NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1680]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1680]

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The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

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11. **Evidence Review Group critique of company response to technical engagement prepared by BMJ Group**
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy

[ID1680]

Document B

Company evidence submission

May 2020

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This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

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In this template any information that should be provided in an appendix is listed in a box.

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Abbreviations

AE	Adverse event
AFP	Alpha-fetoprotein
AIC	Akaike Information Criterion
AUC	Area under curve
BER	Base excision repair
BGCS	British Gynaecological Cancer Society
BIC	Bayesian Information Criterion
BMI	Body mass index
BRCA	Breast cancer susceptibility gene
BRCAmut	Breast cancer susceptibility gene mutation
CA	Commercial arrangement
BRCAwt	Wild type breast cancer susceptibility gene (no mutation)
CAP	Commercial arrangement price
CA-125	Cancer antigen-125
CBC	Complete blood cell
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CFI	Chemotherapy-free interval
CG	Clinical guideline
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
DSU	Decision support unit
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life of Cancer patients questionnaire
EQ-5D	European Quality of Life Scale, 5-Dimensions
EQ-5D-5L	European Quality of Life Scale, 5-Dimensions, 5-level
ERG	Evidence review group
ESMO	European Society for Medical Oncology
FCR	Fear of cancer recurrence
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
FOSI	Functional Assessment of Cancer Therapy – Ovarian Symptom Index
gBRCAmut	Germline BRCA mutation
GCIG	Gynaecologic Cancer InterGroup
G-CSF	Granulocyte colony stimulating factor
GI	Gastrointestinal

GP	General practitioner
β-hCG	Beta-human chorionic gonadotrophin
HGSOC	High-grade serous ovarian cancer
HR	Hazard ratio
HR-d	Homologous recombination deficient
HRD	Homologous recombination deficiency
HR-p	Homologous recombination proficient
HRP	Homologous recombination proficiency
HRQoL	Health-related quality of life
HUI	Health utility index
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
IRC	Independent Review Committee
ITT	Intent-to-treat
KM	Kaplan–Meier
LY	Life years
MDT	Multi-disciplinary team
MRI	Magnetic resonance imaging
N/A	Not applicable
NE	Not estimated
NHS	National Health Service
non-gBRCAmut	Non-germline BRCA mutation
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NICE	National Institute for Health and Care Excellence
OC	Ovarian cancer
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PARP	Poly(adenosine diphosphate ribose) polymerase
PAS	Patient access scheme
PBC	Platinum-based chemotherapy
PD	Progressed disease
PFD	Progression-free disease
PFS	Progression-free survival
PFS2	Progression-free survival on next line of therapy
PLDH	Pegylated liposomal doxorubicin hydrochloride
PP	Per protocol
PR	Partial response
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QD	Once daily
RCT	Randomised controlled trial

RECIST	Response Evaluation Criteria in Solid Tumours
RMI	Risk of malignancy index
SAE	Serious adverse event
SAF	Safety population
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
TFST	Time to first subsequent therapy
TOMT	Time on maintenance treatment
TTD	Time to treatment discontinuation
ULN	Upper Limit of Normal
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor

B.1 Decision problem, description of the technology and clinical care pathway

- Ovarian cancer is rare; in England in 2017 it represented 4.2% of all new cancer cases in women.[1] Around 70% of patients with ovarian cancer are diagnosed at an advanced stage of the disease, meaning that their prognosis is frequently poor.[2] With only 42.6% of patients expected to survive beyond 5 years, survival outcomes for ovarian cancer in England are low, both in comparison to other cancers and in comparison to other European countries.[3,4] Ovarian cancer is responsible for a woman's death every three hours in England.[1] Knowledge of their poor prognosis and survival outcomes can have a negative impact on patients' psychological health as they have little hope for future recovery.
- First-line treatment for patients with newly diagnosed advanced ovarian cancer consists of cytoreductive surgery in conjunction with platinum-based chemotherapy and is curative in intent. Despite relatively high response rates to the combination of surgery and chemotherapy, up to 85% of patients with advanced high-grade ovarian cancer will relapse; at that stage the disease is considered incurable.[5–8] Routine surveillance remains the standard of care after relapse; consequently, there is a significant need to offer patients effective and well-tolerated first-line treatment options that delay or prevent relapse.
- The aim of maintenance therapy after first-line chemotherapy is to prolong the time to disease recurrence and the need for further chemotherapy, or ultimately to prevent relapse altogether and achieve long-term remission. First-line treatment is the only point in the management pathway where treatment is curative in intent and as such it is a critical time for patients with advanced ovarian cancer.
- Niraparib (Zejula) is an oral, highly selective PARP1 and PARP2 inhibitor with a proposed indication as maintenance therapy in patients with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. It is the first PARP inhibitor as monotherapy to show significant clinical efficacy in the first-line setting of ovarian cancer, irrespective of BRCA, mutation status and can thus be considered an innovative treatment.
- PRIMA, the pivotal Phase 3 randomised placebo-controlled trial for niraparib, demonstrated a statistically significant clinical benefit to patients treated with niraparib by extending their time living without disease progression or death

(HR 0.62; 95% CI, 0.50 to 0.76; p<0.001). Patients treated with niraparib achieved a 38% reduction in the risk of disease progression or death compared to those treated with placebo and routine surveillance.[9] The OS data are currently at 11% maturity with an expected final read out in [redacted]. Niraparib demonstrated an acceptable safety profile and patients' quality of life was maintained.[9]

- Niraparib is the only PARP inhibitor to treat all advanced high-grade ovarian cancer patients following response to first-line platinum-based chemotherapy, regardless of BRCA mutation, thereby serving a group of patients with limited treatment options.[9] Considering treatments available through the CDF, 75% of patients do not have a PARP inhibitor treatment option available, thus there is high unmet need in this population.[10]
- A NICE recommendation for niraparib maintenance treatment after first-line chemotherapy would present an opportunity at a critical junction for the patients in terms of long-term outcomes, as currently there are no maintenance treatment options available via routine commissioning in the first-line maintenance setting.

B.1.1 Decision problem

This submission covers the full marketing authorisation for niraparib (Zejula®) as maintenance treatment for patients with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. The decision problem that is addressed in this submission is presented in Table 1

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with advanced high grade ovarian, fallopian tube, or primary peritoneal cancer that has responded (complete or partial) to first-line platinum-based chemotherapy.	Cost-effectiveness analyses are presented for the expected marketing authorisation population, as per scope. The cost-effectiveness results for the marketing authorisation (MA) population, which is defined as the ITT population in the PRIMA trial plus patients with Stage III patients with no visible residual disease after primary cytoreductive surgery (NVRD). Cost-effectiveness results are also presented for the ITT PRIMA population to provide additional confidence in the MA results.	It is anticipated that the MA for niraparib in the first-line maintenance setting will consist of adult patients with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line PBC. The anticipated licensed population includes patients with NVRD; this group of patients has a better prognosis than patients with visible residual disease.[33] The submission explicitly considers the impact of incorporating this population into the analyses. Evidence from additional studies was used to demonstrate this difference in prognosis and to inform the cost-effectiveness analyses in the MA population.
Intervention	Zejula (niraparib)	As per scope	N/A
Comparator(s)	Routine surveillance	As per scope	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • OS • PFS • PFS2, that is PFS on next line of therapy • time to first subsequent therapy • adverse effects of treatment • health-related quality of life	As per scope	N/A
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per scope	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	The availability of any commercial arrangements for the intervention or comparator technologies will be taken into account.		
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include: • subgroups by BRCA mutation status	Clinical efficacy data from the PRIMA trial is presented, including results for the ITT population, as well as by BRCAmut subgroup. Cost-effectiveness analyses are not presented by BRCAmut subgroup.	The clinical data from the PRIMA trial showed that both the BRCAmut population and non-BRCAmut population benefited from a statistically significant PFS HR for niraparib compared with placebo. Patients in both patient populations should thus be considered in discussions around access to this medicine.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	There are no special considerations relating to issues of equity or equality.	N/A

Abbreviations: BRCA, breast cancer susceptibility gene; HR, hazard ratio; ITT, intention-to treat; MA, marketing authorization; OC, ovarian cancer; OS, overall survival; PBC platinum-based chemotherapy; PFS, progression-free survival

B.1.2 Description of the technology being appraised

Table 2 presents a brief description of niraparib as a first-line maintenance treatment. The draft Summary of Product Characteristics (SmPC) can be found in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Niraparib (Zejula®)
Mechanism of action	Niraparib is a potent and selective poly (ADP-ribose) polymerase (PARP)-1 and -PARP-2 inhibitor, which selectively kills tumour cells by preventing repair of damaged DNA. PARP-1 and -2 are zinc-finger DNA-binding enzymes that play a crucial role in DNA repair by the process of base excision repair (BER). PARP detects single strand DNA damage and converts it into intracellular signals that activate the BER pathway. Inhibiting PARP enzymes and BER can cause an accumulation of DNA damage, which requires repair by other processes.[12,13] DNA damage repair deficiencies are common in patients with platinum-responsive ovarian cancer, and therefore, these patients are more sensitive to the effects of PARP inhibition. There is a similarity of effect between platinum-based chemotherapy agents and PARP inhibitors, whereby DNA damage is induced beyond the capacity of the tumour cells to recover and survive.[14] Clinical studies have shown that PARP inhibitors have anti-tumour activity in patients with certain types of cancer, including those with and without deleterious BRCA mutations.[15–18] In particular, clinical trials for niraparib have demonstrated that its anti-tumour activity increases progression-free survival in ovarian cancer patients without negatively impacting quality of life, and these benefits have been shown to extend into the long-term in the relapsed setting.[9,19,20] Niraparib selectively inhibits PARP-1 and -2 enzymes, with minimal off-target activity.[19] In pre-clinical studies, niraparib concentrates in the tumour, delivering selective, greater than 90% durable PARP inhibition, and a persistent anti-tumour effect.[21,22] Niraparib concentrates in the tumour relative to plasma due to moderate binding to plasma proteins and high permeability.[21] Drug resistance to some anti-cancer treatments can be caused by increased expression of membrane drug transporters (including p-glycoprotein, or P-gp) and evidence suggests that this is particularly influential in ovarian cancer when treated with

	paclitaxel and PARP inhibitors.[23] The potential drug resistance inducing effect of P-gp on niraparib, as a substrate, is anticipated to be limited, due in part to the high biomembrane permeability of niraparib.[22] Niraparib is not inhibitory against the drug-metabolising CYP enzymes and is primarily metabolised by carboxylesterases, and as such, has demonstrated a minimal potential for drug-drug interactions in patients with polypharmacy.[22]
Marketing authorisation/CE mark status	A Type II variation application was submitted to the European Medicines Agency in February 2020. [redacted] Marketing authorisation is anticipated in December 2020
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication for niraparib is for maintenance treatment of adult patients with advanced high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. Anticipated contraindications are: • Hypersensitivity to the active substance or to any of the excipients listed in the SmPC • Breast-feeding during treatment and 1 month after the last dose.
Method of administration and dosage	Niraparib is an oral monotherapy. The recommended starting dose of niraparib is 200 mg (two 100 mg capsules), taken once daily. However, for those patients who weigh ≥ 77 kg and have baseline platelet count ≥ 150,000/μL, the recommended starting dose of niraparib is 300 mg (three 100-mg capsules), taken once daily. Patients can continue treatment until disease progression, unacceptable toxicity or for up to 3 years. Patients with evidence of disease at 3 years, who in the opinion of the treating physician can derive further benefit from continuous treatment, can be treated beyond 3 years
Additional tests or investigations	A complete blood count is required weekly for the first month following treatment initiation, followed by monthly complete blood counts for the first year. Heart rate and blood pressure monitoring are required weekly for the first month, followed by monthly monitoring for the first year of treatment. It is anticipated that this monitoring will be self-administered in the home setting, with follow-up with a nurse occurring as required.
List price and average cost of a course of treatment	The list price of niraparib is £4,500 for 1 pack of 56 x 100 mg capsules, and £6,750 for 1 pack of 84 x 100 mg capsules. At the list price, and recommended starting dose of 200 mg daily, a 28-day cycle costs £4,500 per patient

Patient access scheme (if applicable)	A commercial arrangement with a simple discount is currently in operation for the second-line indication [redacted]

Abbreviations: BER, base excision repair; DNA, deoxyribonucleic acid; PARP, poly(ADP-ribose) polymerase; SmPC, Summary of Product Characteristics

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Ovarian cancer (OC) is an umbrella term used to refer to ovarian, fallopian tube and peritoneal cancer. OC is a rare malignancy; with 6,236 new cases diagnosed in England in 2017, it represents 4.2% of all new cancer cases in women.[1] OC is also the seventh deadliest cancer amongst women, with an estimated 3,428 deaths (5.4% of all cancer deaths in women) attributable to OC in England in 2017, and a 5-year survival rate of 42.6%; OC is responsible for a woman's death approximately every three hours in England.[1,4] Around 70% of cases are diagnosed at an advanced stage with poor prognosis; the knowledge of this poor prognosis can have a negative psychological effect on patients as they have little hope for future recovery.[2] The poor survival outcomes experienced by patients with OC are below the G5 and European mean 5-year survival rates, demonstrating a significant unmet for this group of patients and an urgency for more effective treatments in England and Wales.[3] Poor outcomes are likely the combined result of a lack of early warning symptoms, alongside an absence of early screening methods and effective first-line interventions.[2]

OC is treatable but currently rarely cured. First-line treatment options include cytoreductive surgery and platinum-based chemotherapy (PBC) with a curative intent,[2,24] however up to 85% of advanced OC cases recur after completion of standard first-line platinum-based chemotherapy treatment; fear of relapse means that patients often live with high levels of psychological distress, depression and anxiety.[5–8] Once relapse has occurred, OC is generally considered incurable and with each recurrence, the effectiveness of PBC diminishes, PFS and platinum-free intervals shorten, cumulative toxicity increases, and treatment options become severely limited.[25]

The aim of maintenance therapy after first-line chemotherapy is to prolong the time to recurrence and delay the need for further chemotherapy, or ultimately to prevent relapse, while also preserving the quality of life of patients. Having the opportunity of maintenance therapy which extends the period without disease progression can offer

patients psychological as well as physical health benefits therefore offering all patients with OC an effective treatment at this stage is critical.[26] There is a significant need for effective and well-tolerated first-line treatment options that delay or even prevent disease progression, while allowing patients to maintain their quality of life and activities of daily living.

Poly (ADP-ribose) polymerase (PARP) inhibitors have demonstrated sustained clinical benefits to patients across first-, second- and subsequent-line maintenance treatment settings by extending time spent progression-free, without detrimentally impacting patients' quality of life. In England, niraparib is available through the Cancer Drugs Fund (CDF) as a maintenance treatment for advanced platinum-sensitive OC following response to second-line PBC, in patients with or without a BRCA mutation.[27] In third or subsequent lines, niraparib's use as maintenance treatment following response to PBC is limited to patients without a BRCA mutation. Given the importance of providing effective treatment to patients with newly diagnosed advanced OC in the first-line setting, it is proposed that the clinical benefits experienced by patients treated with niraparib in subsequent lines should be extended to allow all patients the opportunity to access maintenance therapy following response to first-line PBC.

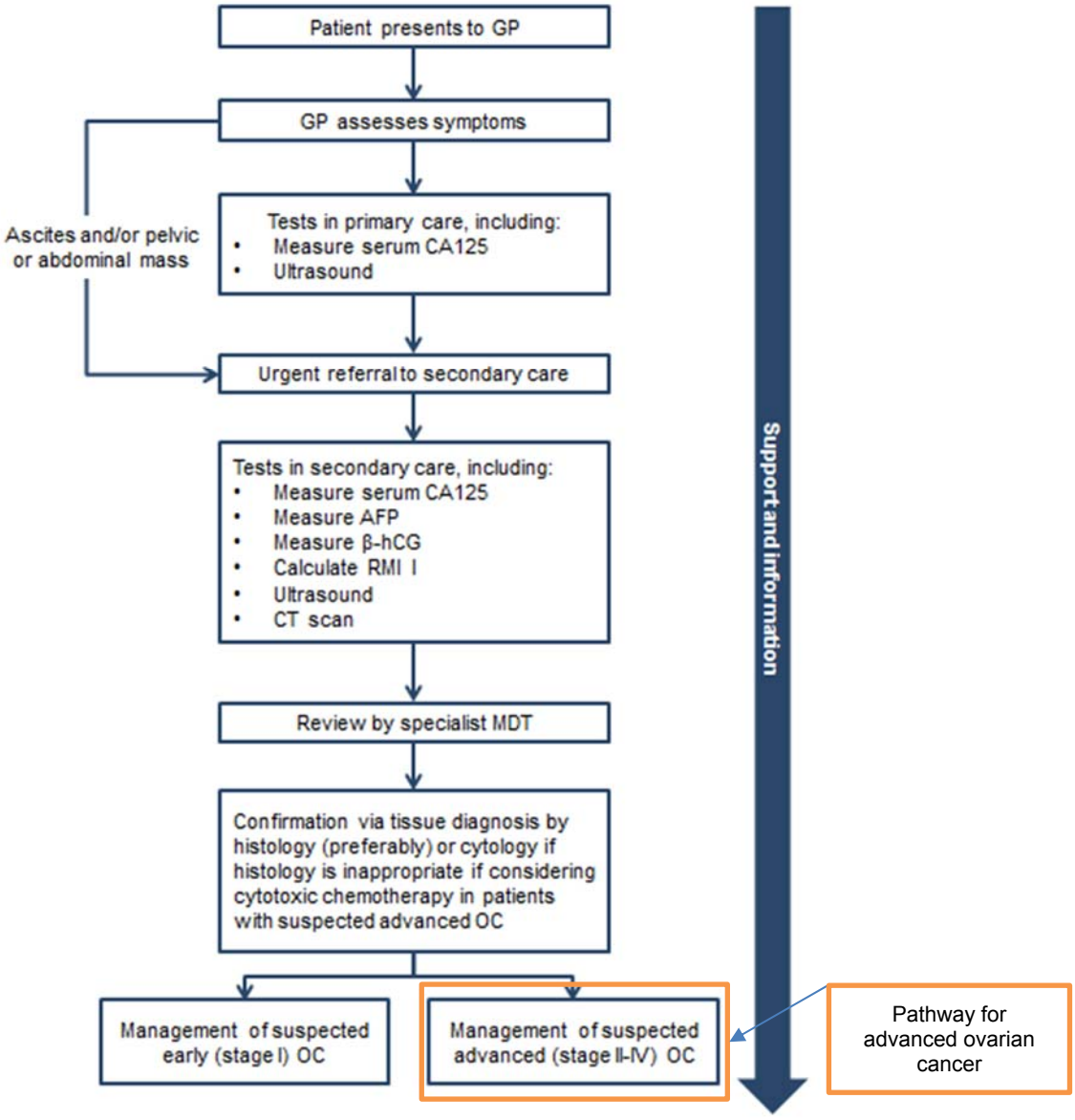
Currently, no first-line maintenance treatments are recommended for routine use in England. Even with the treatment options available through the CDF**,** the majority of patients with OC (75%) are not currently eligible for maintenance treatment with a PARP inhibitor. Olaparib is licenced as a treatment option for patients who possess a BRCA mutation (approximately 25%) following response to first-line PBC.[28] Olaparib is available through the CDF, but not reimbursed through routine commissioning.

