon et al 2018, Holter et al 2015, Hu et al 2018, Toss et al 2019).

The strongest identified risk factors for pancreatic cancer are tobacco smoking, family history of pancreatic cancer, heavy alcohol consumption, and Helicobacter pylori infection (Maisonneuve et al 2015, Rawla et al 2019). Additional potential risk factors include obesity, diabetes, non-O blood type, exposure to chemicals, chronic pancreatitis, and genetic predisposition, including *BRCA* germline mutations (Iqbal et al 2012, Maisonneuve et al 2015, Rawla et al 2019). Breast cancer susceptibility gene mutated cancer is more common among patients with a personal history of cancer or family history of several cancers, including pancreatic, or those of Ashkenazi Jewish heritage (Bannon et al 2018, Chaffee et al 2018, Holter et al 2015).

The Main Existing Treatment Options

There are limited treatment options available for patients, surgery remains the only option for cure. The 2 preferred regimens for initial treatment of metastatic disease include the combination of 5-FU, irinotecan, leucovorin, and oxaliplatin (FOLFIRINOX) or gemcitabine in combination with nab paclitaxel (Ducreux et al 2015, NCCN 2019). Gemcitabine alone or in combination with erlotinib may also be used in the first line treatment setting (Sohal et al 2018).

Few second line regimens are available for the treatment of patients with pancreatic cancer (American Cancer Society 2019), and these agents offer modest benefit (Rahma et al 2013). In 2015 in the US and 2016 in the EU, liposomal irinotecan (Onivyde™) was approved in combination with 5-FU and leucovorin, as second line treatment after progression following gemcitabine-based therapy for patients with metastatic adenocarcinoma of the pancreas. 5-fluorouracil/leucovorin plus oxaliplatin may be considered as second line treatment under certain circumstances, for patients who received gemcitabine plus nab paclitaxel as first line treatment, have an ECOG performance status of 0 or 1 and a relatively favourable co morbidity profile (Ducreux et al 2015, Sohal et al 2018).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Pancreatic cancer is associated with a very poor prognosis. Worldwide in 2018, pancreatic cancer was estimated to be the seventh most common cause of cancer death (432,242 deaths) (Globocan 2018). Pancreatic cancer is the fourth most common cause of cancer-related death in Europe, accounting for 6.6% of all cancer deaths (Ferlay et al 2018a). In the US in 2019, pancreatic cancer is estimated to be the third most common cause of cancer death (45,750 deaths) (American Cancer Society 2019, Siegel et al 2019). The proportion of cases diagnosed with localised, regional, or distant disease in the US is 10%, 29%, and 52%, respectively (therefore 80% of patients are diagnosed at an unresectable stage), and the 5 year survival rate for patients diagnosed with metastatic disease is only 3% (SEER Cancer Fact Sheet, American Cancer Society 2019). In Europe, the overall 5-year survival is 6% to 10% and the median survival for patients with metastatic disease is 2.8 to 5.7 months (Bouvier et al 2017, Carrato et al 2015, Lepage et al 2015, Minicozzi et al 2018). Survival rates have not shown much improvement over the past several decades (Rawla et al 2019). There is some evidence that prognosis for *BRCA* mutation carriers is worse compared to those without mutations (Blair et al 2018, Ferrone et al 2009). The poor outcomes observed for pancreatic cancer are largely due to the late presentation of the disease as optimum screening tests have yet to be identified (McGuigan et al 2018).

Important Co-morbidities:

Data related to comorbidity prevalence among pancreatic cancer patients, including those with *BRCA* mutations, are scarce. Common important co-morbidities expected in many older adults with cancer include hypertension, ischemic heart disease, heart failure, chronic obstructive pulmonary disease, anaemia and diabetes (Williams et al 2016). Some comorbidities may be due to prior treatment.

II: 1.4 Prostate Cancer

Incidence

Prostate cancer is the second most common newly diagnosed cancer in men worldwide, ranking as the fifth leading cause of cancer death among males (Globocan 2020). In the US and Europe, prostate cancer is the leading male cancer diagnosis, ranking as the second and third most common cause of cancer death, respectively (American Cancer Society 2021, Siegel et al 2021, ECIS 2020). In 2020, in the EU-27 countries, there were 335,514 newly diagnosed prostate cancer cases (ECIS 2020). In 2021, it is estimated that there will be 248,530 newly diagnosed prostate cancer cases in the US (American Cancer Society 2021, Siegel et al 2021).

Prevalence

Improvements in screening, usually via prostate specific antigen testing and family history (Djulbegovic et al 2010), and decreases in mortality rates in many countries have led to an increase in the prevalence of prostate cancer worldwide (Bray et al 2018). The estimated five-year prevalence in 2018 was 3.7 million men worldwide, with a prevalence of 813,547 in North America and 1.5 million in Europe (Ferlay et al 2018b). Evidence on the prevalence of CRPC among men with prostate cancer has previously been estimated between 19% and 53% (Berruti et al 2007, Bianco et al 2003).

Demographics of the Population in the Approved Indication and Risk Factors for the Disease

Prostate cancer is generally a disease of older age, with most cases being diagnosed in men in their 60s and 70s (Pettersson et al 2018). The age-specific incidence has shifted in areas where screening has been commonly implemented, and men are more often being diagnosed in their 50s and younger (Lowe et al 2003). In particular, in the US, African-American men and Jamaican men of African descent are more likely to develop prostate cancer than Caucasian men, and they are also more likely to be in an advanced stage at the time of diagnosis, with more aggressive high-grade tumours. A modest increase in prostate cancer risk is also associated with increasing body mass index (MacInnis et al 2006) as well as smoking (Huncharek et al 2010).

Genetic risk factors for prostate cancer have previously been identified; *BRCA* mutations are the most well-known.

The Main Existing Treatment Options

Available therapy for patients with mCRPC in the US and EU includes docetaxel, enzalutamide, abiraterone, cabazitaxel, Radium-223, and olaparib. In the US, sipuleucel-T and rucaparib are also approved.

For patients who have not received prior treatment with docetaxel or an NHA, the preferred NCCN and ESMO regimens (NCCN Prostate Cancer Guidelines 2021, Parker et al 2020) for systemic treatment of M1 CRPC include abiraterone, docetaxel, and enzalutamide. Sipuleucel-T (Category 1; US only) is only recommended for specific patients. Abiraterone and enzalutamide remain preferred Category 1 NHAs after systemic treatment with docetaxel in the M1 CRPC disease state. A Category 1 designation signifies that, based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

New hormonal agents are potent, orally available treatment options with a favourable tolerability profile. Abiraterone and enzalutamide are authorised in the US and EU for the treatment of patients with mCRPC who have received prior chemotherapy containing docetaxel and also for use in the first-line metastatic (pre-chemotherapy) setting. Since their approval in the frontline setting, NHAs have increasingly replaced docetaxel globally as the preferred choice of first-line therapy for mCRPC (Flaig et al 2016, Parker et al 2020).

Olaparib in combination with abiraterone is approved as a first-line treatment for mCRPC; the PARP inhibitor niraparib (in combination with abiraterone) is approved for the treatment of mCRPC in the US and EU, and the PARP inhibitor talazoparib (in combination with enzalutamide) is approved in the US.

All approved therapy options for frontline treatment of mCRPC are also available for later treatments. In addition, cabazitaxel and the PARP inhibitors olaparib (homologous recombination repair gene mutation [HRRm] patients in the US, *BRCAm* patients in the EU) and rucaparib (*BRCAm* patients in the US) are also approved as subsequent therapies for mCRPC.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Prostate cancer is the fifth leading cause of cancer death among men worldwide with the burden expected to increase from 359,000 deaths in 2018 to 740,000 deaths by 2040. This is mostly attributed to the growth and aging of the population since almost 55% of all prostate cancer deaths occur after the age of 65 (Bray et al 2018). Mortality rates are highly variable worldwide, with the highest rates reported in Central America (10.7 per 100,000), and the

lowest rates in Asia (South-Central [3.3], Eastern [4.7] and South-Eastern [5.4]) and Northern Africa [5.8]) (Ferlay et al 2018b).

Metastatic castration-resistant prostate cancer is associated with a range of symptoms but is predominantly characterised by bone pain, fatigue, and urinary dysfunction (Gater et al 2011, Lindqvist et al 2008). Around 90% of patients with mCRPC have bone metastases (de Bono et al 2010, de Bono et al 2011, Scher et al 2012), which leads to significant morbidity, including pain and skeletal-related events such as spinal cord compression and pathological fractures, which require interventions such as bone surgery or radiation therapy (El-Amm et al 2013).

Prostate cancer is amenable to curative therapy if detected early; however, advanced stages are life-threatening. Surgical or medical castration is the mainstay of therapy for advanced prostate cancer. However, many diagnosed patients will eventually experience disease progression, and castration-resistant prostate cancer ensues. Once prostate cancer becomes castration resistant and progresses to a metastatic stage the disease is not curable (median survival ranges from 9 -13 months), and treatment must focus on extending life, delaying disease progression and improving quality of life (Kirby et al 2011). Additionally, mCRPC patients with a homologous recombination repair gene mutation (such as *BRCA2*) have been generally shown to have a poorer prognosis compared with an unselected population (Castro et al 2019).

Important Co-morbidities

Co-morbidities associated with prostate cancer are linked with race, stage, and age at diagnosis (Xiao et al 2013, Evans et al 2008). Analysis of data from a US population-based cancer registry showed that, out of 60,497 patients with prostate cancer identified, the most prevalent co-morbidities were hypertension (42.3%), genitourinary system disease (24.4%), endocrine, nutritional/metabolic and immunity disorders (19.29%), digestive system disease (15.23%), ischemic heart disease (13.86%), musculoskeletal and connective tissue disease (11.75%), and diabetes (10.46%) (Xiao et al 2013).

Venous thromboembolism (VTE) is an important co-morbidity occurring in 1% to 2% of patients with prostate cancer (Cronin-Fenton et al 2010, Van Hemelrijck et al 2010). The risk of VTE increases almost three-fold during the first year and doubles during the second through fifth years after diagnosis of prostate cancer, and is higher in older patients, those with metastases, those with high Gleason scores, and those who underwent surgery (Ording et al 2015). In men on ADT, the incidence of thromboembolic disease increases with the duration of therapy and the risk is highest for those who switched regimen, suggesting that both disease progression and ADT contribute to the propagation of risk of thromboembolic disease (O'Farrell et al 2016).