For patients without a BRCA mutation, no first-line PARP inhibitor is either licensed, currently used or reimbursed for maintenance treatment, leaving patients with limited or no treatment options.[10] After first-line PBC, most patients receive routine surveillance (RS), which is associated with limited long-term benefits. There is therefore a high unmet need for an effective first-line maintenance treatment for patients with newly diagnosed advanced ovarian cancer after a response to first-line PBC, regardless of their BRCA mutation status.

B.1.3.2 Diagnosis and staging

The current NICE CG122 pathway for the recognition and management of patients with OC is summarised in Figure 1.[29] Further detail on the treatment pathway for advanced OC is presented in Section B.1.3.3.

Figure 1: Summary of diagnostic pathway adapted from NICE clinical guideline CG122



Abbreviations: AFP, alpha-fetoprotein; β-hCG, beta-human chorionic gonadotrophin; CT. computed tomography; GP, general practitioner; MDT, multi-disciplinary team; OC, ovarian cancer; RMI, risk of malignancy index.

According to NICE CG122 and the British Gynaecological Cancer Society (BGCS) guidelines, initial investigations for suspected OC should be performed in primary care

if a woman (particularly if aged ≥50 years) reports having any of the following symptoms persistently/frequently:[29,30]

- Persistent abdominal distention
- Feeling full and/or loss of appetite
- Pelvic or abdominal pain
- Increased urinary urgency and/or frequency

Testing should also be considered in patients who report unexplained weight loss, fatigue, and/or changes in bowel habit.

In primary care, clinical factors, ultrasound results, and CA-125 levels are used to calculate the risk of malignancy index (RMI) to determine whether patients should be referred to a specialist multidisciplinary team (MDT). NICE CG12 and the BGCS guidelines recommend that patients with an RMI ≥250 should have further investigation and be referred to the specialist gynaecological centre MDT.[29,31] It is recommended that serum CA-125 levels are measured in all patients with symptoms indicative of OC.[29] An ultrasound of the abdomen and pelvis is recommended in patients with elevated CA-125 levels (defined as ≥35 IU/mL), and patients should be referred to secondary care urgently if the ultrasound results are indicative of OC.[29]

In secondary care, CA-125 levels should be measured (if not already assessed in primary care), and levels of alpha-fetoprotein and beta-human chorionic gonadotrophin are investigated in patients aged <40 years. The extent of disease and confirmation of diagnosis are determined by computerised tomography (CT) imaging and confirmatory tissue diagnosis.

In patients with suspected OC, the BGCS guidelines recommend the use of radiological staging to provide further information about the extent of disease and potential distant metastases or secondary cancers.[31] If cytotoxic chemotherapy is to

be offered, both NICE CG12 and the BGCS guidelines state that a confirmed histological tissue diagnosis must be obtained in all but exceptional cases.[29,31]

Once diagnosed, patients are staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging classification. This is summarised in Table 3; the focus of this appraisal is in patients with Stage III-IV OC.

Table 3: Summary of FIGO staging classification ovarian, fallopian tube, and peritoneal cancer staging system

Stage	Description
I	Tumour confined to the ovaries or fallopian tube(s)
II	Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer
III	Tumour involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IV	Distant metastasis excluding peritoneal metastases
IVA	Pleural effusion with positive cytology

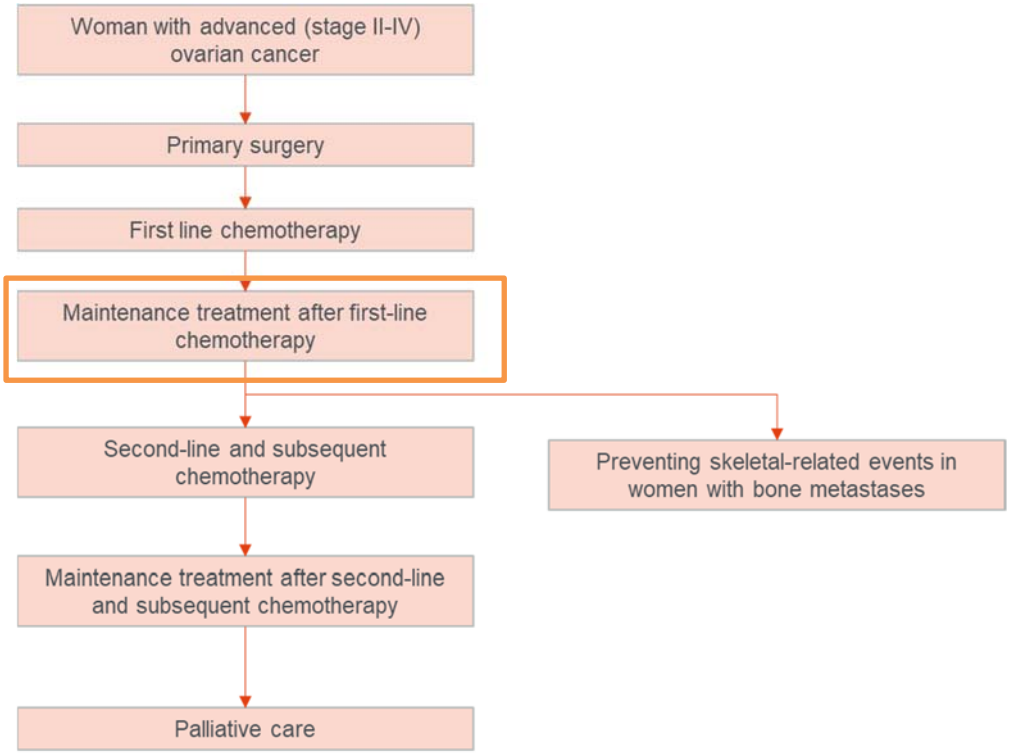
Adapted from Prat et al. 2014[32]

Abbreviation: FIGO: The International Federation of Gynecology and Obstetrics.

B.1.3.3 Management of advanced OC

There are a number of NICE technology appraisals for the use of new and existing therapies for the management of patients with advanced OC.[33–35] These recommendations are generally consistent with the European Society for Medical Oncology (ESMO) and European Society of Gynaecological Oncology (ESGO) consensus recommendations on OC, and the BGCS epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines.[31,36] This appraisal relates to patients who have responded after first-line platinum based chemotherapy as shown in the NICE pathway in Figure 2.[37] The steps shown in the pathway are described below.

Figure 2: OC NICE guidelines – overview and management of advanced disease (Stage II-IV)[37]



Surgery and systemic treatment

First-line treatment is curative in intent and is the best chance that patients will have to achieve long-term remission or cure. Cytoreductive surgery and PBC are usually first-line treatment. NICE guidelines recommend that in patients with advanced (Stage II-IV) OC, a complete resection of all macroscopic disease should be performed, where possible, either before chemotherapy or after neoadjuvant chemotherapy.[29] In cases where all macroscopic disease is successfully removed through primary surgery, patients are classified as having no visible residual disease (NVRD) and are associated with an improved prognosis.[38] In most patients, however, it is not possible to remove the tumour completely.

First-line chemotherapy (usually following surgery) in the treatment of OC includes the options of paclitaxel in combination with a platinum-based compound or platinum-based therapy alone. The chemotherapy regimen recommended by NICE is carboplatin in combination with paclitaxel (3-weekly for six cycles) due to better

tolerability compared with cisplatin.[29,31] Pegylated liposomal doxorubicin hydrochloride (PLDH) may be given as an alternative in patients who cannot tolerate paclitaxel, however the use of PLDH in combination therapy is off-licence in the UK.[30,39] Clinical decisions regarding chemotherapy treatment should be based on the adverse event (AE) profiles of the treatment available, stage of the disease, extent of surgical treatment, and the performance status of the patient.[33]

First-line PBC regimens result in high response rates; in most patients, however, the disease often recurs within two years.[5–8]

Maintenance treatment after first-line chemotherapy

Maintenance therapies have demonstrated significant clinical benefits, including improved PFS, for patients with advanced OC in both the first-line and relapsed settings.[9,40–43] Maintenance therapies are an established part of the treatment armamentarium, with the most recent ESMO/EGSO guidelines recommending the routine use of PARP inhibitors for patients with relapsed, platinum-sensitive OC.[44] The extension of these treatment benefits is now being proposed through earlier use of PARP inhibitors in first-line maintenance treatment.

First-line PARP inhibitors

There is a high unmet need for a first-line maintenance treatment for patients with advanced high-grade OC regardless of *BRCA* mutation status. Approximately 75% of patients with advanced OC do not possess a *BRCA* mutation; these patients currently have no licensed PARP inhibitor maintenance treatment options following response to first-line PBC.[10]

For the estimated 25% of patients who have a BRCA mutation, olaparib monotherapy is licenced as a maintenance therapy for high-grade patients with OC following response to first-line chemotherapy.[28] Olaparib is not reimbursed through routine commissioning, but is available for use within the CDF for the maintenance treatment of patients with *BRCA* mutations who have responded to first-line PBC, under a

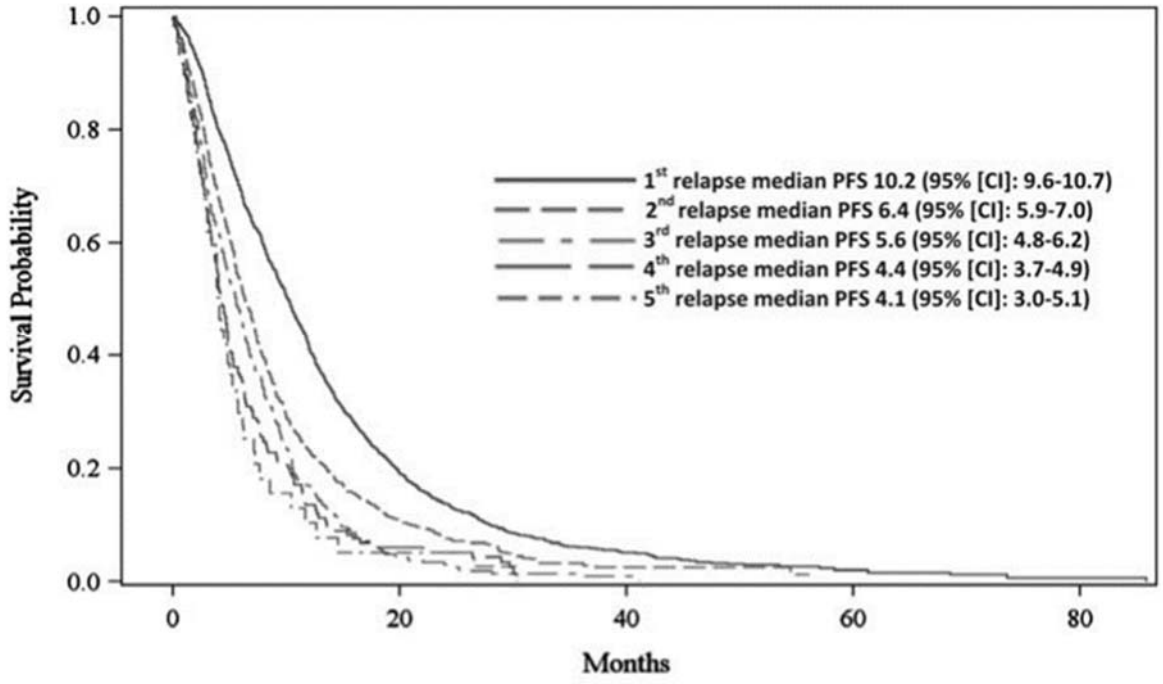
managed access agreement following review in 2019.[27] The data collection period will conclude in December 2023.[45]

Second-line and subsequent chemotherapy

In most patients the disease will recur within 2 years. Relapse rates for epithelial cancer can be as high as 85% for patients diagnosed with advanced (Stage III or IV) disease.[5–8] Patients with relapsed OC are faced with an incurable prognosis, and the goal of treatment for relapsed disease switches from being curative in intent to managing disease and cytotoxic symptoms, preserving quality of life, and improving survival.

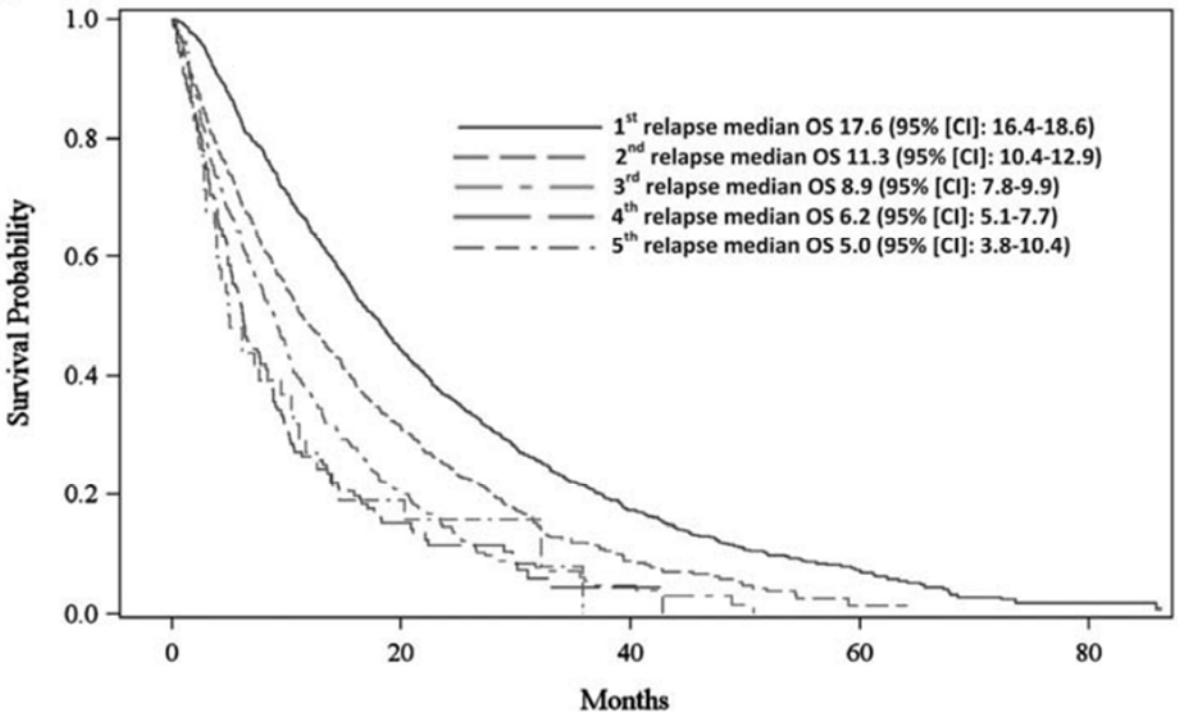
Patients typically undergo systemic treatment with repeated courses of PBC, which is associated with a poor long-term prognosis and a high risk of developing associated toxicities such as alopecia, nausea, neurotoxicity and hypersensitivity reactions. With each course of chemotherapy, the duration of response and the likelihood of continued remission decrease and ultimately patients will become resistant to treatment with platinum therapy. In one analysis,[5] a decrease in the duration of PFS (measured from the date of randomisation) was observed after each relapse, with a decrease from 10.2 months after the first relapse to 6.4 months after the second relapse and to 5.6 after the third. Similarly, median OS decreased with each subsequent relapse from 17.6 months from the first recurrence to 5.0 months for the fifth relapse. The results of these analyses are shown in Figure 3 and Figure 4.

Figure 3: Duration of PFS after subsequent relapses



Source: Hanker *et al.* 2012[5]
Abbreviations: CI, confidence interval; PFS, progression-free survival

Figure 4: Duration of OS after subsequent relapses



Source: Hanker *et al.* 2012[5]
Abbreviations: CI, confidence interval; OS, overall survival

With each relapse, the tumour is more likely to be termed platinum-resistant, at which point patients are faced with limited treatment options and poor outcomes. This once again highlights the importance of offering all patients with advanced OC, irrespective of their *BRCA* status, with clinically effective treatment options as part of the first-line treatment strategy to delay or avoid a second relapse whilst they have the opportunity to benefit most from treatment.

In patients retreated with PBC, who account for 65% of patients at first recurrence,[46,47] combination therapies with platinum re-challenge are recommended.[30,31]

Second- and subsequent-line PARP inhibitor maintenance treatment

Niraparib is currently licensed as a maintenance therapy for platinum-sensitive, relapsed, high grade OC, regardless of BRCA mutation status, who are in response (complete or partial) to PBC. In England, niraparib is available through the CDF as a maintenance treatment for advanced platinum-sensitive OC following response to second-line PBC, in patients with or without a BRCA mutation.[27] In third or subsequent lines, niraparib's use as maintenance treatment following response to PBC is limited to patients without a BRCA mutation.[27]

Olaparib tablets are licenced for the maintenance treatment of advanced, high-grade OC who are in response (complete or partial) to second-line of PBC in patients with or without a BRCA mutation.[48]

Rucaparib is licensed 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 PBC.[49]

Other maintenance treatments

Bevacizumab is an anti-angiogenic agent that binds to vascular endothelial growth factor (VEGF) to inhibit the formation of new tumour vasculature. Unlike PARP inhibitors, bevacizumab is initiated and administered in combination with chemotherapy and as such it is not used in the same way. PARP inhibitors are initiated

after chemotherapy has ceased, and only in those patients that have achieved a complete or partial response to that chemotherapy.

Bevacizumab is indicated for the first-line treatment of adult patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with carboplatin and paclitaxel. It is also indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian cancer in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel. Bevacizumab is licensed at a dose of 15mg/kg for the first-line treatment of advanced OC in combination with carboplatin and paclitaxel and continued as monotherapy.[50] Bevacizumab in combination with carboplatin and paclitaxel is not recommended by NICE for routine use in first-line treatment of advanced OC, but funding is available through the CDF for use at a dose of 7.5 mg/kg which is off-licence and below the recommended dose. The use of bevacizumab is restricted to chemotherapy-naive patients with sub-optimally debulked Stage III OC (debulked but residual disease more than 1cm) who received NACT, or Stage IV OC for a maximum of 13.5 months (18 cycles).[27]

Summary

A summary of the targeted therapies available for the maintenance treatment of OC, accompanied by clinical and cost-effectiveness recommendations, can be found in Table 4.

Table 4: Targeted agents in OC following response to PBC

Treatment	Approved indication in the UK	NICE recommendation and reimbursement	ESMO recommendation[30,44]
First-line maintenance treatment			
Olaparib (first-line)	Indicated as monotherapy for the first-line maintenance treatment of adult patients with	Recommended through the CDF for patients within marketing authorisation.[27]	Patients with recurrent HGSOC and a germline or tumour BRCA mutation should be offered maintenance

Treatment	Approved indication in the UK	NICE recommendation and reimbursement	ESMO recommendation[30,44]
	advanced BRCA-mutated (germline and/or somatic) ovarian, fallopian tube, or primary peritoneal cancer who are in response (CR or PR) to PBC.		olaparib after a response to PBC.[51]
Bevacizumab (first-line)	Bevacizumab is administered in addition to carboplatin and paclitaxel for up to six cycles of treatment followed by continued use of bevacizumab as a single agent until disease progression or for a maximum of 15 months. The recommended dose of bevacizumab is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.[52]	Not recommended for routine use in combination with chemotherapy [53] Funded through the CDF at 7.5 mg/kg (off-licence) in England for use in combination with chemotherapy in high-risk populations: Stage III sub-optimally debulked disease or requiring neoadjuvant chemotherapy due to low likelihood of optimal cytoreductive surgery, or Stage IV for a maximum of 13.5 months (18 cycles)[27]	The addition of bevacizumab is recommended for patients with advanced OC with poor prognostic features such as Stage IV or suboptimal debulking as defined in the ICON-7 trial. Bevacizumab should be given with paclitaxel or carboplatin with a treatment duration of 15 months.
Second-line or subsequent maintenance treatment			
Niraparib (second-line)	Monotherapy maintenance treatment of adult patients with	Recommended through the CDF for patients with recurrent OC.[27]	PARP inhibitors (olaparib, niraparib and rucaparib) when given as

Treatment	Approved indication in the UK	NICE recommendation and reimbursement	ESMO recommendation[30,44]
Niraparib (third or subsequent-line)	platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to PBC.[54]	Recommended through the CDF for non-gBRCAmut patients with recurrent OC.[27]	maintenance therapy following a response to platinum-based second or higher line of treatment have proven benefit with respect to PFS and are recommended by ESMO[55]
Olaparib (second-line)	Maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (CR or PR) to PBC.[48]	Recommended through the CDF for patients with BRCAmut.[27]	PARP inhibitors (olaparib, niraparib and rucaparib) when given as maintenance therapy following a response to platinum-based second or higher line of treatment have proven benefit with respect to PFS and could be recommended.
Olaparib (third or subsequent-line)		Recommended for patients with BRCAmut.[24]	
Rucaparib (second or subsequent line)	Rucaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.	Available through the CDF in line with MA[27]	PARP inhibitors (olaparib, niraparib and rucaparib) when given as maintenance therapy following a response to platinum-based second or higher line of treatment have proven benefit with respect to PFS and could be recommended.

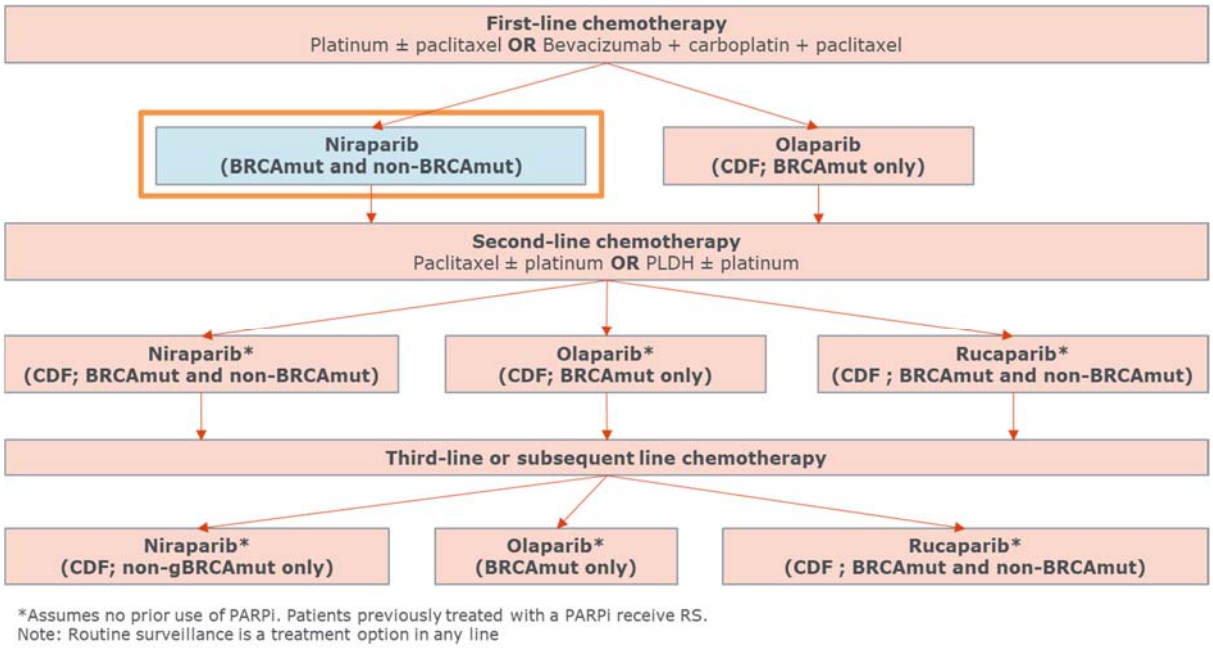
Treatment	Approved indication in the UK	NICE recommendation and reimbursement	ESMO recommendation[30,44]
Bevacizumab (relapsed setting)	In combination with gemcitabine and carboplatin or in combination with paclitaxel and carboplatin in patients who have not received previous bevacizumab therapy or other anti-VEGF therapy (licensed dose 15 mg/kg).[52]	Not recommended[53]	Bevacizumab in combination with platinum-based second-line chemotherapy (gemcitabine or paclitaxel) followed by bevacizumab maintenance has proven benefit with respect to tumour response rate and PFS and could be recommended.[44]

Abbreviations: *BRCA*, breast cancer susceptibility gene; CDF, Cancer Drugs Fund; CR, complete response; g*BRCA*, germline breast cancer susceptibility gene; HGSOC, high-grade serous ovarian cancer; MA, marketing authorisation; OC, ovarian cancer; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; PR, partial response; VEGF, vascular endothelial growth factor.

B.1.3.4 Place of niraparib in the treatment pathway

Niraparib (Zejula) is an oral, highly selective, PARP1 and PARP2 inhibitor that has been studied as maintenance therapy in adult patients with advanced high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line PBC. It is the first PARP inhibitor monotherapy to show significant clinical efficacy in the first-line maintenance setting of OC, irrespective of BRCA mutation status. Niraparib's anticipated place in the treatment pathway is presented in Figure 5, alongside the treatments available through routine commissioning and the CDF across all stages of advanced OC following PBC.

Figure 5: Proposed treatment pathway for advanced OC in line with existing NICE recommendations



Abbreviations: BRCA, breast cancer susceptibility gene; CDF, Cancer Drugs Fund; g*BRCA*, germline breast cancer susceptibility gene; OC, ovarian cancer; PLDH, Pegylated liposomal doxorubicin hydrochloride; RS, routine surveillance
Source: NICE pathways[56]

The standard of care for patients with advanced OC in England is RS after they have undergone surgery and chemotherapy. No first-line maintenance treatments are offered to patients through routine commissioning. Even with the treatment options available through CDF, 75% of patients do not have PARP inhibitor maintenance treatment options available, thus there is high unmet need in this population.

Niraparib is an oral, highly selective PARP1 and PARP2 inhibitor that has been proposed as a monotherapy maintenance treatment for adults with advanced high-grade ovarian, fallopian tube or primary peritoneal cancer that is in response (complete or partial) following completion of first-line PBC. Niraparib has demonstrated a clinical benefit in patients regardless of BRCA mutation status, as shown by increased PFS compared to RS in a broad intention-to-treat (ITT) population in the PRIMA trial, which included patients with and without a BRCA mutation.[9]

In clinical practice, due to the absence of first-line maintenance therapies recommended by NICE, niraparib is expected to be used as an alternative to RS,

irrespective of BRCA mutation status, to extend PFS and maintain quality of life for patients earlier in the treatment pathway prior to disease relapse.

The recommendation of niraparib after first-line chemotherapy treatment would present an opportunity to extend the time to relapse at a critical junction for patients with respect to long-term outcomes, as currently there are no oral maintenance treatment options available irrespective of BRCA mutation status.

B.1.4 Equality considerations

There are no known equality issues relating to the use of niraparib in patients with advanced OC following response to first-line PBC.

B.2 Clinical effectiveness

Summary of clinical effectiveness

- The clinical effectiveness for niraparib is based on the PRIMA trial. PRIMA is a robust, high quality, randomised, double-blinded, placebo-controlled, multi-centre, phase 3 trial to assess the efficacy and safety of niraparib maintenance treatment in advanced, high grade OC following response to first-line PBC. Patients were randomly assigned in a 2:1 ratio to receive either niraparib (n=487) or placebo (n=246) once daily and had a median duration of follow-up of 13.8 months.
- The niraparib and placebo groups were well-matched, with both groups having a median age of 62 years and a similar distribution of patients across FIGO disease stages, ECOG scores and the use of neoadjuvant chemotherapy. All patients had high-grade serous or endometrioid tumours that were classified as FIGO Stage III or IV and had completed between six and nine cycles of platinum-based chemotherapy. Patients received study treatment until disease progression or death, or until the patient reached the trial specified stopping rule (3 years).
- PRIMA demonstrated that niraparib met the primary endpoint of prolonging median PFS compared to placebo in the ITT population. Niraparib statistically significantly reduced the risk of disease progression or death by 38% versus placebo (HR: 0.62; 95% CI 0.50, 0.76; p<0.0001).
- Furthermore, the median PFS was statistically significantly longer in the niraparib group compared to the placebo group, at 13.8 months vs 8.2 months respectively. This provided patients treated with niraparib a median increase of 5.6 months living without disease progression or death compared to those treated with placebo and routine surveillance.
- Subgroup analyses demonstrated that the reduction in the risk of disease progression or death is maintained across all cohorts. Once licensed, niraparib would be the only PARP inhibitor available for first-line maintenance monotherapy treatment that leads to a statistically significant reduction in the risk of disease progression or death for all advanced patients with OC, regardless of BRCA mutation status.
- Maintenance treatment with niraparib led to a statistically significant reduction in the risk of receiving first subsequent anticancer therapy or death. In line with the results for median PFS, niraparib statistically significantly improved TFST

(HR 0.65; 95% CI 0.52, 0.80; [redacted]). At the time of database lock, the data maturity of TFST was 47%.

- Data for PFS2 are immature; at the time of database lock data maturity was only 20%. However, a numerical benefit in PFS2 was observed for patients treated with niraparib (HR 0.81; 95% CI 0.58, 1.14).
- OS data are immature, with 48 (9.9%) and 31 (12.6%) events occurring in the niraparib and placebo groups respectively. A numerical benefit in OS was observed for patients treated with niraparib (HR 0.70; 95% CI 0.44, 1.11). The PRIMA trial is ongoing, with anticipated completion in [redacted], and additional OS data will be available over the coming years.
- Maintenance treatment with niraparib confers clinical benefits without negatively impacting patients' quality of life. Patient reported outcomes remained consistent throughout the trial duration and were not statistically significantly different between patients treated with niraparib and those treated with placebo.
- Niraparib was well tolerated and demonstrated an acceptable safety profile, as evidenced in previous studies. In most cases, AEs were managed through dose reductions. Patients who initiated treatment on an individualised dose experienced a lower incidence of AEs, without a statistically significant loss of efficacy.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant literature regarding the efficacy and safety of maintenance treatment following first-line PBC. Evidence specifically addressing the NICE scope and relevant to niraparib use in the UK was included. Full details of the methodology and results of the SLR are detailed in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

PRIMA was the only identified randomised controlled trial (RCT) to evaluate the clinical efficacy and safety of niraparib as a maintenance treatment of advanced OC after response to first-line PBC. The clinical data and cost-effectiveness analyses presented in this submission are therefore based on this RCT.

Table 5: Clinical effectiveness evidence

Study	PRIMA (PRIMA/ENGOT-OV26/GOG-3012); ClinicalTrials.gov number: NCT02655016; Gonzalez-Martin A. et al. (2019)				
Study design	A randomised, double-blind, placebo-controlled, multicentre, international phase 3 trial.				
Population	Adult patients with newly diagnosed, histologically confirmed high-grade serous or endometrioid tumours of the ovary, peritoneum, or fallopian tube (collectively defined as OC), FIGO Stage III or IV, and who were in response (complete or partial) to first-line PBC. (N=733)				
Intervention(s)	Niraparib (N=487)				
Comparator(s)	Placebo (N=246)				
Indicate if trial supports application for marketing authorisation	Yes	□	**Indicate if trial used in the economic model**	Yes	□
	No			No	
Rationale for use/non-use in the model	PRIMA provides efficacy and safety data concerning the use of niraparib as a maintenance treatment following a response to first-line platinum-based chemotherapy				
Reported outcomes specified in the decision problem	• OS • PFS • PFS2 • TFST • HRQoL • AEs				
All other reported outcomes	N/A				

Abbreviations: AEs, adverse events; HRQoL, health related quality of life; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival-2 (time from the date of randomisation to the date of disease progression on the next anti-cancer therapy following study treatment or death); TFST, time to first subsequent treatment

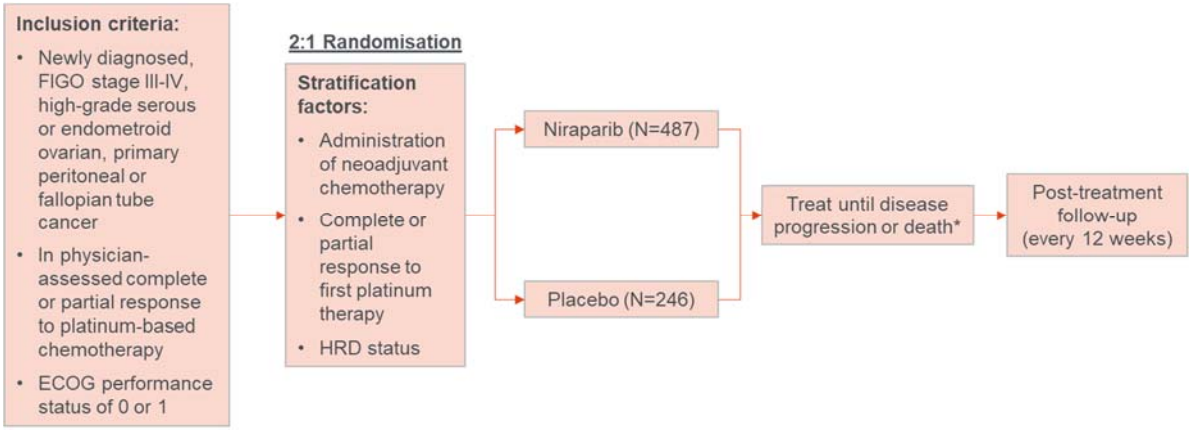
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 *Trial design*

PRIMA was a global (20 countries, 181 clinical sites) randomised, double-blind, multicentre, placebo-controlled, phase 3 trial conducted to assess the efficacy and safety of niraparib in patients with newly diagnosed, advanced (Stage III or IV), high-grade serous or endometrioid OC who had a complete or partial response to first-line PBC.

Information regarding the PRIMA trial has been taken from the published article in the peer-reviewed New England Journal of Medicine, supplemented with information from the clinical study report (CSR).[57,58]

Figure 6: PRIMA study schematic



Source: PRIMA CSR[57]
*A treatment stopping rule of 3 years was recommended in the trial protocol.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency

Patients underwent screening procedures within 28 days prior to randomisation. Randomisation was performed in a double-blind, 2:1 (niraparib to placebo) manner with the use of an interactive Web-response system. Stratification was conducted according to clinical response after first-line PBC (complete or partial response), receipt of neoadjuvant chemotherapy (yes or no), and tumour homologous recombination (HR) status (deficient or others; proficient/not known) as assessed by a clinical trial assay developed by Myriad Genetics, Inc. Patients received randomised oral treatment (niraparib or placebo appearance-matched capsules) as once daily doses in continuous 28-day cycles in a double-blind fashion.

Eligibility criteria

Patients were eligible for inclusion in the PRIMA trial if they had newly diagnosed, FIGO Stage III or IV, high-grade serous or endometrioid ovarian, fallopian tube or primary peritoneal cancer, and were in complete or partial response to first-line PBC. Patients with Stage III disease were eligible to enrol if they had visible residual tumour after primary cytoreductive surgery (PCS), interval cytoreductive surgery or inoperable

disease. Patients who had complete cytoreduction (NVRD) after PCS were excluded from the trial; these patients have been shown to have an improved survival prognosis.[59,60]

Additional details regarding the inclusion and exclusion criteria of patients entering the PRIMA trial are presented in Table 6.