II: 1.5 Endometrial Cancer

Incidence

Endometrial cancer is the sixth most common cancer among women, with 417,367 new cases being recorded worldwide in 2020, and an age-standardised incidence rate of 8.7 per 100,000 women (Sung et al 2021). The highest age-standardised incidence rates of endometrial cancer have been recorded in Europe, North America, Australia/New Zealand, and Polynesia/Micronesia, while the lowest age-standardised incidence rates of endometrial cancer have been recorded in most regions of Africa and South Central Asia (Sung et al 2021).

In Europe, the age-standardised incidence rate per 100,000 women for the year 2020 was 16.4 for Northern Europe, 14.2 for Southern Europe, 12.9 for Western Europe, and 20.2 for Eastern Europe (Sung et al 2021).

Prevalence

Endometrial cancer is the most prevalent gynaecologic cancer in high income countries (Ferlay et al 2015). In 2020, the 5-year prevalence rate for endometrial cancer in Europe was 124.74 per 100,000 women (International Agency for Research on Cancer 2021). In 2023, endometrial cancer was the fourth most prevalent cancer among women in the US (7% of cancer cases) (Siegel et al 2023).

Demographics of the Population in the Proposed Indication and Risk Factors for the Disease

Incidence of endometrial cancer increases with age. Across Europe, the incidence of endometrial cancer is at least 10 times greater among post-menopausal women compared to pre-menopausal women (Bray et al 2005).

Racial differences in endometrial cancer diagnosis have also been observed. For example, a large, prospective, cohort study conducted in the US demonstrated that the risk of endometrial cancer in women of White ethnicity far exceeded that of African Americans, Native Hawaiians, Japanese Americans, and Latinas; however, African Americans had the highest risk of developing advanced cancer, and African Americans and Latinas had the highest risk of developing tumours with aggressive histology (Setiawan et al 2007). Furthermore, a retrospective cohort study of women living in the UK found that women of South Asian ethnicity living were diagnosed at a significantly younger age (mean age: 60.3 years) than women of White ethnicity (mean age: 66.9 years) (Mohammed et al 2021).

Results from meta-analyses have found highly suggestive evidence that body mass index (per 5 kg/m^2), height (per 10 cm), waist circumference (per 10 cm), weight gain (per 5 kg), type 1 and type 2 diabetes mellitus, sedentary behaviour, hypertension, and nulliparity are associated with increased risk of endometrial cancer (Raglan et al 2019).

Additionally, there is suggestive evidence that coffee intake (per one cup/day), physical activity, age at menarche (per 2-year delay), age at last birth (per 5-year increment), metformin use, oral contraceptive use, and smoking are associated with decreased risk of endometrial cancer (Raglan et al 2019).

The Main Existing Treatment Options

The current standard of care for the first-line treatment for patients with advanced or recurrent endometrial cancer comprises platinum-based chemotherapy, with the combination of carboplatin and paclitaxel the preferred regimen (NCCN 2023, Oaknin et al 2022).

For patients who progress following prior platinum-based chemotherapy, pembrolizumab (as monotherapy or in combination with lenvatinib) and dostarlimab (as monotherapy) are approved and recommended in NCCN and ESMO guidelines as second-line treatment for patients who have progressed following prior treatment and who have no satisfactory alternative treatment options, with the choice of treatment guided by a patient's deficient mismatch repair or proficient mismatch repair status (NCCN 2023, Oaknin et al 2022).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Globally, the age-standardised mortality rate for cancer of the corpus uteri is 1.8 per 100,000, with the highest rates in Eastern Europe (3.7 per 100,000), Micronesia/Polynesia (3.5 per 100,000), and Northern America (3.0 per 100,000) (Sung et al 2021). A total of 97,370 deaths worldwide were recorded in 2020 (Sung et al 2021).

Endometrial cancer often presents as post-menopausal bleeding with a median age at diagnosis of 61 years (Crosbie et al 2022). The majority of patients are diagnosed at an early stage (Stage I or II) and these patients have a better prognosis with 5-year survival rates ranging from 74% to 91% (Creasman et al 2006). For patients diagnosed at a later stage or with advanced endometrial cancer the 5-year survival rates range from 50% to 66% for Stage III and 20% to 26% for Stage IV disease (Creasman et al 2006). The poor survival rate for advanced endometrial cancer is due, in part, to the limited treatment options available after first-line chemotherapy (Halla 2022).

Important Co-morbidities

In a retrospective study of 594 endometrial cancer or endometrial lesions cases in Romania, the most common co-morbidities were hypertension (62.28%), obesity (35.01%), and diabetes (22.89%) (Furau et al 2021). Endometrial cancer has also been associated with co-morbid hypertension in meta-analyses (Connaughton and Dabagh 2022) and database studies (Nicholas et al 2014), and compared to patients without endometrial cancer, patients with a diagnosis of endometrial cancer had a higher prevalence of cardiovascular disease at cancer

index date and an increased risk for developing cardiovascular disease including ischemic heart diseases, pulmonary heart disease, and diseases of the veins and lymphatics after endometrial cancer diagnosis (Anderson et al 2022).

Additionally, evidence suggests that metabolic syndrome may be a co-morbidity in endometrial cancer. In a systematic literature review, the prevalence of metabolic syndrome in endometrial cancer patients compared to individuals without endometrial cancer varied based on metabolic syndrome definition, ranging from 6% versus 2% (International Diabetes Federation definition) to 62% versus 38% (Harmonized metabolic syndrome guidelines) (Adambekov et al 2019).

II: 2 MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION

II: 2.1 Summary of Key Safety Findings from Nonclinical Data

Toxicity

Key Issues Identified from Acute Repeat Dose Toxicity Studies

The principal target organ for toxicity following repeat dosing for up to 6 months was the bone marrow, with associated changes in peripheral haematology parameters in both rats and dogs. All haematological changes seen in rats and dogs in the 1-month studies showed full or partial reversibility following a 28-day recovery period. Steady-state exposures at the highest dose levels used in the repeat-dose rat and dog toxicity studies were notably lower than those achieved in humans at the recommended clinical dose.

Studies using human bone marrow cells demonstrated that direct exposure to olaparib can result in toxicity to bone marrow cells in ex vivo assays.

Subsequent postmarketing experience/clinical practice has provided sufficient rationale to exclude this finding as a safety concern for olaparib.

Reproductive and Developmental Toxicity

In female rats, although conception rates were unaffected by pre- and peri-conception dosing, embryofoetal survival was decreased. In embryofoetal development studies in rats, olaparib caused reductions in early embryofoetal survival and foetal weights at exposures that did not induce significant maternal toxicity and were significantly lower than those achieved in humans at the efficacious clinical dose.

These reproductive and development toxicity data indicate that olaparib may cause foetal harm in women of child bearing potential. Effects on embryofoetal survival and abnormal development is included in this RMP as an important potential risk for olaparib.

Genotoxicity

Olaparib was not mutagenic in a bacterial mutation test (Ames), but was clastogenic in a chromosome aberration test *in vitro* and induced micronuclei in the bone marrow of rats following oral dosing.

Genotoxicity has the potential to lead to the development of new malignancies and adversely affect embryofoetal survival and development. MDS/AML, other new primary malignancies and effects on embryofoetal survival and abnormal development are included in this RMP as either important identified or potential risks for olaparib.

Carcinogenicity

Carcinogenicity studies have not been conducted with olaparib in accordance with International Council for Harmonisation Technical Requirements for Pharmaceuticals for Human Use (ICH) S9 guidelines.

II: 3 MODULE SIII: CLINICAL TRIAL EXPOSURE

As of 15 June 2023, an estimated 21,793 patients with ovarian, breast, pancreatic, prostate, gastric or a variety of other solid tumours had received treatment with olaparib in monotherapy and combination therapy, including AstraZeneca sponsored studies, AstraZeneca-Merck Alliance sponsored and investigator sponsored/collaborative studies.

Data in this section are presented from the monotherapy all doses pool, consisting of patients who have received olaparib monotherapy treatment at any dose in AstraZeneca-Merck Alliance sponsored monotherapy studies (N=4865) (see Table II-4 to Table II-8 below).

Data in Section II: 7.3 are presented for the monotherapy therapeutic dose pool, which consists of patients who have received olaparib capsules at the therapeutic dose of 400 mg bd and patients who were intended to receive the tablet formulation of olaparib at a dose of 300 mg bd as a monotherapy and who received olaparib treatment (N=4499). This pool is used to characterise the important identified risk of MDS/AML, and the important potential risk of NPMs. For studies included in the therapeutic dose pool see footnote 1 in this section under capsule and tablet studies.

Exposure data are also presented for olaparib in combination studies:

- DUO-E (maintenance phase): olaparib with durvalumab (see Table II-1, Table II-2, and Table II-3).
- Pooled data from PROpel and Study 8: olaparib with abiraterone (see Table II-9, Table II-10, and Table II-11).
- PAOLA-1: olaparib with bevacizumab (see Table II-12 and Table II-13).

MONOTHERAPY EXPOSURE

Studies Included in the Monotherapy All Doses Pool

Capsule Studies

All studies are completed.

- D0810C00019 (Study 19, pivotal study): Phase II placebo-controlled multicentre study in PSR ovarian cancer[1].
- D0810C00001 (Study 01): Phase I study in Japanese patients with advanced solid tumours[1].
- D0810C00002 (Study 02): Phase I pharmacokinetic (PK) study in advanced solid tumours[1].
- D0810C00007: Phase I PK study in breast cancer[1].
- D0810C00008: Phase II proof-of-concept study in *gBRCA* breast cancer[1].
- D0810C00009 (Study 09): Phase II proof-of-concept study in *gBRCA* ovarian cancer[1].

- D0810C00010 (Study 10): Phase I metabolism, excretion and PK study in advanced solid tumours.
- D0810C00012 (Study 12): Phase II dose-response study versus pegylated liposomal doxorubicin in *gBRCA* recurrent ovarian cancer[1].
- D0810C00020 (Study 20): Phase II study in *gBRCA* or high-grade serous/undifferentiated ovarian cancer, and *gBRCA* or TNBC[1].
- D0810C00024 (Study 24): Phase I relative bioavailability study in advanced solid tumours[1].
- D0810C00042: Phase II study in *gBRCAm* advanced tumours, including ovarian cancer[1].
- D081AC00001: Phase I study of food impact on PK in advanced solid tumours[1].
- D0910C00008: Phase II study in patients with colorectal cancer[1].
- D0816C00012 (ORZORA): Phase IV study in patients with PSR somatic or germline *BRCA* mutated ovarian cancer[1].

[1] These studies are included in the therapeutic dose pool.

Tablet Studies

- D0816C00014 (OReO): Phase IIIb study in epithelial ovarian cancer previously treated with a PARP inhibitor and responding to repeat platinum chemotherapy. Primary analysis DCO: 15 February 2021[1].
- D0816C00018 (LUCY): Phase IIIb study in patients with *gBRCA1/2* mutations in HER-2 negative metastatic breast cancer. Final DCO: 01 September 2021[1].
- D081CC00006 (OlympiA, pivotal study): Phase III study in patients with *gBRCA1/2* mutations in high risk HER2 negative early breast cancer. Primary analysis DCO: 27 March 2020. DCO2: 12 July 2021[1].
- D081DC00007 (PROfound, pivotal study): Phase III study in mCRPC patients with HRR gene mutations who have failed prior treatment with an NHA. Primary analysis DCO: 4 June 2019. OS DCO: 20 March 2021[1].
- D081FC00001 (POLO, pivotal study): Phase III study in *gBRCA* mutated metastatic pancreatic adenocarcinoma. Primary analysis DCO: 15 January 2019. Extended OS DCO: 21 July 2021[1].
- D0816C00010 (SOLO3, FDA Post-approval commitment): Phase III study in *gBRCA* mutated advanced platinum-sensitive relapsed ovarian cancer after at least 2 prior lines of chemotherapy. Final Overall Survival DCO: 16 April 2021[1].
- D0818C00001 (SOLO1, pivotal study): Phase III in newly diagnosed *BRCAm* ovarian cancer. Primary analysis DCO: Main cohort and China cohort 17 May 2018. OS DCO: 5 March 2020. 7 year descriptive analysis DCO: 07 March 2022[1].
- D0816C00002 (SOLO2, pivotal study): Phase III study in platinum sensitive serous ovarian cancer. Primary analysis DCO: Main cohort 19 September 2016; China cohort 16 January 2017. OS DCO: 3 February 2020[1].
- D0819C00003 (OlympiAD pivotal study): Phase III study in HER2-negative breast cancer patients with *gBRCA* 1 or 2 mutations[1].

- D0816C00020 (OPINION): Phase III study in non-germline *BRCA* mutated ovarian cancer[1].
- D0816L00003 (LIGHT): Phase II study in patients with different HRD tumour status, ovarian, fallopian tube, or primary peritoneal cancer after at least 2 prior lines of chemotherapy[1].
- D5336C00001 (VIOLETTE): Phase II study in patients with metastatic triple-negative breast cancer. Only the monotherapy arm included[1].
- D0810C00024 (Study 24): Phase I study of relative bioavailability in advanced solid tumours[1].
- D0816C00004 (Study 04): Phase I food interaction and QT study in advanced solid tumours[1].
- D0816C00005 (Study 05): Phase I hepatic impairment study in advanced solid tumours[1].
- D0816C00006 (Study 06): Phase I renal impairment study in advanced solid tumours[1].
- D0816C00007 (Study 07): Phase I CYP inhibitor and QT study in advanced solid tumours[1].
- D0816C00008 (Study 08): Phase I CYP induction study in advanced solid tumours[1].
- D081BC00001: Phase I Japan monotherapy study in advanced solid tumours[1].
- D081CC00001: Phase I drug-interaction study: olaparib and anti-hormonal agents[1].
- D081BC00002: Phase I China PK study in advanced solid tumours[1].

[1] These studies are included in the therapeutic dose pool.

COMBINATION THERAPY

- D9311C00001 (DUO-E, pivotal study): Phase III, olaparib plus durvalumab as maintenance treatment in patients with newly diagnosed advanced or recurrent endometrial cancer. Primary analysis DCO: 12 April 2023.
- D081SC00001 (PROpel, pivotal study): Phase III study, olaparib plus abiraterone as first-line treatment in patients with mCRPC. Interim analysis DCO: 30 July 2021. DCO3: 12 October 2022.
- D081DC00008 (Study 8): Phase II study, olaparib plus abiraterone in patients with mCRPC with prior docetaxel-containing chemotherapy.
- D0817C00003 (PAOLA-1, pivotal study): Phase III study, olaparib plus bevacizumab as first line maintenance treatment in patients with advanced ovarian cancer. Final analysis PFS2 and interim analysis OS DCO: 22 March 2020. OS DCO: 22 March 2022.

II: 3.1 Exposure for New Indication: Olaparib in Combination with Durvalumab

All patients were female and had endometrial cancer.

Table II-1 Duration of Olaparib Exposure in Combination with Durvalumab (Maintenance Phase)

Duration of exposure Total patient population	Number of patients	Patient years
>0	192	173.6
≥1 week (7 days)	192	173.6
≥1 month (30 days)	187	173.3
≥3 months (91 days)	170	170.2
≥6 months (183 days)	136	156.7
≥12 months (365 days)	76	110.4
≥18 months (548 days)	27	50.1
≥24 months (731 days)	6	13.4
TOTAL PERSON TIME		**173.6**

Table II-2 Olaparib Exposure in Combination with Durvalumab by Age Group (Maintenance Phase)

Age group (years)	Number of patients	Patient years
Total patient population	**192**	**173.6**
<35	3	2.9
35-49	10	9.3
50-64	96	92.3
65-74	68	60.5
75-84	14	7.9
≥85	1	0.6

Table II-3 Olaparib Exposure in Combination with Durvalumab by Ethnic or Racial Origin (Maintenance Phase)

Racial origin	Number of patients	Patient years
Total patient population	**192**	**173.6**
White	113	94.8
Asian	56	56.4
Black or African American	6	7.8
American Indian or Alaska Native	4	2.9
Native Hawaiian or other Pacific Islander	0	0
Other	10	8.7

Racial origin	Number of patients	Patient years
Not reported	3	2.9
Missing	0	0

II: 3.2 Monotherapy Exposure

Table II-4 Monotherapy Exposure by Tumour Type

Tumour type	Number of patients	Patient years
Ovarian cancer	2455	2838.6
Breast cancer	1775	1350.5
Pancreatic cancer	130	132.9
Prostate cancer	280	209.6
Other[a]	226	58.3
TOTAL	**4865**	**4589.4**

Note: this includes all patients, irrespective of *gBRCA* mutation status.

[a] 'Other' are data from studies where olaparib has been used to treat recurrent tumour types, other than ovarian, breast, pancreatic or prostate tumours, after disease progression.

Table II-5 Duration of Monotherapy Exposure

Duration of exposure (at least) Total patient population	Number of patients[a]	Patient years[a]
>0	4865	4589.4
≥1 week (7 days)	4749	4588.2
≥1 month (30 days)	4537	4577.0
≥3 months (91 days)	3766	4449.9
≥6 months (183 days)	2914	4130.0
≥12 months (365 days)	1617	3113.9
≥18 months (548 days)	787	2190.1
≥24 months (731 days)	565	1803.0
≥30 months (913 days)	316	1269.8
≥36 months (1096 days)	206	970.5
≥42 months (1278 days)	150	791.1
≥48 months (1461 days)	125	696.9
≥54 months (1644 days)	111	638.0
≥60 months (1826 days)	90	539.4
≥66 months (2009 days)	62	390.3
≥72 months (2192 days)	32	219.3

Table II-5 Duration of Monotherapy Exposure

Duration of exposure (at least) Total patient population	Number of patients[a]	Patient years[a]
≥78 months (2374 days)	21	150.6
TOTAL PERSON TIME		**4589.4**

[a] Rows are cumulative and patients are included if they have taken treatment up to and including the treatment day based on the calculation.

Table II-6 Monotherapy Exposure by Age Group and Sex

Age group (years)	Number of patients		Patient years	
	Male	Female	Male	Female
Total patient population	**499**	**4366**	**335.6**	**4253.9**
<35	6	327	2.0	270.7
35-49	42	1394	36.3	1309.9
50-64	191	1743	116.1	1782.0
65-74	175	725	123.4	717.4
75-84	79	170	54.8	168.2
≥85	6	7	3.0	5.8

Table II-7 Monotherapy Exposure by Dose and Formulation

Dose of exposure	Number of patients	Patient years
CAPSULE	**1183**	**948.5**
<100 mg bd capsule[a]	48	5.8
100 mg bd capsule	81	24.7
200 mg bd capsule	106	49.6
400 mg bd capsule	943	867.6
600 mg bd capsule	5	0.9
TABLET	**3682**	**3640.9**
150 mg bd tablet	2	0.5
200 mg bd tablet	40	25.4
250 mg bd tablet	21	18.8
250 mg tds tablet (2 weeks on, 1 off)	15	9.0
300 mg bd tablet[b]	3552	3561.8
300 mg od tablet	1	0
350 mg bd tablet	6	2.5
400 mg bd tablet	23	9.1

Table II-7 Monotherapy Exposure by Dose and Formulation

Dose of exposure	Number of patients	Patient years
400 mg bd tablet (1 week on, 1 off)	16	10.4
450 mg bd tablet	6	3.3

[a] <100 mg bd includes the following doses 10 mg od, 10 mg bd, 20 mg od, 30 mg bd, 40 mg od, 50 mg od, 60 mg bd, 80 mg od and 100 mg od.

[b] Includes 16 patients who received the equivalent daily dose of 200 mg tds.

Bd = Twice daily; od = Once daily; tds = Three times daily.

Table II-8 Monotherapy Exposure by Ethnic or Racial Origin

Racial origin	Number of patients	Patient years
Total patient population	**4865**	**4589.4**
White	3915	3697.4
Asian	716	710.7
Black or African American	79	55.3
American Indian or Alaska Native	14	15.1
Native Hawaiian or other Pacific Islander	2	3.1
Other	46	38.3
Missing	93	69.6

II: 3.3 Exposure for Combination Therapy

II: 3.3.1 Pooled exposure for Olaparib in Combination with Abiraterone

All patients were male and had prostate cancer.