Table 6: PRIMA inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Female, ≥18 years of age • Histologically diagnosed high-grade serous or endometrioid, or high-grade predominantly serous or endometrioid ovarian cancer, fallopian tube cancer, or primary peritoneal cancer that was FIGO Stage III or IV • Previously received neoadjuvant chemotherapy if the post-chemotherapy tumour grade was not evaluable • Surgical criteria: o Inoperable Stage III and IV disease OR o Stage IV with operable disease OR o Stage III or IV disease treated with neoadjuvant chemotherapy and interval cytoreductive surgery OR o Stage III disease who had visible residual disease after primary cytoreductive surgery • Completed ≥6 and ≤9 cycles of PBC with a physician assessed CR or PR after ≥3 cycles of therapy • Received ≥ 2 post-operative cycles of PBC following interval cytoreductive surgery • CA-125 in the normal range or CA-125 decrease by more than 90% during their first-line therapy that was stable for at	• Mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer • Stage III patients who had complete cytoreduction (i.e. no visible residual disease) after primary cytoreductive surgery • Patients who had undergone >2 cytoreductive surgeries • Patients who had received prior treatment with a known PARP inhibitor or had participated in a study where any treatment group included administration of a known PARP inhibitor • Patients who were scheduled to receive bevacizumab as maintenance treatment. (Patients who had received bevacizumab with their first-line platinum-based therapy, but were unable to receive bevacizumab as maintenance therapy due to AEs or for any other reason were not excluded from study as long as the last dose of bevacizumab was received ≥28 days prior to signing the main informed consent form) • Patient was pregnant, breastfeeding or expecting to conceive while on study treatment and up to 180 days after last

Inclusion criteria	Exclusion criteria
least 7 days (i.e. no increase >15% from nadir) • HRD test result (Myriad Genetic's MyChoice test) was required for randomisation and stratification • ECOG performance status of 0 or 1 • Adequate organ function defined as: o Absolute neutrophil count ≥1,500/μL o Platelets ≥100,000/μL o Haemoglobin ≥10 g/dL o Serum creatinine ≤1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥60 mL/min using the Cockcroft-Gault equation o Total bilirubin ≤1.5 × ULN o Aspartate aminotransferase and alanine aminotransferase ≤2.5 × ULN unless liver metastases are present, in which case they must be ≤5 × ULN	dose of study treatment

Source: PRIMA CSR[57]
Abbreviations: AE: Adverse event; CR: complete response; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynaecology and Obstetrics; HRD: homologous recombination deficiency; PARP: Poly-ADP ribose polymerase; PBC: Platinum-based chemotherapy; PR: partial response; ULN: Upper Limit of Normal

Interventions

Provided that the patient was receiving benefit and did not meet any other criteria for discontinuation, as defined in the study protocol, niraparib (N=484) or placebo (N=244) were administered continuously until the objective identification of disease progression, completion of treatment (defined as three years) or death, whichever occurred first. Treatment discontinuation was recommended after three years in the study protocol, however, patients were allowed to continue to receive treatment beyond this point if they were still deriving clinical benefit, as assessed by the investigator. Patients receiving placebo were not allowed to cross over to receive treatment with niraparib during the trial.

Concomitant medications were permitted; details of prior and concomitant medication were recorded in the electronic case report form. Any medication that the patient was taking on or after the date of first study drug administration other than the study treatment, including herbal and other non-traditional remedies, was considered a concomitant medication. No other anticancer therapy was permitted during the course of the study treatment for any patient. Palliative radiotherapy (excluding the pelvic region and/or palliative radiotherapy encompassing > 20% of the bone marrow within 1 week of the first dose of study treatment) was allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics, as long as no evidence of disease progression was present. Patients were advised that live virus and bacterial vaccines should not be administered to patients in the study. Prophylactic cytokines (granulocyte colony-stimulating factor) were not permitted to be administered in the first cycle of the study but could be administered in subsequent cycles according to local guidelines.

Starting dose and dose reductions

The initial starting dose for patients on niraparib was a fixed dose of 300mg once daily; however, a retrospective, exploratory multivariable analysis on the use of niraparib in the relapsed setting indicated that baseline body weight and platelet counts were each identified as predictors of early dose modification in patients treated with niraparib at 300 mg once daily. Patients with a body weight <77 kg or platelet counts <150,000/μL at baseline had higher rates of grade 3 thrombocytopenia (35% versus 12%) and were more likely to require early dose modification.

Therefore, the PRIMA protocol was amended on 27 November 2017 to incorporate individualised dosing for patients. After this date, patients with a baseline body weight of <77 kg, a platelet count of <150,000/μL, or both, were given a starting dose of 200 mg once daily. It is anticipated that the licence for niraparib will use individualised dosing, though it is expected that the standard starting dose will be 200 mg once daily, with the dose increased to 300 mg once daily for patients with baseline bodyweight ≥77 kg and platelet count ≥150,000/μL.

Additionally, dose interruption and/or reduction was implemented at any time during PRIMA, at the investigator's discretion, for any grade toxicity considered intolerable by the patient. Dose interruptions and/or reductions were mandated for haematologic toxicities and defined in the protocol. If a grade 3 or 4 non-haematologic toxicity, as outlined in Table 7, was appropriately resolved to baseline or ≤ grade 1 within 28 days of interruption, the patient could restart treatment with niraparib at a reduced dose. If the event recurred at a similar or worse grade, treatment was interrupted again and, upon resolution, a further dose reduction was made. The dose reduction schedules are outlined in Table 8.

Table 7: Dose modifications for haematologic adverse reactions

Adverse reaction	First occurrence
Platelet count <100,000/μL	Withhold treatment for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. If first occurrence and platelet count was <75,000/μL, resume at a reduced dose after recovery. Discontinue treatment if adverse reaction does not resolve in 28 days. Resume treatment at same or reduced dose as per Table 8.
Neutrophil count <1000/μL or haemoglobin <8 g/dL	Withhold treatment for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1500/μL or haemoglobin returns to ≥9 g/dL. Discontinue treatment if adverse reaction does not resolve in 28 days. Resume study treatment at a reduced dose as per Table 8.
Haematologic adverse reaction requiring transfusion	For patients with a platelet count ≤10,000/μL, platelet transfusion should be considered. Resume study treatment at a reduced dose as per Table 8.

Source: PRIMA CSR[57]

Table 8: Dose reduction schedule

Dose level	Initial dose: 3 capsules/day	Initial dose: 2 capsules/day
Starting dose	3 capsules once daily (300 mg/day)	2 capsules once daily (200 mg/day)
First dose reduction	2 capsules once daily (200 mg/day)	1 capsule once daily (100 mg/day)
Second dose reduction	1 capsule once daily (100 mg/day)	Patient must discontinue treatment

Source: PRIMA CSR [57]

The percentage of patients receiving each of the different doses throughout the first 12 months of treatment is shown in Figure 7. As demonstrated in Section B.2.7, no statistically significant difference in efficacy was observed in patients treated with a reduced dose.

Figure 7: Percentage of patients in Safety population of PRIMA ITT receiving either 100 mg, 200 mg or 300 mg of niraparib QD at each month of treatment

If the haematologic toxicity did not recover to the specified levels in Table 7 within 28 days of the dose interruption period, or if the patient had already undergone the maximum number of dose reductions, the patient was required to permanently discontinue study treatment.

Outcomes

The primary efficacy endpoint was PFS as assessed by blinded, independent, central review (BICR), defined as the time from the date of treatment randomisation to the date of first documentation of progression or death due to any cause in the absence of documented progression, whichever occurred first. Determination of radiological

progression was based on imaging assessments according to Response Evaluation Criteria in Solid Tumours v.1.1 (RECIST), and clinical progression was determined through a combination of diagnostic tests and clinical signs and symptoms, plus raised CA-125 levels. Investigator assessed (IA) PFS was included in the trial as a sensitivity analysis.

The following secondary endpoints were assessed:

- OS, defined as the time from the date of randomisation to the date of death by any cause;
- TFST, defined as the time from the date of randomisation to the date of the first subsequent anticancer therapy or death, whichever occurred first;
- PFS2; defined as the time from the date of randomisation to the date of disease progression on the next anti-cancer therapy following study treatment or death by any cause, whichever occurred first;
- Changes over time in patient-reported health-related quality of life (HRQoL) were assessed using the Functional Assessment of Cancer Therapy–Ovarian Symptoms Index (FOSI) (total score), European Quality of Life Scale, 5 Dimensions, (EQ-5D-5L) (Visual Analogue Scale score and EQ-5D index value), European Organisation for Research and Treatment of Cancer Quality of Life of Cancer patients questionnaire (EORTC-QLQ-C30) (subscale scores) and ovarian cancer patients questionnaire EORTC-QLQ-OV28 (subscale scores).

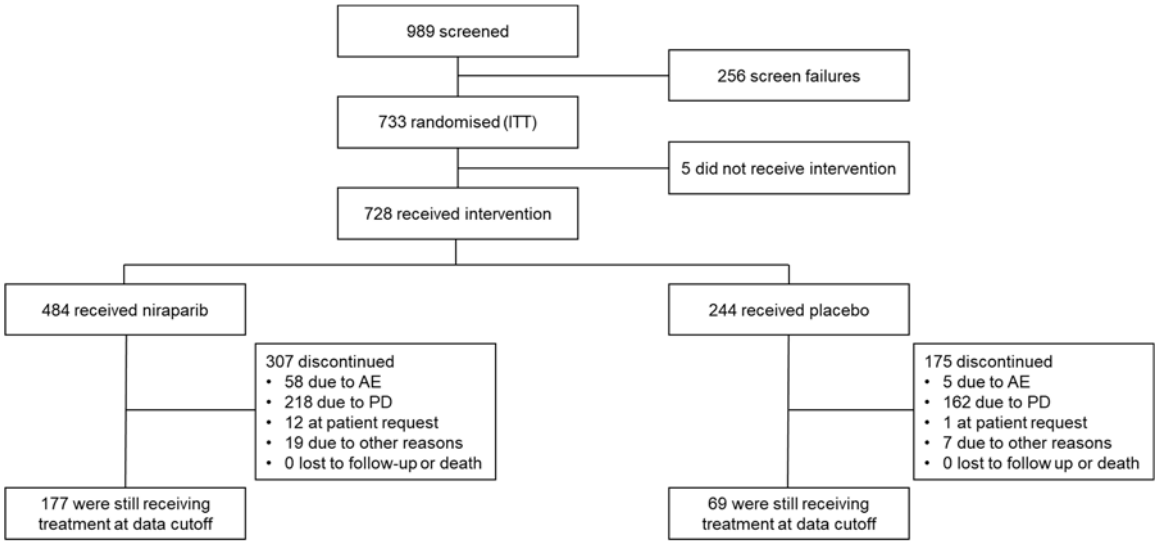
Safety parameters evaluated included the following: treatment-emergent adverse events (TEAEs), clinical laboratory results (haematology, chemistry), vital sign measurements, observations during physical examination, and use of concomitant medications. Treatment emergent AEs (TEAEs) were defined as all AEs or worsening of pre-existing conditions that occurred on or after the start of treatment until the end of 30 days following the last dose of study treatment or when the subject initiated a new chemotherapy regimen, whichever came earlier.

B.2.3.2 *Trial population*

Disposition of patients

A total of 989 patients were screened and 733 patients were randomised into the study and included in the efficacy population. Consistent with the 2:1 randomisation, 487 patients were randomised to niraparib and 246 subjects were randomised to placebo. Five patients did not receive study drug after randomisation and were excluded from the safety analyses. Of the 487 patients randomised to niraparib, 3 patients did not receive treatment; therefore 484 patients received treatment with niraparib. In the placebo group, 2 of the 246 patients randomised did not receive treatment, leaving 244 patients in the placebo group. The disposition of patients within the trial is shown in Figure 8.

Figure 8: Subject disposition flowchart



Source: PRIMA CSR[57] (Adapted from Figure 2)

At the time of the data cut-off (17 May 2019), the median duration of follow-up was 13.8 months. Of the 487 patients randomised to niraparib, 63.0% (n = 307) had discontinued study treatment as had 71.1% (n = 175) of the 246 subjects randomised to placebo. Overall, the primary reason for discontinuation from treatment was disease progression, reported in 44.8% subjects randomised to niraparib compared to 65.9% subjects randomised to placebo. In all enrolled subjects, adverse events leading to discontinuation from treatment occurred in 11.9% of subjects randomised to niraparib

and 2.0% of subjects randomised to placebo. No on-treatment deaths were reported. As of the data cut-off date, 36.3% (n = 177) subjects randomised to niraparib and 28.0% (n = 69) subjects randomised to placebo remained on study treatment.

A smaller proportion of patients treated with niraparib ([redacted]) discontinued from study compared to patients treated with placebo ([redacted]). The reasons for discontinuation from study were death (9.9% for niraparib and 12.3% for placebo), withdrawal of consent ([redacted]), loss to follow-up ([redacted]), and other ([redacted]). One subject ([redacted]) was discontinued from the study because of the Sponsor's decision to terminate the study at one site.

Baseline characteristics

Patients were randomised and stratified for clinical response after first-line PBC, receipt of neoadjuvant chemotherapy, and tumour HR status as these characteristics were considered to influence the prognosis of patients. The niraparib and placebo arms were well-matched with a median age of 62 years in the niraparib and placebo arms of the ITT population. The treatment arms were also evenly matched with respect to patients' functional performance status; in the ITT population, 69.2% of patients in the niraparib group and 70.7% in the placebo group were classified with an ECOG score of 0, whilst the remaining 30.8% and 29.3% of patients achieved an ECOG score of 1 in each group respectively. The proportions of patients receiving neoadjuvant chemotherapy prior to study treatment were evenly matched: 66.1% in the niraparib group compared to 67.9% in the placebo group.

Table 9: Baseline characteristics of the ITT patient population in the PRIMA trial

Characteristic	Niraparib (N=487)	Placebo (N=246)
Median age, years (range)	62 (32-85)	62 (33-88)
Median weight, kg (range)	66.00 (38.0-137.0)	65.55 (37.8-146.5)

(continues)

Characteristic	Niraparib (N=487)	Placebo (N=246)
Race – no. (%)		
White	436 (89.5)	219 (89.0)
Black	10 (2.1)	2 (0.8)
Asian	14 (2.9)	11 (4.5)
American Indian or Alaska Native	1 (0.2)	0
Native Hawaiian or Other Pacific Islander	1 (0.2)	0
Unknown	6 (1.2)	1 (0.4)
Not reported	19 (3.9)	13 (5.3)
ECOG score - no. (%)		
0	337 (69.2)	174 (70.7)
1	150 (30.8)	72 (29.3)
International FIGO stage - no. (%)		
III	318 (65.3)	158 (64.2)
A	7 (1.4)	4 (1.6)
B	16 (3.3)	12 (4.9)
C	285 (58.5)	138 (56.1)
Not specified	10 (2.1)	4 (1.6)
IV	169 (34.7)	88 (35.8)
Primary tumour location - no. (%)		
Ovary	388 (79.7)	201 (81.7)
Fallopian tube	65 (13.3)	32 (13.0)
Peritoneum	34 (7.0)	13 (5.3)
Histologic type - no. (%)		
Serous	465 (95.5)	230 (93.5)
Endometrioid	11 (2.3)	9 (3.7)
Other	11 (2.3)	6 (2.4)
Receipt of neoadjuvant chemotherapy - no. (%)		
Yes	322 (66.1)	167 (67.9)
No	165 (33.9)	79 (32.1)
Clinical response after platinum-based chemotherapy - no. (%)		
Complete response	337 (69.2)	172 (70.0)
Partial response	150 (30.8)	74 (30.0)
Cancer antigen 125 level - no. (%)		
≤ ULN	450 (92.4)	226 (91.9)
> ULN	34 (7.0)	18 (7.3)

Characteristic	Niraparib (N=487)	Placebo (N=246)
Missing data	3 (0.6)	2 (0.8)
No. of cycles of platinum-based chemotherapy - no. (%)		
6	333 (68.4)	170 (69.1)
7-9	124 (25.5)	62 (25.2)
Missing data	30 (6.2)	14 (5.7)

Source: PRIMA CSR [57]
Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; ITT, intention-to-treat

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

PRIMA efficacy and safety analyses were performed in accordance with a comprehensive Statistical Analysis Plan, which is summarised in the CSR.[57]

B.2.4.1 *Analysis populations*

The following analysis sets were defined in the PRIMA study. The ITT population was the primary set for all efficacy analyses. All results focus on the ITT and safety (SAF) populations; data from the per-protocol (PP) population is not presented.

- **ITT population** was defined as all patients randomised into the study. The ITT population is the primary population for efficacy analyses. For this analysis, patients were analysed as randomised. Patients who were incorrectly stratified during randomisation were analysed and presented under the stratum assigned during randomisation.

- **SAF population** was defined as all patients who received at least 1 dose of study drug. Patients were analysed as treated. Patients receiving treatment from more than one treatment group were accounted for based on their first study treatment.

B.2.4.2 *Determination of sample size*

In the original study design for the PRIMA trial, before clinical benefits had been demonstrated in both homologous recombination deficient (HR-d) and homologous

recombination proficient (HR-p) patients, HR-d patients were the primary group to be investigated, and as such the study was powered to identify an interaction treatment effect with homologous recombination status.[19] It was determined that, for the HR-d placebo group, to detect an expected benefit corresponding to hazard ratio of 0.5 with 90% power and a 2:1 randomisation ratio, 99 PFS events were required. It was projected that approximately 50% of all subjects randomised were HR-d. Therefore, enrolment of approximately 620 subjects (310 with HRD) was needed to complete the study in approximately 44 months. This assumed that 15% of subjects would not provide a PFS event for the primary endpoint due to loss to follow-up or discordance between investigator and central reviewer.

B.2.4.3 *Primary efficacy analysis*

A hierarchical testing for the PFS endpoint was used to control the overall Type I error rate. First, the analysis of PFS was conducted in HR-d patients at the 1-sided alpha level of 0.025. If the result was positive, PFS analysis was conducted in the ITT population with the 1-sided alpha level of 0.025; otherwise, PFS analysis was to become exploratory in the ITT population.

PFS was compared between treatment groups using a stratified log rank test using the randomisation stratification factors (i.e. administration of neoadjuvant therapy, best response to platinum therapy, and HRD test status). The hazard ratio (HR) and 2-sided 95% confidence interval (CI) were derived from a stratified Cox proportional hazards model to estimate treatment effect. Graphical displays using Kaplan-Meier (KM) methods were used.

Sensitivity analyses were performed on PFS to assess the robustness of the primary analysis outcome. Analyses of PFS were conducted across demographic and baseline characteristics, including but not limited to age, race, region, and ECOG performance status.

B.2.4.4 *Secondary efficacy analysis*

All time-to-event endpoints for which results were reported were analysed in the same manner as for PFS and based on the ITT population; these included TFST, PFS2, and OS.

B.2.4.5 *Safety analysis*

Safety analyses were conducted using the SAF population. The severity of the toxicities was graded by the Investigator according to the National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) v4.03. Any AEs leading to death or discontinuation of study treatment, events classified as NCI CTCAE v4.03 Grade 3 or higher, study treatment-related events, and SAEs were presented.

The relationship of each AE to the study drug was summarised as assessed by the investigator. Related TEAEs were defined as TEAEs considered possibly related or related to treatment as judged by the investigator. Any TEAEs for which the relationship to study drug was missing was considered as related.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The PRIMA trial is a randomised, double-blinded, placebo-controlled trial. The quality assessment of this trial is noted in Table 10.

Table 10: Quality assessment of PRIMA

Quality assessment	PRIMA	Notes
Was randomisation carried out appropriately?	Yes	Randomisation was performed in a double-blinded manner with the use of an interactive Web-response system, with stratification according to clinical response to PBC, receipt of neo-adjuvant chemotherapy, and status of HRD status.

Quality assessment	PRIMA	Notes
Was the concealment of treatment allocation adequate?	Yes	The identity of the treatments was concealed by the use of study treatments that were identical in appearance, packaging, labelling, and schedule of administration. Patients and investigators were only unblinded to homologous recombination deficiency testing results or study treatment in cases associated with important medical reasons, as determined by the investigator, and for specific non-urgent medical events. The process for unblinding the identity of the assigned treatment was outlined in the Pharmacy Manual. Patients who required unblinding were discontinued from study treatment but were to remain on study until progression or death, withdrawal of consent, or loss to follow-up.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Baseline characteristics were well balanced in each cohort. Stratification at randomisation was used in the PRIMA study to mitigate any potential imbalance in baseline characteristics or prognostic factors that could impact treatment effect.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	The objective assessment of progressive disease was determined by central radiologic and clinical review in a blinded manner, according to RECIST. Study patients, Investigators, study staff, and the Sponsor's study team and its representatives were blinded to the patient's central homologous recombination deficiency testing status and identity of the assigned treatment from the time of randomisation until final database lock. Patients and investigators were not unblinded to homologous recombination deficiency testing results or study treatment except in cases associated with important medical reasons as determined by the Investigator and for specific non-urgent medical events. Patients who required unblinding were discontinued from study treatment but were to remain on study until progression or death, withdrawal of consent, or loss to follow-up.

Quality assessment	PRIMA	Notes
Were there any unexpected imbalances in drop-outs between groups?	No	Among all enrolled patients, 90 (18.6%) patients randomised to niraparib and 55 (22.5%) patients randomised to placebo had discontinued from the study by the time of data cut-off. The reasons for discontinuation from study were death (9.9% for niraparib and 12.3% for placebo), withdrawal of consent (7.4% for niraparib and placebo), lost to follow-up (0.2% for niraparib and 0.4% for placebo), and other (0.8% in niraparib and 2.5% in placebo).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All primary and secondary endpoint analyses are reported in the published PRIMA manuscript.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes, the ITT population is the primary population for efficacy analyses which is referred to as the “overall” population in the PRIMA publication.
Did the authors of the study publication declare any conflicts of interest?	No	None reported

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 *Duration of follow-up*

PFS results for the PRIMA trial are reported for a median duration of follow-up of 13.9 months (CI 13.8, 16.0) and 13.8 months (CI 13.6, 14.1) for the niraparib and placebo groups respectively for patients in the ITT population.

B.2.6.2 *Primary efficacy outcome: PFS*

Maintenance treatment with niraparib led to a statistically significant reduction in the risk of disease progression or death by 38% versus placebo in the ITT population (HR: 0.62; 95% CI 0.50, 0.76; p<0.0001). Results from PRIMA demonstrate that niraparib met the primary endpoint of prolonging PFS compared to placebo in the ITT population. Median PFS was statistically significantly longer in the niraparib group compared to the placebo group, at 13.8 months vs 8.2 months respectively. This provided patients treated with niraparib a median increase of 5.6 months living without

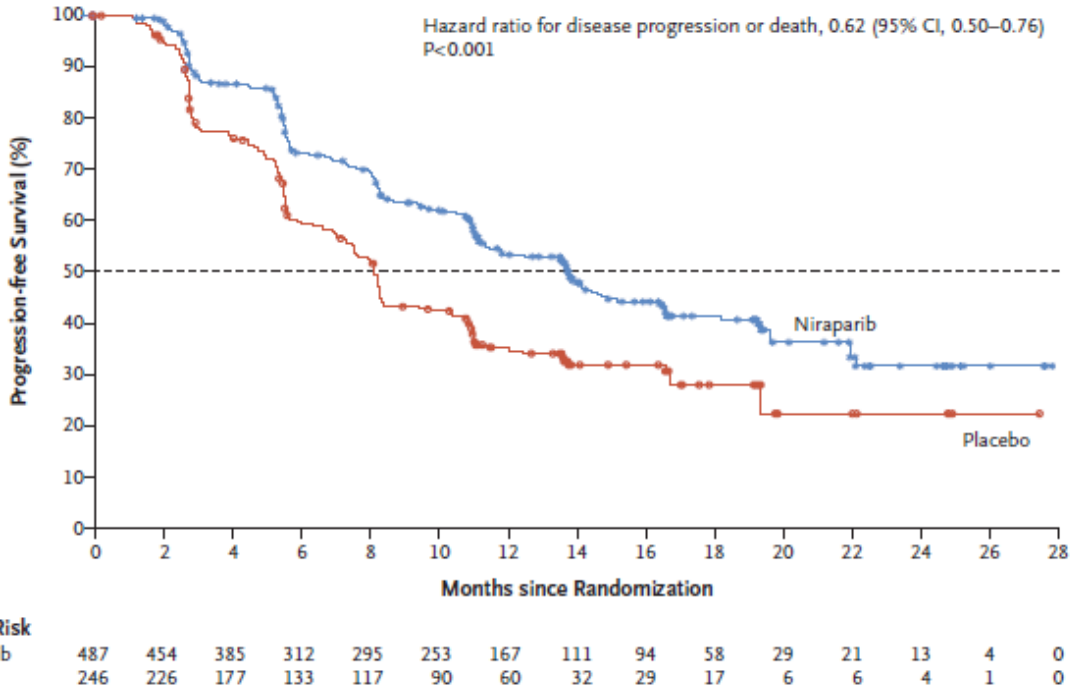
disease progression or death compared to those treated with placebo. A smaller proportion of patients in the niraparib treatment group had progressed or died compared to those in the placebo group (47.6% versus 63.0%). The results of this analysis are summarised in Table 11. The KM plots for PFS with niraparib and placebo are presented in Figure 9.

Table 11: Progression-free survival based on BICR in the ITT population

PFS based on BICR (months)	Niraparib (N=487) n (%)	Placebo (N=246) n (%)
Median (95% CI)	13.8 (11.5,14.9)	8.2 (7.3,8.5)
Censored observations, n (%)	255 (52.4)	91 (37.0)
Event rate, n (%)	232 (47.6)	155 (63.0)
p-value	<0.0001	
Hazard ratio (95% CI)	0.62 (0.502,0.755)	

Source: CSR
Abbreviation: BICR, blinded independent central review; CI, confidence interval

Figure 9: Kaplan-Meier plot of PFS in ITT population



Source: CSR [57]
Abbreviations: ITT, intention-to-treat; PFS, progression-free survival

Patients treated with niraparib maintained a lower risk of death or progression throughout their follow-up period compared to those treated with placebo.

Furthermore, these benefits in PFS occurred early in the treatment period, with a distinct separation between the KM plots for niraparib and placebo demonstrated at the time of the first screening assessment (12 weeks). There was no evidence of a change in the shape of the KM plots over the treatment period, indicating that the effect of treatment on PFS does not wane over time.

Patients underwent computed tomography (CT) or magnetic resonance imaging (MRI) scans at screening and every 12 weeks until confirmation of disease progression by BICR. The three-monthly scans offer some explanation for the “steps” at three monthly intervals on the KM curves.

Sensitivity analysis for PFS

The PFS benefit of niraparib compared to placebo was demonstrated in pre-planned sensitivity analyses. The sensitivity analyses of PFS were highly consistent with the primary efficacy results for PFS, with HRs ranging from 0.60 to 0.64, and these results were statistically significant for every analysis (p<0.0001). The IA PFS results are closely aligned with the BICR PFS results which indicates a robust and consistent set of PFS results, with confidence in the improvements gained by patients treated with niraparib over those treated with placebo. In the niraparib group, the IA median PFS was 13.8 months (CI 11.3, 14.2) compared to the BICR assessed PFS of 13.9 months (CI 11.5, 14.9). A summary of the sensitivity analyses conducted is displayed in Table 12.

Table 12: Sensitivity analyses of PFS results for ITT population

	Niraparib (N=487)	Placebo (N=246)
Investigator assessment (ITT population)		
Median (months)(95% CI)	13.8 (11.3,14.2)	8.2 (7.6,9.8)
p-value	<0.0001	
Hazard ratio (95% CI)	0.63 (0.514,0.763)	
Alternative censoring rules (ITT population)		
Median (months)(95% CI)	[redacted]	[redacted]
p-value	[redacted]	
Hazard ratio	[redacted]	
Stratification values from the prior treatment eCRF (PP population)		
Median (months)(95% CI)	[redacted]	[redacted]

	Niraparib (N=487)	Placebo (N=246)
p-value	[redacted]	
Hazard ratio	[redacted]	
Alternative event times (ITT population)		
Median (months)(95% CI)	[redacted]	[redacted]
p-value	[redacted]	
Hazard ratio	[redacted]	
BICR radiology data (ITT population)		
Median (months)(95% CI)	[redacted]	[redacted]
p-value	[redacted]	
Hazard ratio	[redacted]	
Stratification values from the prior treatment eCRF (PP population)		
Median (months)(95% CI)	[redacted]	[redacted]
p-value	[redacted]	
Hazard ratio	[redacted]	
Subsequent anticancer therapy (ITT population)		
Median (months)(95% CI)	[redacted]	[redacted]
p-value	[redacted]	
Hazard ratio	[redacted]	
Alternative Randomisation Stratification Factors (ITT population)		
Median (months)(95% CI)	[redacted]	[redacted]
p-value	[redacted]	
Hazard ratio	[redacted]	

Source: CSR [57]
Abbreviations: BICR: blinded independent central review; eCRF: electronic case report form; ITT: intention-to-treat; PFS: progression-free survival

B.2.6.3 *Secondary efficacy outcomes*

A summary of the key secondary efficacy endpoints for niraparib versus placebo can be found in Table 13.

Niraparib led to a statistically significant reduction in the risk of receiving first subsequent anticancer therapy or death. In line with the results for PFS, niraparib statistically significantly improved TFST (HR 0.65; 95% CI 0.521, 0.802; p<0.0001). At the time of database lock, the data maturity of TFST was 47%, which is more mature than results for PFS2.

Data for PFS2 are immature but show a numerical benefit for niraparib (HR 0.81; 95% CI 0.577, 1.139; [redacted]). As of the data cut-off of 17 May 2019 for reporting, in the ITT population, 81.1% of niraparib treated patients and 78.5% of placebo treated patients were censored; as such, the data maturity is only 20%. The niraparib group of the ITT population achieved a median PFS2 of [redacted] months. The median PFS2 in the placebo group was not estimable due to the immaturity of the data. Patients in the PRIMA trial were eligible for subsequent treatment with PARP inhibitors, which would increase PFS2. Since more patients on placebo received subsequent PARP inhibitor treatment than patients on niraparib (niraparib: 1.4%, placebo, 4.5%) this analysis is somewhat biased in favour of placebo.

OS data are immature, with 48 (9.9%) and 31 (12.6%) events occurring in the niraparib and placebo groups respectively. Data for median OS are currently immature but demonstrate a numerical benefit in favour of treatment with niraparib (HR 0.70; 95% CI 0.44, 1.11; [redacted]). In the interim analysis of the key secondary endpoint of OS (performed after the deaths of 79 of 733 patients [10.8%] in the ITT population), the median estimated KM probability of survival at 24 months was 84% in the niraparib group and 77% in the placebo group (HR for death, 0.70; 95% CI 0.44, 1.11). The OS for the ITT population is summarised in Figure 10.

OS results for the PRIMA trial are reported for a median duration of follow-up of [redacted] months (CI: [redacted]) and [redacted] months (CI: [redacted]) for the niraparib and placebo groups respectively for patients in the ITT population.

Table 13: Secondary efficacy endpoint efficacy outcomes for the ITT population

	Niraparib (N=487)	Placebo (N=246)
Time to First Subsequent Therapy		
Median TFST (95% CI)	18.6 ([redacted])	12.0 ([redacted])
Censored observations, n (%)	[redacted]	[redacted]
Event rate, n (%)	[redacted]	[redacted]
p-value	0.0001	
Hazard ratio (95% CI)	0.65 (0.521,0.802)	
Progression-Free Survival 2		
Median PFS2 (95% CI)	[redacted]	[redacted]
Censored observations, n (%)	[redacted]	[redacted]

	Niraparib (N=487)	Placebo (N=246)
Event rate, n (%)	[redacted]	[redacted]
p-value	[redacted]	
Hazard ratio (95% CI)	0.81 (0.577,1.139)	
Overall Survival		
Median OS (95% CI)	[redacted]	[redacted]
Censored observations, n (%)	[redacted]	[redacted]
Event rate, n (%)	48 (9.9)	31 (12.6)
p-value	[redacted]	
Hazard ratio (95% CI)	0.70 (0.442,1.106)	

Source: CSR [57]
Abbreviation: CI, confidence interval; ITT, intention-to-treat; NE, not estimable; OS, overall survival; PFS2, progression-free survival 2; TFST, time to first subsequent therapy

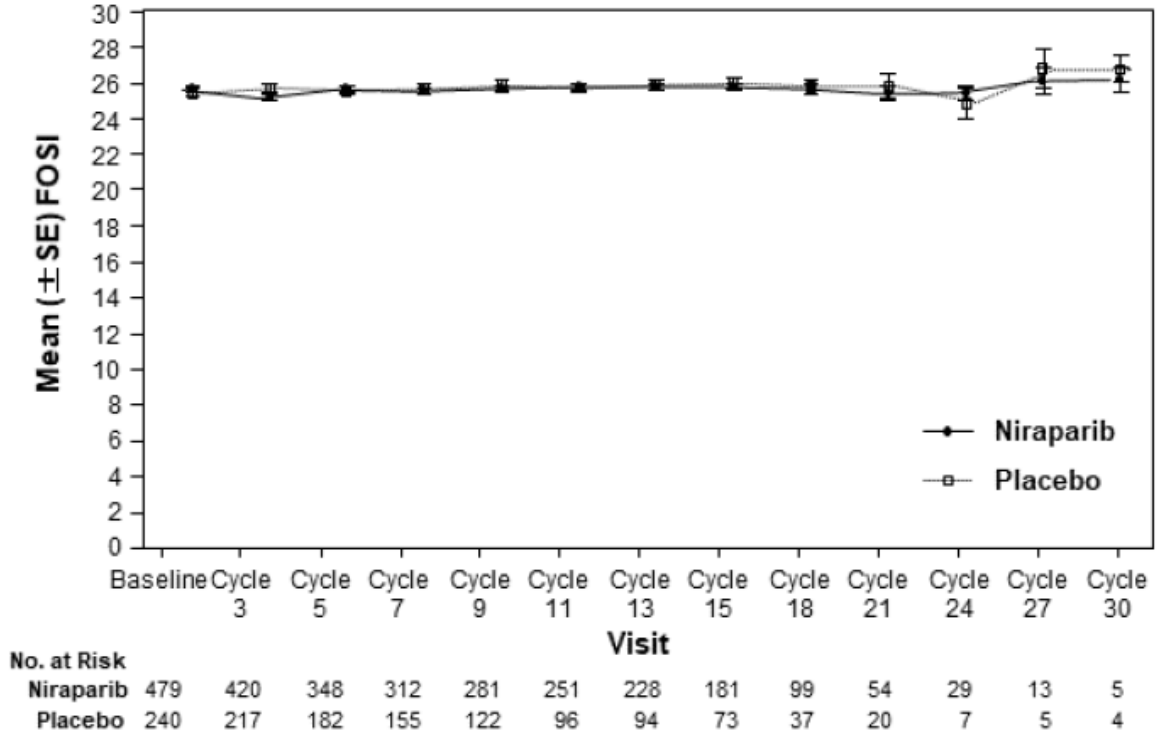
Figure 10: Kaplan-Meier plot of OS for ITT population

Source: CSR [57]
Abbreviations: HR, hazard ratio; ITT, intention-to-treat; OS, overall survival

Patient reported outcomes

Baseline symptoms and quality of life, as measured by FOSI were equivalent between niraparib and placebo groups in the ITT population (niraparib mean: [redacted] versus placebo overall FOSI mean: [redacted]). Similar results were observed throughout the study in the ITT population with no observed differences in changes from baseline over study visits during the follow-up period. The adjusted means and associated standard errors for FOSI by study visit are illustrated in Figure 11.