Table II-9 Duration of Olaparib Exposure in Combination with Abiraterone

Duration of exposure Total patient population	Number of patients on active treatment	Patient years
>0	469	737.5
≥1 week (7 days)	469	737.5
≥1 month (30 days)	465	737.3
≥3 months (91 days)	422	729.6
≥6 months (183 days)	360	705.9
≥12 months (365 days)	275	641.6
≥18 months (548 days)	218	571.6
≥24 months (731 days)	170	487.9
≥30 months (913 days)	135	409.4
≥36 months (1096 days)	64	211.2
≥42 months (1278 days)	13	47.7
TOTAL PERSON TIME		**737.5**

Table II-10 Olaparib Exposure in Combination with Abiraterone by Age Group

Age group (years)	Number of patients	Patient years
Total patient population	**469**	**737.5**
<35	0	0.0
35-49	8	9.8
50-64	139	258.8
65-74	208	330.9
75-84	106	131.7
≥85	8	6.2

Table II-11 Olaparib Exposure in Combination with Abiraterone by Ethnic or Racial Origin

Racial origin	Number of patients	Patient years
Total patient population	**469**	**737.5**
White	348	520.9
Asian	67	129.5
Black or African American	15	26.0
Native Hawaiian or other Pacific Islander	2	3.2
American Indian or Alaska Native	1	0.2

Racial origin	Number of patients	Patient years
Other	14	22.5
Missing	22	35.2

II: 3.3.2 Exposure for Olaparib in Combination with Bevacizumab

All patients were female and had ovarian cancer.

Ethnic or racial origin was not collected.

Table II-12 Duration of Olaparib Exposure in Combination with Bevacizumab

Duration of exposure (at least) Total patient population	Number of patients on active treatment	Patient years
>0	535	689.1
≥1 week (7 days)	526	689.0
≥1 month (30 days)	506	688.2
≥3 months (91 days)	468	681.9
≥6 months (183 days)	415	661.6
≥12 months (365 days)	331	601.2
≥18 months (548 days)	260	509.7
≥24 months (731 days)	133	271.7
≥30 months (913 days)	2	5.8
TOTAL PERSON TIME		**689.1**

Note: this includes all patients, irrespective of *gBRCA* mutation status.
Exposure data in the olaparib + bevacizumab combination includes patients randomised to receive olaparib for up to 2 years. During this time, patients continued to receive bevacizumab (in combination with olaparib) for up to 15 months in total.

Table II-13 Olaparib Exposure in Combination with Bevacizumab by Age Group and Sex

Age group (years)	Number of patients	Patient years
Total patient population	**535**	**689.1**
<35	2	3.3
35-49	64	90.8
50-64	265	345.7
65-74	172	213.5
75-84	31	33.8
≥85	1	2.0

II: 4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

II: 4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table II-14 Important Exclusion Criteria in the Pivotal Clinical Studies

Exclusion criterion	Reason for exclusion	Missing information	Rationale for NOT being missing information
Patients receiving strong inhibitors and inducers of CYP3A4	CYP3A4/5 have been shown to be the major isozymes responsible for the metabolism of olaparib in vitro. Strong inhibitors of cytochrome CYP3A4 have the potential to increase olaparib exposure and hence toxicity due to interaction. Strong inducers of cytochrome CYP3A4 have the potential to decrease olaparib exposure and hence to decrease efficacy of olaparib.	No	Data from studies D0816C00007 and D0816C00008 have provided evidence of altered olaparib exposure in patients concomitantly treated with strong inhibitors or inducers of CYP3A4. The possible outcome of this drug-drug interaction is increased toxicity or reduced efficacy, respectively. Section 4.4 of the SmPC includes wording to reduce the dose of olaparib if a strong or moderate CYP3A inhibitor must be co-administered, as well as a warning that Lynparza co-administration with strong or moderate CYP3A inducers may result in a substantial reduction in the efficacy of Lynparza. Considering the available data and the warnings and precautions provided in the SmPC, this utilisation is not considered missing information.

Table II-14 Important Exclusion Criteria in the Pivotal Clinical Studies

Exclusion criterion	Reason for exclusion	Missing information	Rationale for NOT being missing information
Resting electrocardiogram with QTc >470 msec on 2 or more time points within a 24 hour period or family history of, or congenital, long QT syndrome. In D081DC00007 (PROfound), patients with a resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator.	To ensure interpretation of safety and efficacy findings were not confounded by the presence of pre-existing QTc prolongation.	No	Data from studies D0816C00004 and D0816C00007 showed that no clinically relevant effect on the QTc interval was observed after single (300 mg and 100 mg, respectively) or multiple (300 mg) oral dosing of olaparib tablet. Therefore, a different safety profile to that characterised for the general target population is not anticipated in this population.
Patients with abnormal organ and bone marrow function	Criteria are based on standard exclusions for oncology clinical studies to allow adequate assessment of the safety profile of olaparib without potentially confounding haematological abnormalities at baseline. Haemoglobin <9.0 g/dL (<10 g/dL later studies), Absolute neutrophil count $<1.5 \times 10^9$/L, Platelet count $<100 \times 10^9$/L	No	Administration to this population is not expected due to wording on haematological toxicity in Section 4.4 of the SmPC. Considering these warnings and precautions, usage in these patients is not considered to be relevant for inclusion as missing information.
Patients with MDS/AML	Excluded in clinical studies of olaparib due to irreversible abnormality of bone marrow and inability to fulfil haematological criteria for starting olaparib treatment.	No	Administration to this population is not expected due to wording on MDS/AML in Section 4.4 of the SmPC. Considering these warnings and precautions, usage in these patients is not considered to be relevant for inclusion as missing information.

Table II-14 Important Exclusion Criteria in the Pivotal Clinical Studies

Exclusion criterion	Reason for exclusion	Missing information	Rationale for NOT being missing information
Hepatic impairment	Patients with serum bilirubin >1.5 times ULN and aspartate aminotransferase/alanine aminotransferase >2.5 times ULN (or >5 times ULN if patient had liver metastases) were excluded as no safety or PK data were available in hepatically impaired patients.	No	Data from study D0816C00005 provides evidence that Lynparza can be administered to patients with mild or moderate hepatic impairment with no dose adjustments. The study of patients with severe hepatic impairment is neither feasible nor warranted. Consequently use in this patient population is not classified as an area of missing information.
Renal impairment	Patients with serum creatinine >1.5 times ULN were excluded, as no safety or PK data were available in renally impaired patients.	No	Data from study D0816C00006 provides evidence that Lynparza can be administered to patients with mild renal impairment (creatinine clearance 51 to 80 ml/min), with no dose adjustments. The posology section of the SmPC states that the dose of Lynparza for patients with moderate renal impairment (creatinine clearance 31 to 50 ml/min) should be reduced. The study of patients with severe renal impairment and end stage renal disease is neither feasible nor warranted. Consequently use in this patient population is not classified as an area of missing information.
Pregnant women	There are no data for use of olaparib in pregnant women. Studies in animals have shown reproductive toxicity.	No	Use in this population is not expected as the SmPC states that Lynparza should not be used during pregnancy due to the potential for embryofoetal toxicity identified in nonclinical studies; embryofoetal survival and development is an important potential risk. Considering these factors, use in this population is not classified as an area of missing information.
Breast feeding women	There are no animal studies on the excretion of olaparib in breast milk and is unknown whether olaparib/or its metabolites are excreted in human milk.	No	Breast feeding during olaparib treatment, and for 1 month after receiving the last dose, is contraindicated, therefore this population is not relevant for the proposed indication.

Table II-14 Important Exclusion Criteria in the Pivotal Clinical Studies

Exclusion criterion	Reason for exclusion	Missing information	Rationale for NOT being missing information
Children/ adolescents	The indications under development involve cancers found in the adult population.	No	Use in these populations is not indicated, therefore this population is not relevant for the proposed indication.
Patients with a known hypersensitivity to olaparib or any of the excipients of the product.	These patients should not be treated with olaparib.	No	Hypersensitivity to Lynparza is contraindicated, therefore this population is not relevant for inclusion as missing information.
Patients with known active hepatic disease (ie, Hepatitis B or C)	Safety related: to ensure patients are able to tolerate study treatment without it impacting on existing hepatic disease.	No	There is no reason to suspect a different safety profile in these patients compared to the general target population, provided patients with active hepatic disease have adequate haematological parameters and absence of hepatic impairment and are not taking concomitant medication that would preclude Lynparza use. Therefore this population is not considered to be an area of missing information.
Immuno-compromised patients eg, patients who are known to be serologically positive for human immunodeficiency virus	To ensure interpretation of safety findings were not confounded by the presence of symptoms associated with these conditions and to minimise early withdrawal of patients who would not have been eligible to continue in the study in the event that they required active treatment with anti−retroviral agents, many of which are known to be strong CYP3A inhibitors and therefore were not to be used in the olaparib programme.	No	There is no reason to suspect a different safety profile in these patients compared to the general target population, provided that these patients have normal haematological parameters and are not taking concomitant medication that would preclude Lynparza use. Therefore this population is not considered to be an area of missing information.
Previous treatment with other PARP inhibitors	To eliminate the unknown impact of potential resistance mechanisms from prior use of other similar agents on the evaluation of efficacy and safety of olaparib.	No	A different safety profile from that established in the target population is not anticipated in this population, therefore this is not classified as an area of missing information.

Table II-14 Important Exclusion Criteria in the Pivotal Clinical Studies

Exclusion criterion	Reason for exclusion	Missing information	Rationale for NOT being missing information
Patients receiving other systemic chemotherapy/ radiotherapy within a specified period prior to study treatment or persistent toxicities ≥CTCAE Grade 2 caused by previous cancer therapy	To minimise the impact of previous chemotherapy/ radiotherapy toxicities on the evaluation of efficacy and safety.	No	There is no reason to suspect a different safety profile in these patients compared to the general target population, provided that patients have adequate haematological parameters and are not taking concomitant medication that would preclude Lynparza use. Therefore this population is not considered to be an area of missing information.
Patients with uncontrolled seizures and symptomatic uncontrolled brain metastases	To ensure interpretation of safety findings was not confounded by patients with symptomatic uncontrolled brain metastases or seizures.	No	There is no reason to suspect a different safety profile in these patients compared to the general target population, provided that patients have adequate haematological parameters and are not taking concomitant medication that would preclude Lynparza use. Therefore this population is not considered to be an area of missing information.
Patients with ECOG performance status >2	To ensure that patients were well enough to comply with study procedures and to allow adequate assessment of the efficacy and safety profile of olaparib.	No	There is no clinical reason why patients with ECOG performance status >2 should be at any higher risk from Lynparza ADRs, compared to the target population, therefore this is not considered to be an area of missing information.