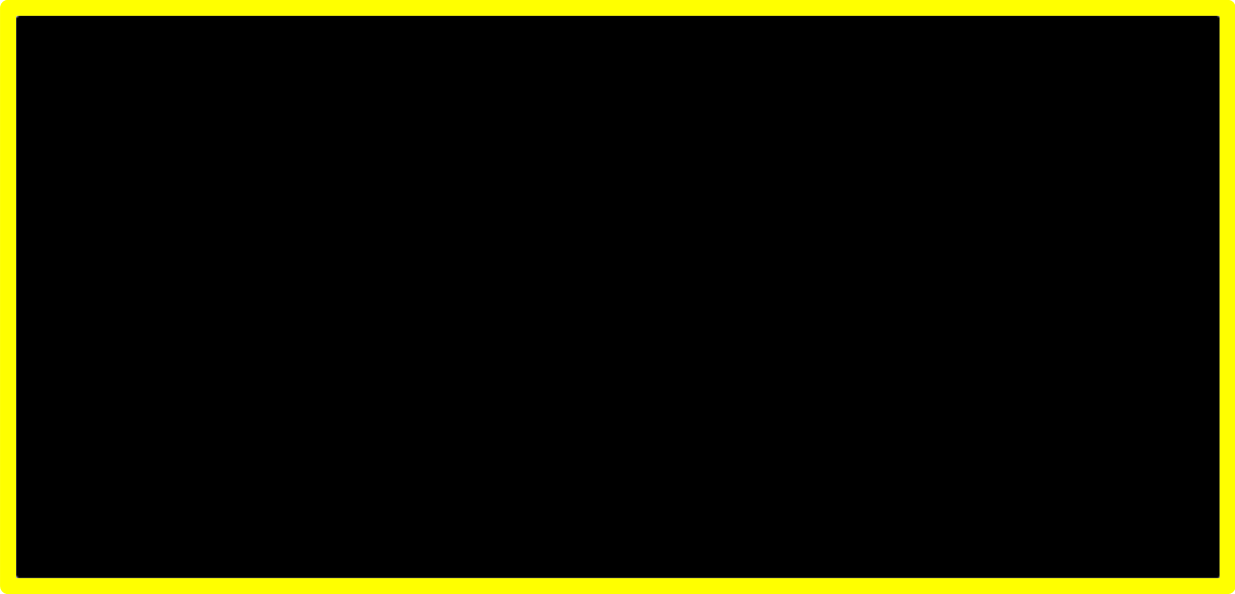
Figure 11: Adjusted Means and Associated Standard Error for FOSI by Study Visit in ITT Population



Source: CSR [57]
Abbreviations: FOSI, Functional Assessment of Cancer Therapy – Ovarian Symptom Index; SE, standard error

EQ-5D data were collected every 8 weeks during the first 56 weeks of treatment using the 5L questionnaire and then every 12 weeks thereafter whilst the patient was receiving study treatment. PRO data were recorded within 7 days of treatment discontinuation of study treatment, and at 4, 8, 12 and 24 weeks thereafter. The EQ-5D-5L data was summarised and converted into weighted health state utility values (EQ-5D index values) per study visit by applying a country-specific valuation set to the profile that represents the comparative value of health states. For purpose of analysis, the US value set was used. Baseline EQ-5D-5L scoring was similar between niraparib and placebo patients in the ITT population (niraparib mean health utility index: [redacted] versus placebo mean: [redacted]). Similar results were observed throughout the study with no observed differences in changes from baseline during the follow-up period. The adjusted mean EQ-5D values are presented graphically by study visit in Figure 12.

Figure 12: Adjusted Means and Associated Standard Error for EQ-5D-5L by Study Visit in ITT Population



Source: CSR [57]
Abbreviations: EQ-5D-5L, EuroQoL 5-dimensions 5-levels; SE, standard error

B.2.7 Subgroup analysis

PFS results were consistent across subgroup analyses. Niraparib performed better than placebo in every subgroup analysed. PFS was statistically significantly higher in patients treated with niraparib compared to placebo regardless of whether the patient had a CR or PR, whether they were BRCAmut or BRCAwt, and whether they were HRD deficient or proficient. Additionally, the HRs for the fixed and individualised starting dose groups were 0.59 (95% CI: 0.457,0.757]; [redacted] and [redacted] 0.69 (95% CI: 0.481,0.982; [redacted] respectively. The test of interaction showed a non-statistically significant p-value (0.30), indicating that change in dose had a non-statistically significant effect on efficacy for these patient populations (fixed vs. individualised).

Figure 13: Forest Plot of Hazard Ratios (95% CI) for PFS by Subgroup in the ITT Population

Source: CSR [57]
Abbreviations: BRCA: breast cancer susceptibility gene; BRCAmut: mutation in BRCA; tBRCAwt: BRCA wildtype; CA-125: cancer antigen 125; CI: confidence interval; CR: complete response; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; HR: hazard ratio; HRD: homologous recombination deficiency; HRDnd: homologous recombination deficiency test status not determined; HRDneg: homologous recombination deficiency test negative, referring to homologous recombination proficient (HR-proficient) tumours; HRDpos: homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumours; ITT: intent-to-treat; non-tBRCAmut: without a germline BRCA mutation; PFS: progression-free survival; PR: partial response; ULN: upper limit of normal.

B.2.8 Meta-analysis

All efficacy and safety data relevant to this appraisal are provided from one relevant Phase 3 RCT, PRIMA, therefore, it was not necessary to conduct a meta-analysis.

B.2.9 Indirect and mixed treatment comparisons

PRIMA is a robust RCT, directly comparing niraparib and RS (placebo), the comparator of interest outlined in the NICE scope. Therefore, an indirect treatment comparison is not considered necessary to provide additional evidence to support this submission.

B.2.10 Adverse reactions

B.2.10.1 *Overview*

Niraparib was well tolerated and has an acceptable and predictable safety profile, as demonstrated in previous studies.[19,61] The safety results are presented overall across all 728 patients who received at least 1 dose of study drug (safety population) to provide a comprehensive evaluation of the safety profile of niraparib.

B.2.10.2 *Exposure*

The median drug exposure from first to last dose for niraparib- and placebo-treated patients was 11.1 months and [redacted] months, respectively, and the median time on treatment was [redacted] months and [redacted] months, respectively. The median number of cycles (equal to one month) was [redacted] cycles for niraparib-treated patients and [redacted] cycles for placebo-treated patients, with a higher proportion of patients in the niraparib group starting more than 12 cycles compared to patients in the placebo group ([redacted]% versus [redacted]% respectively). The mean dose intensity in the niraparib and placebo groups was [redacted]mg/day and [redacted]mg/day, respectively, and the mean relative dose intensity was [redacted]% and [redacted]%, respectively.

B.2.10.3 *Dosage*

Dose reductions and interruptions were allowed in the trial for the management of AEs. In the niraparib group, 385 patients (79.5%) had at least one study drug interruption

due to AEs (versus [redacted] patients ([redacted]%) in the placebo group). Overall, 362 patients (74.8%) in the niraparib group and [redacted] patients ([redacted]%) in the placebo group had a dose reduction in the ITT population. Dose interruptions were most frequent during [redacted].[57] The mean dose intensity was [redacted] mg [redacted] in the niraparib group compared to the placebo group with a mean dose intensity of [redacted] mg (SD [redacted]) and [redacted] mg (SD [redacted]) in each respective group (Table 14). Table 8 in Section B.2.3.1 shows the percentage of patients receiving each dose intensity throughout the trial.

Table 14: Summary of dose intensity, exposure and the need for dose reductions and dose interruptions in the PRIMA trial

Parameter	Niraparib (N=484)	Placebo (N=244)
Overall Treatment Exposure (months)		
Mean (SD)	[redacted]	[redacted]
Median	11.1	[redacted]
Min, Max	[redacted]	[redacted]
Time on Study (months)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Dose Intensity (mg/day)		
Mean (SD)	[redacted]	[redacted]
Median	181.3	[redacted]
Min, Max	[redacted]	[redacted]
Relative Dose Intensity (%)		
Mean (SD)	[redacted]	[redacted]
Median	62.6	[redacted]
Min, Max	[redacted]	[redacted]
Overall Dose Interruptions, n (%)	385 (79.5)	[redacted]
Overall Dose Reductions, n (%)	362 (74.8)	[redacted]

Source: CSR [57]
Abbreviation: Max, maximum; Min, minimum; SD, standard deviation

B.2.10.4 *Safety profile*

Incidence of adverse events

In the safety population, most subjects in both treatment groups experienced at least one TEAE, including 478 (98.8%) of 484 subjects who received niraparib and 224

(91.8%) of 244 subjects who received placebo. The high rate of TEAEs in the placebo group indicates the severity of the subjects' underlying OC signs and symptoms and the burden of chemotherapy. In the niraparib group 96.3% of patients experienced a treatment-related AE compared to 68.9% of patients in the placebo group. The proportions of patients experiencing a grade ≥3 adverse events were 65.3% and 6.6% in the niraparib and placebo groups respectively. In the niraparib group, 12.0% of AEs resulted in treatment discontinuation compared to 2.5% in the placebo group. Myelosuppressive adverse events were the main reason for discontinuation but were infrequent (4.3% for thrombocytopenia in the niraparib group). In each group 0.4% of patients experienced an adverse event leading to death. A summary of the treatment-emergent AEs is presented in Table 15.

Table 15: Summary of Treatment-Emergent Adverse Events (Safety Population)

Characteristic	Niraparib (N=484) n (%)	Placebo (N=244) n (%)
Total number of TEAEs	9,047	2,460
Any TEAE	478 (98.8)	224 (91.8)
Any related TEAE	466 (96.3)	168 (68.9)
Any TEAE with CTCAE Toxicity Grade ≥3	341 (70.5)	46 (18.9)
Any treatment-related TEAE with CTCAE Toxicity Grade ≥3	316 (65.3)	16 (6.6)
Any serious TEAE	156 (32.2)	32 (13.1)
Any treatment-related serious TEAE	118 (24.4)	6 (2.5)
Any TEAE leading to study drug interruption	385 (79.5)	44 (18.0)
Any TEAE leading to study drug dose reduction	343 (70.9)	20 (8.2)
Any TEAE leading to study drug withdrawal	58 (12.0)	6 (2.5)
Any TEAE leading to death	2 (0.4)	1 (0.4)
Any pregnancy	0	0

Source: CSR [57]
Abbreviations: CTCAE, common terminology criteria for adverse events; TEAE, treatment-emergent adverse events

Common adverse events

The most common adverse events are presented in Table 16. Among the most common grade ≥3 adverse events in the niraparib group were anaemia (31.0% of the patients), thrombocytopenia (28.7%), decreased platelet count (13.0%), and

neutropenia (12.8%). Safety improved with the implementation of the individualised dosing regimen, as shown in Table 17.

Table 16: Treatment-emergent Adverse Events Occurring in ≥10% of Patients (Safety Population, N=728)

MedDRA Preferred Term	Niraparib (n=484) no. (%)		Placebo (n=244) no. (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anaemia	307 (63.4)	150 (31.0)	43 (17.6)	4 (1.6)
Nausea	278 (57.4)	6 (1.2)	67 (27.5)	2 (0.8)
Thrombocytopenia	222 (45.9)	139 (28.7)	9 (3.7)	1 (0.4)
Constipation	189 (39.0)	1 (0.2)	46 (18.9)	0
Fatigue	168 (34.7)	9 (1.9)	72 (29.5)	1 (0.4)
Platelet count decreased	133 (27.5)	63 (13.0)	3 (1.2)	0
Neutropenia	128 (26.4)	62 (12.8)	16 (6.6)	3 (1.2)
Headache	126 (26.0)	2 (0.4)	36 (14.8)	0
Insomnia	119 (24.6)	4 (0.8)	35 (14.3)	1 (0.4)
Vomiting	108 (22.3)	4 (0.8)	29 (11.9)	2 (0.8)
Abdominal pain	106 (21.9)	7 (1.4)	75 (30.7)	1 (0.4)
Decreased appetite	92 (19.0)	3 (0.6)	20 (8.2)	0
Diarrhea	91 (18.8)	3 (0.6)	55 (22.5)	1 (0.4)
Dyspnea	88 (18.2)	2 (0.4)	30 (12.3)	2 (0.8)
Arthralgia	85 (17.6)	2 (0.4)	47 (19.3)	0
Neutrophil count decreased	82 (16.9)	37 (7.6)	5 (2.0)	0
Hypertension	82 (16.9)	29 (6.0)	17 (7.0)	3 (1.2)
Asthenia	78 (16.1)	4 (0.8)	31 (12.7)	2 (0.8)
White blood cell count decreased	74 (15.3)	12 (2.5)	8 (3.3)	0
Cough	74 (15.3)	0	35 (14.3)	1 (0.4)

Source: CSR [57]
Abbreviation: MedDRA, medical dictionary for regulatory activities

Haematological adverse events

An individualised dosing regimen was introduced to allow patients with platelet count below 150,000/µL and/or weighing below 77kg to start on a lower dose of 200mg per day. Patients on an individualised dose had a lower incidence of grade ≥3 haematologic TEAEs, with 35.6% of patients (n=112) in the fixed dose niraparib group experiencing anaemia compared to 22.5% of patients (n=38) in the individualised dose

group. A lower incidence of all grade ≥3 haematologic TEAEs is recorded in the individualised dose group compared to the fixed dose group for patients treated with niraparib; the results are presented in Table 17.

Table 17: Grade ≥3 Haematologic TEAEs in Patients Receiving a Fixed Versus Individualised Dose of Niraparib (Safety Population, N=728)

	Niraparib		Placebo	
	Fixed Dose (n=315)	Individualised Dose (n=169)	Fixed Dose (n=315)	Individualised Dose (n=169)
Thrombocytopenia	114 (36.2)	25 (14.8)	0 (1)	1.2 ()
Anaemia	112 (35.6)	38 (22.5)	3 (1.9)	1 (1.2)
Platelet count decreased	51 (16.2)	12 (7.1)	0	0
Neutropenia	46 (14.6)	16 (9.5)	2 (1.3)	1 (1.2)
Neutrophil count decreased	28 (8.9)	9 (5.3)	0	0
Febrile neutropenia	3 (1)	1 (0.6)	0	0
Myelodysplastic syndrome	1 (0.3)	0	0	0
Pancytopenia	1 (0.3)	0	0	0
Neutropenic sepsis	0 (1)	0.6 (0)	0	0

Source: CSR [57]
Abbreviations: TEAE, treatment-emergent adverse events

B.2.11 Ongoing studies

The PRIMA trial is currently ongoing and is anticipated to finish in [redacted]; further OS data of advanced maturity will be reported over the coming years.

There are no other trials assessing the safety and efficacy of niraparib in line with the indication being appraised in this submission (monotherapy maintenance treatment for advanced OC following first-line platinum-based chemotherapy) that are anticipated in the next 12 months.

B.2.12 Innovation

Currently there is no maintenance treatment approved for routine use in the first-line maintenance setting in England and Wales. Patients who do not possess a BRCA

mutation (approximately 75% of patients) have no PARP inhibitor treatments available as a first-line maintenance treatment either through routine commissioning or the CDF. Therefore, there is an urgent unmet need to provide patients with advanced OC a medication that can delay progression following first-line platinum-based treatment.

When licensed, niraparib will be the first medicine to offer this benefit to patients with advanced OC, irrespective of BRCA mutation status. In the PRIMA trial, niraparib demonstrated a statistically significant improvement in PFS whilst maintaining patients' quality of life. In addition, the prolonged PFS due to maintenance treatment with niraparib has the potential to provide clinical benefit not only in delaying disease symptoms, but also in delaying the toxicity burden of additional PBC. This represents an advancement for patients with OC and provides choices to patients. By treating OC at an earlier stage, niraparib can prolong the time until relapse and enable patients to live longer lives without impacting their quality of life.

B.2.13 Interpretation of clinical effectiveness and safety evidence

The efficacy and safety of niraparib as maintenance therapy for advanced high-grade OC following first-line PBC has been conclusively demonstrated in PRIMA, a large, international, placebo-controlled, Phase 3 trial involving over 700 patients, performed in centers in Europe and North America. Data have been reported for a median duration of follow-up of 13.8 months.

Niraparib is the only PARP inhibitor monotherapy that has demonstrated improvements in PFS across the spectrum of advanced patients with OC, regardless of BRCA mutation status. The majority of patients with OC are underserved by current treatment options with extremely restricted choice of long-term maintenance therapies available to patients following response to first-line PBC, through any commissioning route, leaving them with just hope as they are managed by a "watch and wait" approach.

In particular, patients without a BRCA mutation, who account for approximately three quarters of patients living with OC, have an unmet need for effective PARP inhibitor

maintenance treatments in England; RS remains the standard of care following response to first-line PBC and has been shown to have limited long-term benefits.[10,24]

Survival rates for patients with OC in England have remained low and are amongst the lowest in Europe.[35] OC treatment is curative in intent when patients are newly diagnosed; cytoreductive surgery in conjunction with or followed by PBC and a maintenance treatment appears to offer patients the maximum opportunity of remaining disease-free.[24] Once patients relapse following PBC their disease is generally considered incurable and the window of opportunity for a cure closes. It is therefore important that all patients with advanced high-grade OC have the opportunity to access treatment following response to first-line PBC.

B.2.13.1 *Pharmacological properties*

Several pharmacological properties of niraparib support its ease of use in clinical practice. Niraparib is a potent, highly-selective PARP 1/2 inhibitor; when licensed it would be the only once-daily, oral, maintenance therapy available to treat patients with advanced high-grade OC following response to first-line PBC. Additionally, the flexible, individualised dosing, and simple straightforward regimen of niraparib provides patients and healthcare professionals with an effective means to manage dose changes that may be required in response to TEAEs. The once daily administration of two 100 mg capsules is facilitated by niraparib's long terminal half-life and not only offers convenience for patients in day to day administration, it means dose reductions can be performed, in consultation with their healthcare professional, by simply taking one (or two) fewer capsules per day, thereby removing the need to renew prescriptions. Further convenience is offered by the biochemical properties of niraparib that allow it to be taken with or without food, unlike other PARP inhibitors.[62]

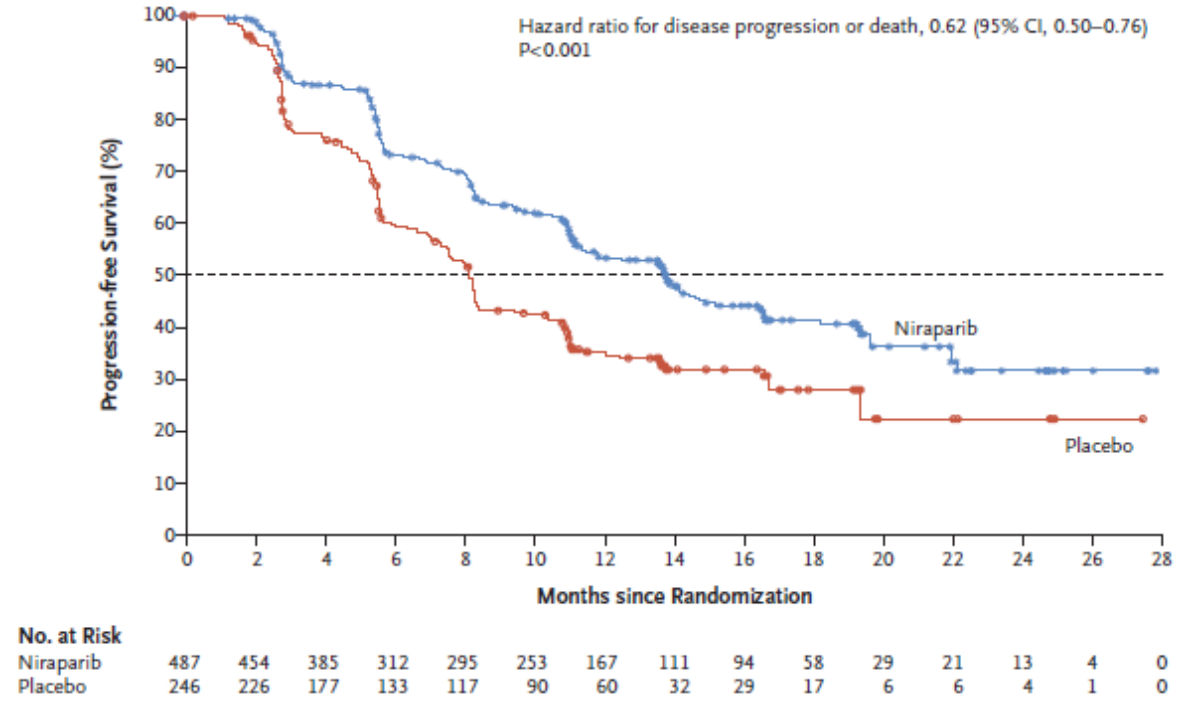
Niraparib also benefits from a minimal risk of drug-drug interactions, with low potential for interactions with major drug-metabolising enzymes (e.g. CYP enzymes) and drug transporters demonstrated in *in vitro* studies.[22] Consequently, no dose adjustment is required for niraparib to be administered concomitantly with these therapies.

Niraparib is a potent and selective PARP-1 and PARP-2 inhibitor with high bioavailability, wide tissue distribution and high membrane permeability, enabling effective delivery to tumour cells. Niraparib reaches high concentrations in the tumour, delivering selective PARP-1/2 inhibition with >90% durability that produces a persistent anti-tumour effect with minimal off-target activity.[19,21] The high permeability of niraparib enables it to pass the blood-brain barrier. Brain metastases are a rare occurrence in OC, but with an increasing prevalence.[63] Therefore, the ability for treatments to cross the blood-brain barrier may provide a further benefit of niraparib.

B.2.13.2 *Clinical effectiveness*

The PRIMA trial demonstrated that in patients treated with niraparib time to progression or death was statistically significantly longer than in patients treated with placebo and RS. Patients in the niraparib group had an increased median PFS time of 5.6 months compared to those in the placebo group (13.8 months versus 8.2 months respectively), as determined by BICR based on RECIST criteria. The PFS gained by patients treated with niraparib was statistically significant compared to that of patients treated with placebo, with a 38% reduction in the risk of progression or death (HR 0.62 [CI 0.50, 0.76]) (Table 11). PFS time consistently favoured niraparib throughout the treatment period observed (median follow-up 13.9 months and 13.8 months in the niraparib and placebo groups respectively). The extended time free of disease progression, following response to first-line PBC, comes at a critical time in a patient's journey; beyond this stage, following disease relapse, interventions are no longer curative in intent.

Figure 14: Kaplan-Meier plot of Progression-Free Survival (PFS) in ITT population



Abbreviations: ITT, intention-to-treat; PFS, progression-free survival

The PFS results are strongly consistent across the full range of sensitivity analyses undertaken, which supports the reliability of the primary endpoint analysis.

The secondary endpoint analyses support the favourable PFS results, with hazard ratios observed in OS of 0.70 (95% CI 0.44, 1.11) and PFS2 of 0.81 (CI 0.58, 1.14). However, given that the majority of patients enrolled in the trial are still alive, the data remain immature for OS and PFS2 (10% and 12% maturity for OS with niraparib and placebo respectively, and 20% maturity for PFS2). The TFST data were 47% mature at the time of the database lock, providing confidence in the statistically significant result that demonstrated a delayed time to subsequent treatment in the niraparib group compared to the placebo group: TFST HR: 0.65 (CI 0.52, 0.80). By delaying the first relapse, patients are able to live their lives whilst maintaining their quality of life (as observed in the EQ-5D results). The extended time free of disease progression also allows patients avoid the emotional and physical pain of undergoing chemotherapy following disease relapse.

B.2.13.3 *Safety*

Niraparib has been licenced for over five years in Europe and has an established safety profile. It is well tolerated by patients; this is reflected by the maintained quality of life that patients report whilst receiving treatment with niraparib in the PRIMA trial and the established and ongoing use of niraparib as second-line maintenance treatment of relapsed platinum-sensitive OC.

In addition, after the PRIMA trial protocol was amended to allow individualised dosing, patients treated with an individualised dose of niraparib, rather than a fixed dose, experienced a lower incidence of haematological adverse events (Section B.2.10.4). The most common grade ≥3 TEAEs experienced in the PRIMA trial were thrombocytopenia and anaemia; 36.2% (n=114) and 35.6% (n=112) patients in the niraparib fixed dose group experienced thrombocytopenia and anaemia respectively, versus 14.8% (n=25) and 22.5% (n=38) of patients in the niraparib individualised dose group respectively. The recommended starting dose of niraparib has been reduced from 300 mg daily to 200 mg daily in the recent licence variation (pending EMA approval) to minimise the incidence of TEAEs.

B.2.13.4 *Strengths of the clinical evidence*

PRIMA was a large, robust, double-blinded, randomised, placebo-controlled, multi-centre trial involving 733 patients; niraparib and the comparator of interest within the scope of this appraisal were directly compared in a cohort of patients with advanced, high-grade serous or endometrioid OC in response to first-line PBC. The quality assessment (Section B.2.5) identified a low risk of bias in the PRIMA trial design.

The trial included 10 sites in the UK and enrolled subjects representative of the patients who would receive niraparib in routine clinical practice in the UK. Therefore, the patient population is representative of those in UK clinical practice, and it is expected that the benefits reported from this trial are likely to be reflected in clinical practice in England and Wales.

PFS is a well-recognised and meaningful outcome, to both patients and healthcare professionals, as identified by the Society of Gynecologic Oncology.[5] The large patient

population and the duration of the trial thus far have provided sufficient evidence to observe a statistically significant difference between the median PFS with niraparib compared with placebo (13.8 months vs 8.2 months [HR 0.62, 95% CI 0.50, 0.76, p value: <0.0001]). The sensitivity analyses for PFS were all consistent with the baseline results assessed by blinded investigator central review (BICR), each providing a highly statistical difference with HRs between [redacted] and [redacted].

Pre-specified secondary endpoints showed a statistically significant improvement in TFST in patients treated with niraparib with a reduction of 6.6 months in median TFST between niraparib and placebo; this is consistent with the PFS improvements observed. OS and PFS2 showed numerical improvements in the niraparib group with HRs of 0.70 (95% CI 0.44, 1.11) and 0.81 (95% CI 0.58, 1.14) respectively.

HRQoL was measured as a patient-reported outcome in the PRIMA trial, giving important insight into how patients viewed their health. Health status was maintained whilst patients received treatment with niraparib, consistent with patients treated with placebo, providing data sourced directly from patients receiving study treatment in the trial. HRQoL outcomes were measured using NICE's preferred generic patient preference tool, EQ-5D.

The PRIMA trial continues to follow-up patients and further data will be collected, analysed and published, with the next read out expected in [redacted]. The continued patient follow-up will enhance the robustness of the long-term data, such as OS.

B.2.13.5 *Limitations of the clinical evidence*

Most patients enrolled in the PRIMA trial are still alive ([redacted]% in the niraparib group, [redacted]% in the placebo group) and therefore the OS data is only 10% to 12% mature. However, the current OS data show a numerical advantage for niraparib compared to RS, and it is anticipated that the PRIMA data analysis results expected in [redacted] following longer follow-up will give greater statistical power to the OS benefits observed. The uncertainty around the magnitude of OS effect is reflected in the application to place niraparib into the CDF, where revaluation can be made with updated clinical data in four years' time.

The ITT population of the PRIMA trial did not include patients with Stage III disease with no visible residual disease (NVRD) after PCS, and as such is not fully aligned with the anticipated MA. Patients with Stage III NVRD disease after primary surgery have an improved prognosis compared to patients with residual disease.[11] The submission explicitly considers the impact of incorporating this population into the economic model.

B.2.14 Additional clinical evidence generation

Extrapolation of the ITT population to the MA population

The population defined in the approved FDA label and anticipated EMA label is broader than the ITT population of the PRIMA trial. The MA applies to all patients with newly diagnosed, advanced (Stage III or IV) ovarian cancer after a response to first-line PBC, whereas the PRIMA trial population did not include Stage III patients with NVRD after PCS. The PRIMA trial recruited the highest risk population with the greatest unmet need in the knowledge that if niraparib demonstrated a benefit in this group of patients, it would also be effective in a lower risk patient group, which is evident from other PARP inhibitor trials.

For this submission, a comprehensive package of activities, described below in further detail, was carried out with the aim of further understanding this population and bridging the gap between the ITT and MA populations. These included:

1) Review of the NICE clinical guidelines
2) A UK advisory board
3) A targeted literature review, to assess the outcomes of the different patient populations
4) A retrospective real-world evidence study
5) Literature review of PARP inhibitor treatment options in the first-line setting
6) Review of PRIMA trial outcomes

7) Understanding of regulatory discussions

The main conclusions from such activities are as follows:

- Patients with Stage III NVRD following PCS constitute approximately [redacted] of the MA population.
- Patients with Stage III NVRD following PCS have a better prognosis than patients with Stage III/IV VRD, irrespective of the treatment received.
- Nevertheless, patients with Stage III NVRD are still at risk of recurrence and death and therefore have a high unmet need.
- PARP inhibitors demonstrate improved clinical outcomes in patients with Stage III NVRD (as observed in the PAOLA-1 and SOLO-1 trials).[43,64]

A limitation of the PRIMA trial is the absence of patients with Stage III NVRD, reducing the ability to use observed data to reflect the entire MA population. However, the clinical evidence and physician opinion presented in this submission demonstrate that it is appropriate to conduct an extrapolation to the Stage III NVRD and validate the assumptions necessary to conduct this extrapolation. It is important that any treatment recommendation includes the Stage III NVRD cohort, in line with the NICE scope, to ensure that post-surgical assessment does not indirectly discriminate against patients who have NVRD.

Details of the comprehensive package of activities listed above are presented below.

1) Review of the clinical guidelines

The NICE guidelines for advanced (Stage II to IV) OC, as presented in Figure 2, recommend that “If performing surgery for patients with ovarian cancer, whether before chemotherapy or after neoadjuvant chemotherapy, the objective should be complete resection of all macroscopic disease”.

Patients whose surgeries result in macroscopically complete resection of all visible tumours are referred to as NVRD patients, R0 patients or patients with complete cytoreduction. Not all surgeries will achieve complete cytoreduction, and therefore some patients will have VRD. There are various reasons why complete resection is not always possible. One key reason is that there are no guidelines or defined way for surgeons to report outcomes following cytoreductive surgery. This can mean that accuracy for determining the presence or absence of VRD remains dependent on the individual surgeon, which can be impacted by their experience in this rare malignancy. It can also be complicated by the difficulty of differentiating between the disease and changes due to surgical dissection. In addition, post-operative imaging can often be inaccurate and therefore does not always support the surgeon's decision-making.[65]

2) A UK clinical advisory board

An advisory board consisting of nine UK clinicians was conducted in late 2019 and focussed on the overall submission to NICE, including the population of interest.[66] The attendees recommended that it would be appropriate to include the Stage III NVRD group, therefore endorsing the approach of pursuing a NICE recommendation within the MA population, in line with the NICE scope. The clinicians explained that although the Stage III NVRD group experience better outcomes than patients with Stage III VRD, they are still at risk of disease recurrence and therefore have a high unmet need.

The members of this advisory board also agreed that PARP inhibitors are efficacious in this patient group and the experts advised that it would be sensible to extrapolate niraparib data to meet the full MA population. In addition, they highlighted that it is difficult for a surgeon to be certain that no disease is remaining and highlighted the importance of not restricting a recommendation based on surgical outcomes.

3) Targeted literature review

The objective of the targeted literature review was to determine the OS and PFS associated with patients with advanced (Stage III/IV) OC receiving first-line treatment in the US and Europe who had NVRD after PCS, and to compare these to outcomes in patients with VRD.

The review focused on studies published in the last five to ten years, as the definition of surgical outcome success has recently changed from <2cm as the best outcome to NVRD, and therefore more recent studies can now truly differentiate between complete cytoreduced patients (NVRD) and others. The more dated studies would classify microscopic residual disease as negative/no residual disease (RD). An additional study, although outside of the time limit applied, was added (Dubois et al. 2009) to capture the widely referenced source.

Please see full report and the extracted data included in Appendix M.

Fourteen studies have been published in the past 10 years from the US and Europe that report OS or PFS by RD status following OC surgery; the studies are summarised in Table 18. These studies consistently show that survival times are longer for patients with “complete cytoreduction” or “no RD” compared to those with VRD following surgery.

Table 18: Studies conducted in the US or Europe reporting overall survival or progression-free survival by residual disease status among ovarian cancer patients

Author, Year	Country	Patients	Study design	Treatment	Residual disease: definition	Residual disease: category	Overall survival (median months)	Overall survival: HR (95% CI)*	PFS (median months)
Delga 2020[67]	France (Nantes & Marseille cancer centers)	N=1260, Stage III & IV	1985-2015	Cytoreductive surgery (PCS, ICS or FCS) with or without chemotherapy	Definition of "complete" not further defined	Complete cytoreduction	55.1 *(PCS: 59.7, ICS: 56; FCS: 48.6)*	1.0	--
						Any RD	24.6	2.1 (1.8-2.5)	--
Ghirardi 2020 (abstract)[68]	Italy	n=207, Stage IIIC-IV	Retrospective, 2010-2016	PCS	Compared 1-10 mm RD at PCS vs. no gross RD at IDS	No gross RD-IDS	52.4	--	18.9
						1-10 mm-PCS	41.4	--	16.2
Liang 2019 (abstract)[69]	USA (UCLA)	N=91, advanced	n/a	NACT and IDS	No gross RD vs. visible (<1 cm)	None	38.7	--	16.3
						<1 cm	12	--	10
Babayeva 2018 (abstract)[70]	Germany (Tumor Bank Ovarian Cancer)	N=164, mostly advanced	Prospective database	PCS	Any tumor residual	None	70.0	--	--
						Any	24.7	--	--
Kobal 2018[71]	Slovenia	N=157, Stage III & IV	Retrospective, 2008-2012	PCS or NACT+IDS	Complete cytoreduction (RD=0)	0 mm	PCS, NACT 54.7, 36.3	All patients: 1.0	PCS, NACT 20.7, 19.9
						1-9 mm	34.7, 25.6	1.66 (0.96-2.82)	11.2, 14.5
						>= 10 mm	31.3, 16.1	2.82 (1.79-4.46)	13.3, 8.0

Phillips 2018 (abstract)[72]	United Kingdom	N=398	Retrospective, 2007-2017	NACT and IDS (<5 cycles vs. >=5 cycles)	Complete cytoreduction = no RD	Complete (NVRD)	<5, >=5 cycles: 51.1, 53.0	--	--
						Optimal (<1cm)	36.1, 24.7	--	--
						Suboptimal (>=1)	34.3, 22.1	--	--
Torres 2018[73]	USA (Mayo clinic)	N=334, serous type, Stage III-IV	Prospective database, 1994-2011	PCS	Largest residual tumor diameter	0	72.0	1.0	
						0.1-0.5 cm	39.6	1.34 (0.96-1.88)	
						0.6-1.0 cm	25.4	2.07 (1.34-3.22)	
						>1 cm	21.2	2.59 (1.74-3.86)	
Sorensen, 2018[74]	Denmark (Danish Gynecological Cancer Database)	N=2092, Stage IIIB-IV	1 Jan 2005 to 30 June 2016	PCS	Extent of intra-abdominal macroscopic visible disease after PCS	0 cm	Stage IIIB-C, IV 60.8, 43.4	Stage IIIB-C, IV 1.0, 1.0	
						<=1 cm	29.5, 24.9	1.7 (1.5-2.0), 1.6 (1.1-2.2)	
						>1 and <=2 cm	27.8, 17.2	1.5 (1.2-1.9), 1.9 (1.2-3.1)	--
						> 2	19.8, 14.3	2.4 (2.0-2.8), 2.4 (1.8-3.2)	--
						n/a	15.2, 13.2	4.5 (2.2-9.1), 2.2 (0.8-6.2)	--
Sioulas 2018 [75]	USA (Memorial Sloan Kettering)	N=496, Stage IIIC	Retrospective, 2001-2010	PCS	Reported RD	None	83.4	--	26.7
						1-5 mm	54.5	--	20.7
						6-10 mm	43.8	--	16.2
						> 10 mm	38.9	--	13.6
Ataseven 2016 (abstract)[76]	Austria	N=286, stage IV	Retrospective, 2000-2014	PCS	Macroscopic resection	0	50	1.0	--
						1-10 mm	25	1.50 (1.01-2.23)	--

						> 10 mm	16	2.17 (1.43-3.70)	--
Horowitz 2015[77]	USA	N=2655, Stage III & IV	Patients enrolled in GOG-182 trial	PCS followed by 1 of 5 chemotherapy regimens	Complete surgical resection (microscopic, NVRD) or 0.1 to <1 cm (macroscopic)	0 cm (NVRD)	76.9	--	28.9
						NVRD > to <1 cm	40.6	--	15.3
Rutten 2015[38]	Netherlands	N=689, Stage IIIC & IV	Observational cohort, 1998-2010	PCS or IDS	None, minimal (<1cm), gross (>=1 cm)	None	PCS, IDS* 59.2, 43.6	PCS, IDS* 1.0	PCS, IDS 23.7, 17.4
						Minimal	36.7, 26.7	2.0 (1.1-3.8), 1.8 (1.3-2.5)	16.7, 11.9
						Gross	35.6, 21.5 *disease specific survival (DSS)	1.8 (1.1-3.2), 3.1 (2.0-4.8)	12.5, 9.0
Vergote 2010[78]	EORTC institutions	N=632, Stage IIIC or IV	RCT	PCS + platinum chemotheraphy or NACT+IDS	Optimal: no RD, suboptimal: 1-10 mm, other: > 10	Optimal	PCS, NACT: 45, 38	--	--
						Suboptimal	32, 27	--	--
						Other	26, 25	--	
Wimberger 2010[79]	Germany	N=573, stage IV	Retrospective (AGO-OVAR-3/5/7)	Chemotherapy and primary surgery	Macroscopic complete resection	0 cm	54.6	1.0	--
						0-1 cm	25.8	1.9 (1.2-2.9)	--
						>1 cm	23.9	2.1 (1.4-3.2)	--

Abbreviations: CI: confidence interval; FCS: final cytoreductive surgery; HR: hazard ratio; ICS: interval cytoreductive surgery; IDS: interval cytoreductive surgery; NACT: neoadjuvant chemotherapy; PCS: primary cytoreductive surgery; PCS: primary cytoreductive surgery; PFS: progression free survival; RD: residual disease
*multivariate analyses presented.