II: 4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

II: 4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table II-15 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure	
	Number of patients	Patient years
Pregnant women	Not included in the clinical development programme	
Breast feeding women		
Patient with relevant comorbidities:		
• Patients with hepatic impairment	Patients enrolled in olaparib studies had either normal hepatic function or mild hepatic impairment at study entry (total bilirubin ≤1.5 x ULN and aspartate aminotransferase/alanine aminotransferase ≤2.5 x ULN [≤5x ULN if liver metastases were present]). Patients with moderate or severe hepatic impairment were not included in the clinical development programme.	
• Patients with renal impairment in monotherapy pool[a]		
° Severe	6	6.7
° End stage renal disease	11	9.4
• Patients with renal impairment in maintenance phase olaparib + durvalumab[a]		
° Severe	0	0.0
° End stage renal disease	0	0.0
• Patients with renal impairment in combination with bevacizumab[a]		
° Severe	0	0
° End stage renal disease	0	0
• Patients with renal impairment in olaparib + abiraterone pool		
° Severe	0	0.0
° End stage renal disease	0	0.0
• Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme	
Patients with relevant different ethnic origin		
• In monotherapy pool		
° Black or African American	79	55.3
° Asian	716	710.7
° Other	46	38.3

Table II-15 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure	
	Number of patients	Patient years
• In maintenance phase olaparib + durvalumab		
° Black or African American	6	7.8
° Asian	56	56.4
° Other	10	8.7
• In olaparib + abiraterone pool		
° Black or African American	15	26.0
° Asian	67	129.5
° Other	14	22.5
Subpopulations carrying relevant genetic polymorphisms		
• In monotherapy pool		
° *BRCA* mutated[b]	3340	3644.3
° HRR gene mutated without *BRCA* mutation[b]	205	154.4
° HRD positive without *BRCA* mutation[b]	68	39.2
• In maintenance phase olaparib + durvalumab		
° *BRCA* mutated[b]	12	13.5
° HRR gene mutated without *BRCA* mutation[b]	22	23.7
° pMMR	151	131.1
° dMMR	41	42.5
• In combination with bevacizumab		
° *BRCA* mutated[b]	158	242.9
° HRR gene mutated without *BRCA* mutation[b]	34	36.8
° HRD positive without *BRCA* mutation[b]	97	137.1
• In olaparib + abiraterone pool		
° *BRCA* mutated[b]	49	98.5
° HRR gene mutated without *BRCA* mutation[b]	73	110.6

[a] Renal impairment was defined using CHMP criteria (EMA/83874/2014): Normal renal elimination capacity GFR ≥90 mL/min; mildly decreased renal elimination capacity GFR 60-89 mL/min; moderately decreased renal elimination capacity GFR 30-59 mL/min; severely decreased renal elimination capacity GFR 15-29 mL/min; end stage renal disease GFR <15 mL/min or requiring dialysis treatment.

[b] *BRCA* patient numbers are not absolute as not all patients were tested.

BRCA = Breast cancer susceptibility gene; CHMP = Committee for Medicinal Products for Human Use; dMMR = deficient mismatch repair; GFR = Glomerular filtration rate; HRD = Homologous recombination deficient; HRR = Homologous recombination repair; pMMR = proficient mismatch repair.

II: 5 MODULE SV: POST-AUTHORISATION EXPERIENCE

II: 5.1.1 Method Used to Calculate Exposure

The post-marketing patient exposure data presented is estimated based on olaparib's monthly actual ex-factory sales volume from each local marketing company. These data represent all olaparib formulations delivered to various distribution channels (for example wholesalers, pharmacies etc) worldwide.

The sales volume is provided as the number of individual capsules/tablets sold as of 31 May 2023. For olaparib capsules, the estimated post-marketing patient exposure data for the reporting period is an approximation based on the assumption that each patient took 16 capsules of olaparib a day. Therefore, a patient-year worth of exposure is calculated by multiplying 16 capsules per day by 365 days (5840 capsules per patient-year).

For olaparib tablets, the estimated post-marketing patient exposure data for the reporting period is an approximation based on the assumption that each patient took 4 tablets of olaparib a day. Therefore, a patient-year worth of exposure is calculated by multiplying 4 tablets per day by 365 days (1460 tablets per patient-year).

The current methodology does not distinguish between sales that are related to initial prescriptions versus those related to repeat prescriptions. Therefore, it is not possible to estimate the number of patients exposed to olaparib. More detailed patient-level data (eg, gender, ethnicity, age category, off-label use, specific populations etc) are not available.

II: 5.1.2 Exposure

The cumulative global post-marketing patient exposure for olaparib capsules and olaparib tablets since launch (24 December 2014) through to 31 May 2023 has been estimated to be approximately 18,485 patient years for capsules and 149,071 patient-years for tablets. As of December 2021, olaparib capsules are no longer manufactured and the formulation is in the process of being removed from all global licences.

The cumulative regional exposure data are presented in Table II-16.

Table II-16 Cumulative Exposure by Region

Formulation	Europe	International	North America	Japan	Total
Capsules	68,531,105	24,907,969	14,516,096	0	107,955,170
Tablets	70,629,731	72,420,372	50,475,717	24,118,304	217,644,124

II: 6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Not applicable for olaparib.

II: 7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II: 7.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

II: 7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

II: 7.3 Details of Important Identified Risks, Important Potential Risks and Missing Information

Data presented for MDS/AML and NPMs are based on the monotherapy therapeutic dose pool; this consists of patients who have received olaparib capsules at the therapeutic dose of 400 mg bd and patients who were intended to receive the tablet formulation of olaparib at a dose of 300 mg bd as a monotherapy and who received olaparib treatment (N=4499). Data are presented for events that occurred up to the final DCO for studies within the pool.

In the majority of studies MDS/AML and the development of NPMs was actively solicited beyond the 30 day follow-up period, regardless of causality assessment; however, in the POLO study, these events were not actively solicited after the 30-day follow-up period and were not captured in the POLO study database although, where reported, they were captured in the AstraZeneca Patient Safety database.

II: 7.3.1 Presentation of Important Identified Risks

Myelodysplastic Syndrome/Acute Myeloid Leukaemia

Potential Mechanisms

The pathogenesis of MDS and AML is not completely understood, but like other cancers involves the stepwise acquisition of oncogenic driver mutations. MDS and AML are clonal processes that are thought to develop from a single transformed hematopoietic progenitor cell (Walter et al 2012, Will et al 2012, Woll et al 2014). In MDS, studies suggest that the cell of origin has acquired multiple mutations resulting in dysplasia and ineffective haematopoiesis, therefore, the cytopenias and myelosuppression are an effect and consequence of the underlying disease (MDS), rather than a cause of the disease (Pang et al 2013). Olaparib is not mutagenic in the Ames test. Olaparib does demonstrate clastogenicity in vitro in a Chinese hamster ovary (CHO) mammalian cell assay and *in vivo* micronuclei in the bone marrow of rats, but the positive result in these studies could be expected due to the non-repair of replication errors occurring at a natural rate during cell division. Treatment with PARP inhibitors, which leads to the accumulation of DNA damage in some cells and apoptosis, could potentially contribute to the development of new primary malignancies, including MDS/AML, by creating genomic instability in the absence of apoptosis (see also New primary malignancies – Potential mechanisms section).

MDS/AML usually occurs years after cytotoxic chemotherapy and/or radiotherapy which, beside the direct induction of DNA damage, raises the role of genetic predisposition and also a stochastic occurrence of a second cancer. McNerney et al suggest that chemotherapy and/or radiotherapy directly promote clonal selection of pre-existing mutant haematopoietic stem cells (McNerney et al 2017). There are instances where blood cells contain somatic mutations of genes known to be recurrently mutated in hematologic malignancies (frequently referred to as clonal haematopoiesis) with absence of morphological evidence of disease. Recently, Bolton et al investigated the relationship between clonal haematopoiesis and PARP inhibitor therapy and found that patients exposed to PARP inhibitor therapy were more likely to have clonal haematopoiesis (33%), particularly those in the DNA damage response pathway compared to those exposed to other systemic therapies or radiation (18%), or untreated patients (16%) (Bolton et al 2020).

Evidence Source(s) and Strength of Evidence

Case reports of MDS/AML have been received from clinical studies and through spontaneous reporting.

Characterisation of the Risk

Table II-17 Important Identified Risk: Myelodysplastic Syndrome/Acute Myeloid Leukaemia

		Frequency	Seriousness		Outcome (at time of reporting)				Severity (CTCAE grade)				
		n (%) patients with AEs	Serious	Non-serious	Fatal	Ongoing	Recovered	Not reported	<3	3	4	5	Not reported
Monotherapy therapeutic dose pool (N=4499)[a]		40 (0.9)	37	3	21	13	5	1	3	14	11	12	0
Combination data	Olaparib + bevacizumab (N=535)[b]	6 (1.1)	6	0	3	1	2	0	0	1	3	2	0
	Olaparib + abiraterone (N=469)[c]	2 (0.4)	2	0	0	2	0	0	0	0	2	0	0
	Olaparib + durvalumab (N=192)[d]	0	0	0	0	0	0	0	0	0	0	0	0

[a] Data are provided to a DCO of 12 April 2023 for the monotherapy therapeutic dose pool

[b] Data are provided to a DCO of 22 March 2022 for olaparib + bevacizumab data (PAOLA-1)

[c] Data are provided to a DCO of 12 October 2022 for olaparib + abiraterone pool (Study 8 and PROpel)

[d] Data are provided to a DCO of 12 April 2023 for olaparib + durvalumab data (DUO-E; maintenance phase in the ITT population)

AE = Adverse event; CTCAE = Common Terminology Criteria for Adverse Events; DCO = Data cut-off; N = Total number of patients.

Risk Factors and Risk Groups

Risk factors include prior treatment with cytotoxic chemotherapy and/or irradiation, occupational exposure, and smoking (Strom et al 2008). Secondary MDS/AML occurs as a late toxicity of cancer treatment, usually following exposure to alkylating agents such as cyclophosphamide, melphalan or platinum agents (cisplatin, carboplatin) or concurrent radiation with a latent period of 5 to 7 years, or the DNA topoisomerase II inhibitors (shorter latency period of 2 years) (Leone et al 1999, Travis et al 1999). Both acquired aplastic anaemia following immunosuppressive treatment and genetic Fanconi anaemia can evolve into MDS. Patients with Fanconi anaemia have a higher risk of MDS and AML (Kutler et al 2003). There is some evidence that the risk of MDS/AML may be increased in patients with BRCA mutation (Friedenson 2007, Cole and Strair 2010), but there is not sufficient published data to quantify this risk due to the rarity of the event and historical lack of routine *BRCA* mutation screening. Germline *BRCA* mutation is known to predispose patients to the development of solid tumours, notably ovarian and breast tumours and Cole and Strair have hypothesised that a deficiency in the expression of *BRCA* genes may also render patients more vulnerable to the adverse effects of chemotherapy and therefore put them at an increased risk of MDS/AML (Cole and Strair 2010).

Preventability

No data are available on preventability.

Section 4.4 of the SmPC provides advice to prescribers on the avoidance and management of haematological toxicity caused by previous anti-cancer therapy.

Impact on the Risk-benefit Balance of the Product

MDS is associated with significant morbidity and mortality. Morbidity is related to the degree of cytopenia and may include hospital admissions for bleeding episodes, infections and transfusion dependent anaemia. Mortality is mainly due to neutropenic sepsis and transformation to AML.

Public Health Impact

There is no public health impact.

II: 7.3.2 Presentation of Important Potential Risks

New Primary Malignancies

Potential Mechanisms

The observation that secondary cancers are linked to treatment with DNA damaging agents, raises the potential risk that treatment with PARP inhibitors, which lead to the accumulation of DNA damage in some cells, could also contribute to the development of these conditions by creating genomic instability. PARP inhibition does not directly cause DNA damage but impairs the ability of cells to repair DNA single strand breaks and, in cells that have a

deficient homologous recombination pathway, this leads to the accumulation of un-repaired double strand breaks that eventually cause the death of the target cell. Normal cells, even those from patients with a *gBRCA* mutation and only one functional *BRCA* allele in all cells, would be expected to have an intact homologous recombination DNA repair mechanism and therefore be able to adequately repair the double strand breaks induced by inhibiting PARP. However, the overall burden of single and double strand breaks will be increased in all dividing cells by PARP inhibition and this is the basis for the potential risk that this may contribute to the development of second primary cancers.

Evidence Source(s) and Strength of Evidence

Case reports of NPMs have been received from clinical studies and post-marketing use.

Characterisation of the Risk

Table II-18 Important Potential Risk: New Primary Malignancies

		Frequency	Seriousness		Outcome (at time of reporting)				Severity (CTCAE grade)				
		n (%) patients with AEs	Serious	Non-serious	Fatal	Ongoing	Recovered	Not reported	<3	3	4	5	Not reported
Monotherapy therapeutic dose pool (N=4499)[a]		65 (1.4)	62[b]	5[b]	4[b]	21[b]	38[b]	4[b]	11[b]	49[b]	4[b]	3[b]	0[b]
Combination data	Olaparib + bevacizumab (N=535)[c]	20 (3.7)	20	0	5	11	4	0	3	10	5	2	9
	Olaparib + abiraterone (N=469)[d]	18 (3.8)	15	3	2	9	7	0	5	11	0	2	0
	Olaparib + durvalumab (N=192)[e]	1 (0.5)	0	1	0	0	1	0	1	0	0	0	0

[a] Data are provided to a DCO of 12 April 2023 for the monotherapy therapeutic dose pool.

[b] Data presented are for number of events (65 patients experienced 67 events).

[c] Data are provided to a DCO of 22 March 2022 for olaparib + bevacizumab data (PAOLA-1).

[d] Data are provided to a DCO of 12 October 2022 for olaparib + abiraterone pool (Study 8 and PROpel).

[e] Data are provided to a DCO of 12 April 2023 for olaparib + durvalumab data (DUO-E; maintenance phase in the ITT population).

AE = Adverse event; CTCAE = Common Terminology Criteria for Adverse Events; DCO = Data cut-off; N = Total number of patients.

Risk Factors and Risk Groups

Patients with ovarian cancer, breast cancer and *BRCA* mutations are at risk of developing other common cancers (Bergfeldt et al 1995, Fowble et al 2001, Wesolowski et al 2007). Therapy induced risk factors, including previous radiotherapy or chemotherapy with DNA damaging agents, are known to increase the incidence of malignant disease (eg, bladder cancer, lymphoma and leukaemia).

Other common risk factors include:

- Exposure to ultraviolet-light which can induce DNA damage, causing skin cancer
- Exposure to environmental factors eg, formaldehyde, asbestos
- Dietary factors in cancer of colon and breast
- Hormonal factors eg, oestrogen dependent (endometrial and breast cancers)
- Smoking, which has been connected to several types of cancer eg, lung
- Immunological factors: some cancer patients have depressed immunological function and certain states of immunosuppression can predispose for specific malignant disease.

Preventability

Good medical care and screening can help detect new cancers early. Appropriate attention to potential symptoms and prompt action will contribute to controlling the risk.

Impact on the Risk-benefit Balance of the Product

Cancer is associated with significant morbidity and mortality, and therefore if confirmed, it could potentially impact benefit risk. The reported incidence of new primary malignancies in the olaparib programme is low and consistent with the observed incidence in epidemiological data of patients treated for advanced ovarian and breast cancer.

Public Health Impact

There is no public health impact.

Effects on Embryofoetal Survival and Abnormal Development

Potential Mechanisms

Based on its mechanism of action (PARP inhibition), Lynparza could cause effects on embryofoetal survival and abnormal development.

Evidence Source(s) and Strength of Evidence

Nonclinical studies in rats have shown that olaparib causes adverse effects on embryofoetal survival and induces major foetal malformations at exposures below those expected at the recommended human dose of 300 mg bd. Olaparib was not mutagenic in a bacterial mutation test (Ames), but was clastogenic in a chromosome aberration test in vitro and induced micronuclei in the bone marrow of rats following oral dosing.

Characterisation of the Risk

Table II-19 Important Potential Risk: Effects on Embryofoetal Survival and Abnormal Development[a]

Frequency/ seriousness/ outcomes	Frequency	Seriousness		Outcome (at time of reporting)				
	n	Serious	Non-serious	Healthy baby	Congenital abnormality	Spontaneous abortion	Elective termination	Unknown
	15	5	10	2	0	3	0	10

[a] Cases involving exposure during pregnancy in the AZ Global Safety Database, included spontaneous reports (10 cases) and clinical trial cases (5 cases) from unblinded studies. Data are provided to a DCO of 15 June 2023.

Risk Factors and Risk Groups

Not known.

Preventability

Section 4.4 of the SmPC provides wording which states that Lynparza should not be used during pregnancy and provides advice on contraception for female and male patients. Cautionary statements have also been made in the SmPC in Section 4.6 'Fertility, pregnancy and lactation'.

Impact on the Risk-benefit Balance of the Product

Exposure to olaparib during pregnancy has the potential to have serious consequences such as severe foetal developmental abnormalities or loss of the pregnancy, and could therefore impact benefit risk.

Public Health Impact

There is no public health impact.

II: 7.3.3 Presentation of Missing Information

Long Term Exposure to/Potential Toxicity to Olaparib

Evidence Source

Long term exposure to/potential toxicity to olaparib is missing information due to the extension of the indication to include breast cancer; the limited availability of data to date in this population; and the associated increase in exposure caused by inclusion of this target population.

No activities are planned to further characterise this safety concern.

II: 8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

II: 8.1 Summary of the Safety Concerns

Table II-20 Summary of Safety Concerns

Important identified risks	Myelodysplastic syndrome/acute myeloid leukaemia
Important potential risks	New primary malignancies Effects on embryofoetal survival and abnormal development
Missing information	Long term exposure to/potential toxicity to olaparib

III: PART III: PHARMACOVIGILANCE PLAN

III: 1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Specific Adverse Reaction Follow-up Questionnaires

Follow-up targeted safety questionnaires are in place to enable more complete data collection and assessment of the following important identified and potential risks:

- MDS/AML: to obtain detailed information about the patient, the underlying disease, all potential risk factors and the sequence of events, such as previous chemotherapy details, exposure to radiotherapy, diagnostic details and classification of MDS, clinical progression and final outcome.
- New primary malignancies: to obtain detailed information about the patient, the underlying disease, all potential risk factors and the sequence of events, such as previous chemotherapy details, exposure to radiotherapy, diagnostic details, classification, staging of NPM, clinical progression, complications and final outcome.

Other Forms of Routine Pharmacovigilance Activities

Cumulative Reviews of MDS/AML

- MDS/AML: Collection and assessment of data from the ongoing clinical programme and post-marketing sources to further characterise the important identified risk of MDS/AML. A cumulative assessment of MDS/AML cases is provided within the annual PBRER (previously categorised as a required additional pharmacovigilance activity).

III: 2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no ongoing or planned additional pharmacovigilance activities for olaparib.

III: 3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable.

IV: PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table IV-1 Planned and On-going Post-authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorisation				
D0818C00001 (SOLO1) A phase III, randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with *BRCA* mutated advanced (FIGO stage III-IV) ovarian cancer following first line platinum-based chemotherapy Ongoing	**Primary Objective:** To determine the efficacy by PFS (using investigator assessment of scans according to modified RECIST 1.1) of olaparib maintenance monotherapy compared with placebo in *BRCA* mutated high risk advanced ovarian cancer patients who are in clinical CR or PR following first line platinum-based chemotherapy. **Secondary Objective:** To determine the efficacy of olaparib maintenance monotherapy compared with placebo in *BRCA* mutated high risk advanced ovarian cancer patients who are in clinical CR or PR following first line platinum-based chemotherapy by assessment of OS, time to earliest progression by RECIST or CA-125, or death, and PFS2.	Further evidence of efficacy and safety in *gBRCAm* patients	Interim analysis PFS2 Interim analysis OS Final report	3Q2020 3Q2020 4Q2029

Table IV-1 Planned and On-going Post-authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
D9311C00001 (DUO-E) A phase III, randomised double blind, placebo controlled, multicentre study of first line carboplatin and paclitaxel in combination with durvalumab, followed by maintenance durvalumab with or without olaparib in patients with newly diagnosed advanced or recurrent endometrial cancer Ongoing	**Primary Objective:** To demonstrate the efficacy of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) when compared to platinum-based chemotherapy (Arm A) by assessment of PFS (per RECIST 1.1 as assessed by investigator), in patients with newly diagnosed advanced or recurrent endometrial cancer. **Secondary Objective:** To determine the efficacy of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) when compared to platinum-based chemotherapy (Arm A) in newly diagnosed advanced or recurrent endometrial cancer patients by assessment of: PFS2, OS, ORR, DoR, TFST, TSST, and TDT	Further evidence of efficacy and safety of durvalumab and olaparib in the first line treatment of endometrial cancer	Interim OS analysis Final report	4Q2025 4Q2026
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				

BRCA = Breast cancer susceptibility gene; CR = Complete response; DoR = Duration of response; ORR = Objective response rate; OS = Overall survival; PFS= Progression-free survival; PFS2 = Second progression-free survival; PR = Partial response; TDT = Time to treatment discontinuation or death; TFST = Time to first subsequent therapy or death, TSST = Time to second subsequent therapy or death.

V: PART V: RISK MINIMISATION MEASURES

V: 1 ROUTINE RISK MINIMISATION MEASURES

Table V-1 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
MDS/AML	Routine risk communication: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: **SmPC Section 4.4:** Guidance is provided for monitoring and management. **PL Section 2:** Advice regarding low blood counts and the signs and symptoms to look out for. **PL Section 4:** Provides information on side effects and signs and symptoms, commonly shown in blood tests, to look out for.
New primary malignancy	There are no routine risk minimisation activities for new primary malignancy.
Effects on embryofoetal survival and abnormal development	Routine risk communication in: • SmPC Sections 4.4, 4.6 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: **SmPC Section 4.4, 4.6:** Advice on contraception and pregnancy. **PL Section 2:** Advice on contraception and pregnancy
Long term exposure to/potential toxicity to olaparib	None.

V: 2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V: 1 are sufficient to manage the safety concerns of the medicinal product.

Removal of Additional Risk Minimisation Activities

Not applicable.

V: 3 SUMMARY OF RISK MINIMISATION MEASURES

Table V-2 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
MDS/AML	Routine risk minimisation measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up targeted safety questionnaire • Cumulative assessment (provided within each annual PBRER)
New primary malignancy	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up targeted safety questionnaire
Effects on embryofoetal survival and abnormal development	Routine risk minimisation measures: • SmPC Sections 4.4, 4.6 • PL Section 2	Routine
Long term exposure to/potential toxicity to olaparib	None	Routine

VI: PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR LYNPARZA (OLAPARIB)

This is a summary of the RMP for Lynparza. The RMP details important risks of Lynparza, how these risks can be minimised, and how more information will be obtained about Lynparza's risks and uncertainties (missing information).

Lynparza's SmPC and its PL give essential information to healthcare professionals and patients on how Lynparza should be used.

This summary of the RMP for Lynparza should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Lynparza's RMP.

VI: 1 THE MEDICINE AND WHAT IT IS USED FOR

Lynparza is a PARP (poly [adenosine diphosphate-ribose] polymerase) inhibitor. PARP inhibitors destroy cancer cells by exploiting deficiencies in DNA pathways. These specific cancer cells can be identified by response to platinum chemotherapy or by looking for faulty (mutated) DNA repair genes, such as *BRCA* (BReast CAncer) genes.

Lynparza is authorised, as monotherapy, for the maintenance treatment of *BRCA*-mutated relapsed ovarian, cancer, once the cancer has responded to platinum-based chemotherapy, and for the maintenance treatment of adult patients with newly diagnosed advanced *BRCA*-mutated ovarian cancer, who are in response to first-line platinum-based chemotherapy.

Lynparza is also authorised as monotherapy for the treatment of adult patients with germline *BRCAm* HER2-negative metastatic breast cancer who have previously been treated with chemotherapy. These patients could have received chemotherapy in the neoadjuvant, adjuvant or metastatic setting (see SmPC for the full indications). Patients with HR-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy (see SmPC for the full indications).

Lynparza is also used as monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline *BRCA1/2*-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.

Lynparza is also used as monotherapy for treatment of a type of pancreatic cancer (*BRCA* mutated), that has responded to the first treatment with standard platinum-based chemotherapy. A test is used to find out whether you have *BRCA*-mutated pancreatic cancer.

Lynparza is also used as monotherapy for treatment of adult patients with metastatic castration-resistant prostate cancer and *BRCA1/2* mutations (germline and/or somatic) who have progressed following prior therapy that included new hormonal agent.

Lynparza in combination with bevacizumab is used 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) following completion of first-line platinum-based chemotherapy with bevacizumab and whose cancer is associated with HRD positive status defined by either a *BRCA1/2* mutation and/or genomic instability.

Lynparza in combination with abiraterone and prednisone or prednisolone is used for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated.

Lynparza in combination with durvalumab is used for the maintenance treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair proficient (pMMR) whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel.

The tablets contain Lynparza as the active substance and are given by oral administration.

Further information about the evaluation of Lynparza's benefits can be found in Lynparza's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.
http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/003726/human_med_001831.jsp.

VI: 2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Lynparza, together with measures to minimise such risks and the proposed studies for learning more about Lynparza's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Lynparza, these measures are supplemented with additional risk minimisation measures mentioned under the relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Benefit-Risk Evaluation Report (PBRER) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Lynparza is not yet available, it is listed under 'missing information' below.

VI: 2.1 List of Important Risks and Missing Information

Important risks of Lynparza are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lynparza. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long term use of the medicine).

Table VI-1 List of Important Risks and Missing Information

Important identified risks	Myelodysplastic syndrome/Acute myeloid leukaemia
Important potential risks	New primary malignancies Effects on embryofoetal survival and abnormal development
Missing information	Long term exposure to/potential toxicity to olaparib

VI: 2.2 Summary of Important Risks

Table VI-2 Important Identified Risks

MDS/AML	
Evidence for linking the risk to the medicine	Case reports of MDS/AML have been received from clinical studies and through spontaneous reporting.
Risk factors and risk groups	Risk factors include prior treatment with cytotoxic chemotherapy and/or irradiation, occupational exposure, and smoking (Strom et al 2008). Secondary MDS occurs as a late toxicity of cancer treatment, usually with a combination of radiation and the radiomimetic alkylating agents such as bisulfan or procarbazine (with a latent period of 5 to 7 years) or the DNA topoisomerase inhibitors (2 years). Both acquired aplastic anaemia following immunosuppressive treatment and genetic Fanconi anaemia can evolve into MDS. Patients with Fanconi anaemia have a higher risk of MDS and AML (Kutler et al 2003). There is some evidence that the risk of MDS/AML may be increased in patients with *BRCA* mutation (Friedenson 2007, Cole and Strair 2010), but there is not sufficient published data to quantify this risk due to the rarity of the event and historical lack of routine *BRCA* mutation screening. Germline *BRCA* mutation is known to predispose patients to the development of solid tumours, notably ovarian and breast tumours and Cole and Strair have hypothesised that a deficiency in the expression of *BRCA* genes may also render patients more vulnerable to the adverse effects of chemotherapy and therefore put them at an increased risk of MDS/AML (Cole and Strair 2010). Recently, Bolton et al investigated the relationship between clonal haematopoiesis and PARP inhibitor therapy and found that patients exposed to PARP inhibitor therapy were more likely to have clonal

Table VI-2 Important Identified Risks

MDS/AML	
	haematopoiesis (33%), particularly those in the DNA damage response pathway compared to those exposed to other systemic therapies or radiation (18%), or untreated patients (16%) (Bolton et al 2020).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up targeted safety questionnaire • Cumulative assessment (provided within each annual PBRER)

Table VI-3 Important Potential Risks

New primary malignancies	
Evidence for linking the risk to the medicine	Case reports of NPMs have been received from clinical studies and post-marketing use.
Risk factors and risk groups	Patients with ovarian cancer, breast cancer and *BRCA* mutations are at risk of developing other common cancers (Bergfeldt et al 1995, Fowble et al 2001, Wesolowski et al 2007). Therapy induced risk factors, including previous radiotherapy or chemotherapy with DNA damaging agents, are known to increase the incidence of malignant disease (eg, bladder cancer, lymphoma and leukaemia). Other common risk factors include: • Exposure to ultraviolet-light which can induced DNA damage, causing skin cancer • Exposure to environmental factors eg, formaldehyde, asbestos • Dietary factors in cancer of colon and breast • Hormonal factors eg, oestrogen dependent (endometrial and breast cancers) • Smoking, which has been connected to several types of cancer eg, lung • Immunological factors: some cancer patients have depressed immunological function and certain states of immunosuppression can predispose for specific malignant disease.
Risk minimisation measures	There are no routine risk minimisation activities for new primary malignancy.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up targeted safety questionnaire

Table VI-3 Important Potential Risks

New primary malignancies	
Effects on embryofoetal survival and abnormal development	
Evidence for linking the risk to the medicine	Nonclinical studies in rats have shown that Lynparza causes adverse effects on embryofoetal survival and induces major foetal malformations at exposures below those expected at the recommended human dose of 300 mg bd. Lynparza was not mutagenic in a bacterial mutation test (Ames), but was clastogenic in a chromosome aberration test in vitro and induced micronuclei in the bone marrow of rats following oral dosing.
Risk factors and risk groups	Not known.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4, 4.6 • PL Section 2

Table VI-4 Missing Information

Long term exposure to/potential toxicity to olaparib	
Risk minimisation measures	None
Additional pharmacovigilance activities	None

VI: 2.3 Post-authorisation Development Plan

VI: 2.3.1 Studies Which are Conditions of the Marketing Authorisation

The following studies are conditions of the marketing authorisation:

Study D0818C00001 (SOLO1): A study of the safety and efficacy of Lynparza tablets in women with advanced ovarian cancer with certain changes in their *BRCA1* or *BRCA2* genes (mutations), whose cancer has responded (reduced in size or disappeared) to first line platinum chemotherapy.

Purpose of the study: To investigate the efficacy of Lynparza tablets by PFS (using investigator assessment of scans according to modified RECIST 1.1) as maintenance monotherapy in *BRCA* mutated advanced ovarian cancer patients who achieved complete or partial response following first line platinum-based chemotherapy.

Study D9311C00001 (DUO-E): A study of the safety and efficacy of first line carboplatin and paclitaxel in combination with intravenous durvalumab, followed by maintenance durvalumab with or without Lynparza tablets in women in newly diagnosed advanced of recurrent endometrial cancer.

Purpose of the study: To investigate the efficacy of intravenous durvalumab in combination with standard of care platinum-based chemotherapy (carboplatin and paclitaxel) followed by maintenance durvalumab with or without Lynparza tablets compared to standard of care

platinum-based chemotherapy by PFS (using investigator assessment of scans according to RECIST 1.1) in patients with newly diagnosed or recurrent endometrial cancer.

VI: 2.3.2 Other Studies in Post-authorisation Development Plan

There are no studies required for Lynparza.

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EU RMP Part VII Annex 4

Drug Substance Olaparib

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR OLAPARIB

Part VII ANNEX 4 - SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Active substance(s) (INN or common name)	Olaparib
Product(s) concerned (brand names(s))	Lynparza™
Name of Marketing Authorisation Holder or Applicant	AstraZeneca

TABLE OF CONTENTS

1. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

- MDS/AML Targeted Safety Questionnaire
- New Primary Malignancy Targeted Safety Questionnaire

AstraZeneca

LYNPARZA™ (Olaparib):
MYELOID NEOPLASM QUESTIONNAIRE
Request for additional information

AZ Date of Receipt: _____

AZ ref: _____

Please provide as much information as possible, note that relevant laboratory reports may be attached as an alternative to completing appropriate sections.

1. Patient Demographic Information

Initials:_____ Gender: ☐ Male ☐ Female Age at diagnosis of MDS/AML:_____yrs	Country of origin: Ethnicity

2. Details of Cancer Treated with Olaparib (✓ all that apply)

Site of primary tumour:	Date of diagnosis (DD/MM/YYYY)	Bone metastases of primary tumor:
☐ Ovary (1) ☐ Breast (2) ☐ Other (specify) (3)	Primary tumor 1 (Ovary): Primary tumor 2 (Breast): Primary tumor 3 (Other):	☐ Yes ☐ No

BRCA status

☐ gBRCA ☐ BRCA1 ☐ BRCA2 ☐ BRCA wild type ☐ BRCA mutation identified in tumour testing ☐ Unknown

3. Previous Radiotherapy: Yes ☐ No ☐ (if yes please provide details)

Field	Total Dose	Start date (DD/MM/YYYY)	End date (DD/MM/YYYY)

4. All Chemotherapy Exposure (including prior and during olaparib therapy)

Drug name (generic)	Indication	No. of cycles	Line of treatment (1st, 2nd,3rd,...)	Start date (DD/MM/YYYY)	End date (DD/MM/YYYY)

5. Relevant Patient's and Family History (✓ all that apply and provide details)

Does the patient have any known risk factors for MDS/AML other than prior chemo-radiotherapy for the treatment of the primary tumor?

☐ Family history of haematological neoplasm (e.g. MDS. AML. MPN)
Describe family relation and tumour type:

☐ Family history of non-hematological neoplasm
Describe family relation and tumour type:

☐ Inherited genetic syndromes more likely to develop MDS (e.g. Fanconi anemia, Shwachman-Diamond syndrome; Diamond Blackfan anemia, Familial platelet disorder associated with a monoallelic germ-line mutation in RUNX1, Severe congenital neutropenia, Dyskeratosis congenita). If yes, please name:

☐ Environmental / Professional Exposures:
☐ High-dose radiation exposure (e.g. nuclear accident)
☐ Long-term workplace exposure to solvents or agricultural chemicals benzene, pesticides, herbicides, organic chemical radiation. If yes, please name:
☐ Tobacco Use: specify weekly amount and total years of use_____

6. Details of MDS and/or AML. If MDS progresses to AML, please provide details for the two events separately below (Please indicate worsening of a pre-existing MDS or AML where applicable)

Date of (DD/MM/YYYY)	
Latency (years/months) between first chemotherapy for treatment of primary tumour and MDS/AML diagnosis	

Please turn the page

Latency (years/months) between first radiotherapy for treatment of primary tumour and MDS/AML diagnosis	
Latency (years/months) between first dose of olaparib and MDS/AML diagnosis	
Was the patient diagnosed of MDS prior to the AML diagnosis?	Yes ☐ No ☐
Was the patient diagnosed of Myeloproliferative Neoplasm (MPN) prior to the AML diagnosis?	Yes ☐ No ☐

Outcome of MDS/AML (✓)
☐ Ongoing ☐ Recovered ☐ Fatal ☐ Unknown ☐ Recovered with sequelae, (specify)

7. Under the 2016 WHO Classification of Myeloid Neoplasms and Acute Leukemia, this event is categorized as:
(✓ all that apply, provide results of the test performed, and/or attach a copy of the respective report)

☐ Acute Myeloid Leukemia and Related Neoplams **(AML)**
☐ Myelodysplastic Syndrome **(MDS)**
☐ Myelodysplastic / Myeloproliferative Neoplasm **(MDS/MPN)** [includes CMML]
☐ Myeloproliferative Neoplasm **(MPN)**
☐ Other (please specify, e.g. acute leukemia of ambiguous lineage, myeloid / lymphoid neoplasm, etc.)

☐ Complete Blood Count & peripheral blood smear at time of AML diagnosis:
White blood cell absolute count (please specify units): Blast %:
Neutrophils absolute count (please specify unit): Hemoglobin (please specify unit):
Platelets (please specify unit): Examination of peripheral smear:

☐ Bone marrow core biopsy and aspirate analysis, including immunophenotyping and cytochemistry
Summary of findings (including Blast%):

☐ Cytogenetic analysis findings (Karyotype +/- FISH)
- ☐ normal karyotype
- ☐ complex karyotype (≥3 clonal cytogenetic abnormalities)
- ☐ monosomal karyotype (≥2 autosomal monosomies, or a single monosomy with an additional structural abnormality)
- ☐ monosomy 5 (-5)
- ☐ monosomy 7 (-7)
- ☐ other (please specify)

☐ Molecular analysis findings (KIT, FLT3 [ITD and TKD], NPM1, CEBPA, IDH1, IDH2, TP53, DNMT3A, other mutations)

- ☐ no mutations detected
- ☐ mutations detected (please specify):

8. Details of Relevant Laboratory Test Results
Please provide details to include: values at time of MDS/AML diagnoses. Please indicate if laboratory test reports are attached and provide laboratory units. Please add in the available spaces further laboratory test results you believe to be relevant.

Laboratory Parameter	At MDS/AML diagnosis	Laboratory Parameter	At MDS/AML diagnosis	Laboratory Parameter	At MDS/AML diagnosis
Potassium		AST		Serum B12	
Sodium		ALT		Serum ferritin	
Creatinine		ALP		Iron	
Urea		LDH		Other:	
Bilirubin		RBC folate for MDS pat.)			

9. Details of Death (if applicable)

Did the patient die? ☐ Yes ☐ No	Date of death?(DD/MM/YYYY)
Was autopsy done? ☐ Yes ☐ No	Autopsy report attached? ☐ Yes ☐ No
Primary cause of death?	
Provide details on cause of death and summary of autopsy report if available	

10. Details of anything else considered relevant for this event of MDS/AML that you have not already included in the above sections.		
11.Reporter details		
Reporter's Address: Telephone #: Fax #:	Is the reporter a healthcare professional (HCP)? ☐ Yes ☐ No If yes, please provide specialty:	If no, please confirm if we can contact the HCP? ☐ Yes ☐ No If yes, please provide contact information of the HCP

Thank you for completing this form

Name of the reporter_____ Signature_____

LYNPARZA™ (Olaparib): New Primary Malignancy (NPM) QUESTIONNAIRE (excluding MDS / AML) Request for additional information

AZ Date of Receipt: _____

AZ ref: _____

Please provide as much information as possible, note that relevant laboratory reports may be attached as an alternative to completing appropriate sections.

1. Patient Demographic Information

Initials:_____ Gender: ☐ Male ☐ Female Age at diagnosis of NPM:_____yrs	Country of origin: Ethnicity

2. Details of Cancer Treated with Olaparib (✓ all that apply)

Site of primary tumour: Date of diagnosis (DD/MM/YYYY) ☐ Ovary (1) ☐ Breast (2) _____/_____/_____ ☐ Other (specify) (3)	**Site of metastases:** ☐ Lung ☐ Liver ☐ Bone ☐ None ☐ Other (specify)

BRCA status

☐ gBRCA ☐ BRCA mutation identified in tumour testing

☐ BRCA1 ☐ BRCA2 ☐ BRCA wild type ☐ Unknown

3. Previous Radiotherapy: Yes ☐ No ☐ (if yes please provide details)

Field	Total Dose	Date range administered (DD/MM/YYYY)

4. All Chemotherapy Exposure (including prior and during olaparib therapy)

Drug name (generic)	Indication	No. of cycles	Line of treatment (1st, 2nd,3rd,...)	Start date (DD/MM/YYYY)	End date (DD/MM/YYYY)

5. Relevant Patient's and Family History (✓ all that apply and provide details)

Family history of malignancy? Yes ☐ No ☐ ☐ 1st degree ☐ 2nd degree	Describe family relation and tumour type of each family member
Any other previous cancers prior to the cancer under treatment with olaparib? (patient) Yes ☐ No ☐ (please specify):	Any previous myeloproliferative disease? (patient) Yes ☐ No ☐ (please specify):
Relevant previous occupations or exposure to radiation, pesticides, herbicides, organic chemicals? Yes ☐ No ☐ (please specify):	Smoking? Yes ☐ No ☐ (please specify weekly amount and dates of exposure)
Alcohol consumption? Yes ☐ No ☐ (please specify weekly amount and dates of exposure)	Use of herbal/Chinese medicine? Yes ☐ No ☐ (please specify and provide weekly amount and dates of exposure)
Other relevant concomitant medical conditions / comorbidities? Yes ☐ No ☐ (please specify and provide details)	

Please turn the page

AstraZeneca

6. Details of New Primary Malignancy (NPM)	
Adverse event term	Worst CTCAE grade
Start date (DD/MM/YYYY)	Related to Olaparib Yes ☐ No ☐
Other potential or contributory causes:	
Outcome (✓) ☐ Ongoing ☐ Recovered ☐ Fatal ☐ Unknown ☐ Recovered with sequelae, (specify)	Histology and classification of NPM (please specify) ☐ (✓)Please indicate if report is attached
Site of NPM (please specify)	TNM Stage of NPM
Any known genetic mutation e.g. adenomatous polyposis coli gene mutations if colon cancer?	Specify site of metastases of NPM (if applicable)
Cancer biomarker(s) for NPM (please specify) ☐ (✓)Please indicate if report is attached	

7. Details of relevant Signs and Symptoms (free text field)
No relevant clinical signs / symptoms (please ✓ box to confirm) ☐ No

8. Details of Any Treatment for the NPM			
Drug or procedure name	**Dosage (if applicable)**	**Start Date** (DD/MM/YYYY)	**Stop Date** (DD/MM/YYYY)

9. Details of Death (if applicable)	
Did the patient die? ☐ Yes ☐ No	Date of death?(DD/MM/YYYY)
Was autopsy done? ☐ Yes ☐ No	Autopsy report attached? ☐ Yes ☐ No
Primary cause of death?	
Provide details on cause of death and summary of autopsy report if available	

10. Details of anything else considered relevant for this event of NPM that you have not already included in the above sections. Please attach additional pages if required
☐ I have attached additional pages

11. Reporter details		
Reporter's Address: Telephone #: Fax #:	Is the reporter a healthcare professional (HCP)? ☐ Yes ☐ No If yes, please provide specialty:	If no, please confirm if we can contact the HCP? ☐ Yes ☐ No If yes, please provide contact information of the HCP

Thank you for completing this form

Name of the reporter_____ Signature_____