One study was conducted in the UK; it showed that OS was 53 months for patients with NVRD and 22.1 months for those with at least 1cm VRD.[72]

Among the studies with larger sample sizes (N>500):[38,67,74,77–79]

- The median OS ranged from 55 months to 77 months for patients with NVRD and roughly 20 months to 40 months for patients with VRD.
- The median OS for patients with and without VRD was generally higher in patients with Stage III OC compared to those with Stage IV OC.

Several studies reported the multivariate HR for the association between RD status and OS; results consistently showed patients with NVRD have improved OS compared to those with any amount of VRD (HR range: 1.5-3.0).[38,67,71,73,74,76,79] A recent study of 1,260 Stage III and IV patients in France reported longer OS for patients with NVRD compared to VRD following cytoreductive surgery, and therefore a worse HR was calculated for those with VRD compared to those with NVRD (HR= 2.1, 95% CI: 1.8-2.5).[67]

Fewer studies reported PFS by VRD status among patients with OC. The median PFS ranged from 16 months to 29 months for those with NVRD and roughly 8 to 16 months for patients with VRD.[38,68,69,71,75,77] No studies from the period of interest (past 10 years) reported the HR for associations between VRD and PFS.

Results from Du Bois 2009, a study of 3,129 ovarian cancer patients from three prospective trials in Europe, showed a HR for PFS of 2.03 for patients with 1-10mm residual tumor compared with those who had 0mm.[80] OS and PFS studies published prior to the past 10 years are summarised in a previous review by Chang et al. with similar findings.[81]

It can be concluded from these studies that patients with NVRD have a better prognosis than those with VRD, irrespective of the treatment received in the first-line setting of ovarian cancer. However, patients with NVRD are still at risk of recurrence and therefore in need of efficacious maintenance treatments.

4) Retrospective real-world evidence study

To better understand the long-term outcomes of the patient population in the PRIMA study and quantify the difference between this population and the MA population, a retrospective database analysis was conducted with the help of a team at the University of Edinburgh, using the University of Edinburgh Ovarian Cancer Database.

The database contains outcome data for patients diagnosed with OC in the South East region of Scotland ([redacted]). In order to obtain reliable follow-up data, patient identification was restricted to patients with newly diagnosed OC who had not received any active maintenance therapy, diagnosed between the 1st January 2000 and the 21st December 2015 and followed up until last patient record or until January 2019 (please see Appendix L for research study protocol).

Due to its historic nature, and the absence of alternative treatments at the time, the data were assumed to be reflective of the RS arm within the economic analysis. The research study aimed to capture the following cohorts:

- The anticipated MA population for niraparib
- Then disaggregated into:
    - A simulated-PRIMA ITT population (Stage III/IV patients with VRD after PCS)
    - A Stage III population with NVRD after PCS (i.e. patients included in the MA population but not in the simulated-PRIMA cohort).

The MA cohort and simulated-PRIMA cohort were obtained by applying the inclusion and exclusion criteria set out in Table 19.

Table 19: Inclusion and exclusion criteria used to obtain the MA cohort and simulated-PRIMA cohort from the University of Edinburgh Ovarian Cancer Database

MA cohort		Simulated-PRIMA cohort	
Inclusion criteria	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**
• Patient must have histologically confirmed, advanced (Stage III or IV) high-grade serous or endometrioid ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who have completed first line platinum-based chemotherapy (neoadjuvant or adjuvant). • Patient must have clinical complete response or partial response following completion of chemotherapy course. • All Stage III and IV patients are eligible, irrespective of VRD, after primary or interval cytoreductive surgery or inoperable disease.	• Patient has mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer. • Patient has undergone more than two cytoreductive surgeries. • Patient is to receive bevacizumab. • Patient has had treatment with a known PARP inhibitor. • Demonstrate stable or progressive disease in response to first line chemotherapy.	• Patient must have histologically confirmed, advanced (Stage III or IV) high-grade predominantly serous or endometrioid ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who have completed first line platinum-based chemotherapy (neoadjuvant or adjuvant). • Patient must have clinical complete response or partial response following completion of chemotherapy course. • All Stage IV patients are eligible, irrespective of residual disease, after primary or interval cytoreductive surgery. Stage III patients are required to have VRD after primary surgery.	• Patient has mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer. • Patient has undergone more than two cytoreductive surgeries. • Patient is to receive bevacizumab. • Patient has had treatment with a known PARP inhibitor. • Demonstrate stable or progressive disease in response to first line chemotherapy. • Patients diagnosed at Stage III with NVRD

MA cohort		Simulated-PRIMA cohort	
Inclusion criteria	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**
		Patients with inoperable Stage III and IV disease are eligible.	

The data extracted included patient characteristics and overall survival estimates. Baseline characteristics from the cohorts were similar to those observed in PRIMA. However, the simulated-PRIMA population from the University of Edinburgh data set were a slightly more severe patient population (as assessed by their ECOG score and proportion of patients achieving NVRD status after interval cytoreductive surgery) compared to those included in the RS arm of PRIMA. [redacted]. Thus, [redacted] of the MA population was classified as Stage III NVRD after cytoreductive surgery.

Table 20: Patient characteristics in the MA cohort and simulated-PRIMA cohort from the University of Edinburgh Ovarian Cancer Database

Characteristic		MA cohort		Simulated-PRIMA cohort	
		n	%	n	%
-	Cases	[redacted]	[redacted]	[redacted]	[redacted]
Age at diagnosis	Median years	[redacted]	[redacted]	[redacted]	[redacted]
Histological subtype	HGS	[redacted]	[redacted]	[redacted]	[redacted]
	HG endo	[redacted]	[redacted]	[redacted]	[redacted]
Documented primary site	Ovary	[redacted]	[redacted]	[redacted]	[redacted]
	Fallopian Tube	[redacted]	[redacted]	[redacted]	[redacted]
	Peritoneum	[redacted]	[redacted]	[redacted]	[redacted]
	FT/ovary	[redacted]	[redacted]	[redacted]	[redacted]
FIGO stage at diagnosis	IIIA	[redacted]	[redacted]	[redacted]	[redacted]
	IIIB	[redacted]	[redacted]	[redacted]	[redacted]
	IIIC	[redacted]	[redacted]	[redacted]	[redacted]
	III NS	[redacted]	[redacted]	[redacted]	[redacted]
	IV	[redacted]	[redacted]	[redacted]	[redacted]
Germline BRCA status	BRCAm	[redacted]	[redacted]	[redacted]	[redacted]
	BRCAwt / VUS	[redacted]	[redacted]	[redacted]	[redacted]
	untested	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS	0	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic		MA cohort		Simulated-PRIMA cohort	
		n	%	n	%
	3	[redacted]	[redacted]	[redacted]	[redacted]
	NA	[redacted]	[redacted]	[redacted]	[redacted]
Chemo type	Adjuvant	[redacted]	[redacted]	[redacted]	[redacted]
	Neoadjuvant	[redacted]	[redacted]	[redacted]	[redacted]
Residual disease	Zero macroscopic	[redacted]	[redacted]	[redacted]	[redacted]
	Macroscopic	[redacted]	[redacted]	[redacted]	[redacted]
	NA	[redacted]	[redacted]	[redacted]	[redacted]
Vital status at last follow-up	Alive	[redacted]	[redacted]	[redacted]	[redacted]
	Deceased	[redacted]	[redacted]	[redacted]	[redacted]
Median follow-up	median years	[redacted]	[redacted]	[redacted]	[redacted]
Median OS	median years	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS	median years	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FIGO, International Federation of Gynaecology and Obstetrics; BRCA, BRCA1 or BRCA2; FT, fallopian tube; HG endo, high grade (grade III) endometrioid; HGS, high grade serous; NA, not available; NS, not specified; OS, overall survival; PFS, progression-free survival, RD, residual disease following cytoreductive surgery; VUS, variant of unknown clinical significance;

The median OS was approximately [redacted] in the simulated-PRIMA group, compared with [redacted] in the Stage III NVRD cohort. By combining the two cohorts to estimate the median OS for the MA population, it can be demonstrated that the MA curve lies above the simulated-PRIMA curve with a median OS of approximately [redacted] (Figure 15).

Figure 15: Overall survival of the simulated-PRIMA, Stage III NVRD and MA cohorts of the Edinburgh Ovarian Cancer Database

Abbreviations: MA, marketing authorisation; NVRD, no visible residual disease

The estimated OS of the MA population presented in Figure 15 is consistent with the findings of the targeted literature review described above; patients with Stage III NVRD have improved OS compared to those in the simulated-PRIMA and MA cohorts, but are still at high risk of death over their lifetime.

Figure 15 also shows that there is a small group of patients who will continue to live beyond 7 years, and who are described in this submission as being in long-term remission.

The results from this analysis were also used to aid the selection of the appropriate OS distributions of the RS arm within the economic analysis (see Section B.3.3). As, the patients studied as part of the Edinburgh database had more advanced disease than the trial population, the survival data obtained from the Edinburgh OC database should be used as a minimum benchmark for the validation of the RS survival curve.

5) Review of PARP inhibitor treatment outcomes and their application to PRIMA data

Efficacy data from other PARP inhibitors can be used to understand the expected treatment effect of niraparib in the Stage III NVRD population. A targeted clinical literature review was conducted to identify relevant RCTs that have assessed PARP inhibitors in the first-line setting.

Two studies were identified, SOLO-1 and PAOLA-1; SOLO-1 assessed olaparib as a monotherapy and PAOLA-1 assessed olaparib as a combination therapy with bevacizumab. Both studies provided efficacy results for the Stage III NVRD population after cytoreductive surgery. Table 21 demonstrates the following:

1) The median PFS is greater in the Stage III NVRD population compared to the Stage III/IV VRD population: in PAOLA-1, median PFS was 24.9 months compared with 16.6 months in the Stage III NVRD and Stage III/IV VRD populations of the placebo group, respectively.[64,82]

2) The treatment effect may be different in the Stage III NVRD and Stage III/IV VRD populations. In PAOLA-1, a HR of 0.45 was observed in the Stage III NVRD population compared with 0.65 in the Stage III/IV VRD population, but this difference was not statistically significant.[64,82]

Table 21: PFS results from the SOLO-1 and PAOLA-1 trials

Trial	Population	Treatment arm	Median PFS (in months)	HR
SOLO-1[43,83]	ITT	Olaparib (n=260)	NR	0.30 (95% CI 0.23–0.41)
		Placebo (n=131)	13.8	
	Stage III, upfront surgery, NVRD	Olaparib (n=114)	NR	0.32 (95% CI 0.20-0.51)
		Placebo (n=58)	21.9	
PAOLA-1[64,82]	Stage III patients with PCS and VRD, patients who had received NACT, Stage IV patients	Olaparib + bevacizumab (n=399)	22.0	0.65 (95% CI 0.51-0.82)
		Placebo + bevacizumab (n=196)	16.6	

Trial	Population	Treatment arm	Median PFS (in months)	HR
	Stage III patients with PCS and NVRD	Olaparib + bevacizumab (n=138)	NR	0.45 (95% CI 0.27-0.75)
		Placebo + bevacizumab (n=73)	24.9	

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treatment; NACT, neoadjuvant chemotherapy; PCS, primary cytoreductive surgery; PFS, progression-free; VRD, visible residual disease

Although the populations within these studies are not directly comparable to the patients in PRIMA due to differences in study design and patient inclusion criteria, the results from the placebo groups support previous findings that patients with Stage III NVRD are associated with better clinical outcomes than patients with Stage III/IV VRD. Further, the PFS HRs are useful for understanding the impact of PARP inhibitor maintenance treatment options compared to placebo in these populations.

Given that the results above provide evidence that there is likely a positive treatment effect for Stage III patients with NVRD compared to Stage III/IV patients with VRD, the PRIMA study outcomes were explored to assess whether they could be used to inform the magnitude of the expected treatment effect in the Stage III NVRD population.

As demonstrated in subgroup analyses (Figure 13 in Section B.2.7), patients in PRIMA with Stage III OC responded better to treatment with niraparib than those in the ITT population, with a HR for PFS of 0.54 (95% CI: 0.42-0.80) compared with 0.62 (95% CI 0.50-0.76) respectively.

The treatment effect observed in the Stage III VRD cohort in PRIMA can therefore be used as a minimum benchmark of the treatment effect for the Stage III NVRD cohort. This assumption is based on the evidence that demonstrates patients with NVRD have an improved treatment response, regardless of the treatment provided, compared to those with VRD, as presented in Table 18 and Table 21. Therefore, as a conservative estimate, a PFS HR of at least 0.54 would be expected to be achieved in the Stage III NVRD population treated with niraparib.

6) Regulatory discussions

There have been no questions raised regarding the difference in the PRIMA ITT and MA populations during the regulatory discussions with the EMA to date. However, GSK is relatively early in the regulatory process and only the Preliminary Assessment Reports have been received from EMA.

B.3 Cost effectiveness

Summary of the cost-effectiveness analysis

- A three-state cohort-based partitioned survival model was developed to evaluate the cost-effectiveness of niraparib versus RS in patients with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy.
- The model structure comprises three health states of progression-free disease (PFD), split into two sub states (on treatment and off treatment), progressed disease (PD) and death, and is populated with clinical data (time to-event outcomes, health state based utilities by EQ-5D, subsequent treatment options and adverse events) from the PRIMA study and supplemented with relevant clinical and economic literature. A three-year stopping rule (in line with the PRIMA protocol) was modelled such that [redacted]% of patients remaining on treatment discontinued at three years.
- For the population of patients with newly diagnosed, histologically confirmed advanced cancer of the ovary, peritoneum, or fallopian tube, relevant to this appraisal, efficacy data were extrapolated from the PRIMA ITT dataset to the MA population based on evidence from external data sources (primarily the PAOLA-1 clinical trial to produce curves for Stage III patients with no visible residual disease after cytoreductive surgery (NVRD).[64] Curves for the MA population were produced by weighting the curves for the ITT and Stage III patients with NVRD.
- In the ITT data set of PRIMA, PFS was modelled using a standard parametric approach through the fitting of survival functions to the observed KM data from the PRIMA trial for niraparib and RS. For the ITT dataset, OS with RS was modelled based on PRIMA KM in the same way as PFS. Due to the immaturity of the trial data, the choice of extrapolated curves for the RS arm were validated with real world evidence from the University of Edinburgh Ovarian Cancer Database. For the niraparib arm, due to highly immature OS data (9.9%), a

mean ΔPFS:ΔOS relationship of 1:2 was applied to simulate the niraparib OS curve. PFS and OS were modelled over a lifetime horizon of 39 years.

- To capture the progression of the disease in clinical practice, patients that remain progression-free for at least 7-years after response to first-line platinum chemotherapy were considered long-term survivors of OC and no longer at risk of relapse. After year 7, mortality in this group of patients was modelled as being unrelated to OC. Alternative landmarks were applied in sensitivity analysis.
- For the MA population, the base case estimated that niraparib is cost effective, providing [redacted] additional QALYs, with an incremental cost of £[redacted]. The cost per QALY gained versus RS was £13,870. In the probabilistic analysis, the corresponding cost per QALY gained was £13,792, and niraparib has a 100% probability of being cost-effective at a willingness to pay threshold of £30,000. Niraparib is also shown to be cost-effective in the ITT population. This gives increased confidence for decision making in the MA population, which shows a slightly improved cost effectiveness due to the addition of patients with NVRD who are associated with an improved prognosis.

B.3.1 Published cost-effectiveness studies

An economic SLR was performed to identify published studies reporting cost-effectiveness evaluations, quality-of-life and cost and resource use of patients with ovarian cancer. The cost-effectiveness review focussed on maintenance therapies only. Full details of the cost effectiveness SLR are presented in Appendix G: Published cost-effectiveness studies.

Following first and second pass screening of the 8,631 references retrieved in the SLR, a total of 56 studies met the selection criteria for the cost-effectiveness (29), cost and resource use (23), and quality-of-life (41) review questions and were extracted. The cost and resource use and quality-of-life studies are summarised in later sections. A summary of the economic evaluation studies is provided in Table 22 below.

All 29 economic evaluation references (n=24 unique studies) reported the cost-effectiveness of maintenance therapy in platinum-sensitive ovarian cancer patients that had a complete or partial response to therapy. The cost-effectiveness references described patients who had received one line of previous chemotherapy (n=3) and at least two lines of prior chemotherapy (n=26). Maintenance therapies in other settings (two lines of prior chemotherapy or more) were included to provide evidence on model structure as well as AE, cost, and resource use inputs. A total of six studies adopted a UK perspective. A partitioned survival model structure was adopted in six studies, a decision tree structure was adopted in two studies, a Markov model structure was adopted in six studies and the nine studies report a decision analytic structure. One study stated that no model structure was developed and instead survival was divided by total costs to give cost per life year. Three references were identified in the first-line maintenance setting; NICE 2019 (TA598), Tan 2019 and CADTH 2019).

Table 22: Summary of economic evaluations identified in the SLR

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
NICE (TA598)[84]	2019	-Olaparib -RS	Region, currency: UK, GBP Perspective: UK NHS and PSS Model design: Partitioned survival model Health states included: PFD, PD and death Time horizon: Lifetime (50 years)	Patients with newly diagnosed advanced high grade epithelial ovarian, fallopian tube or primary peritoneal cancer -BRCA1/2-mutated	NR (redacted)	NR (redacted)	ICER £/LYG: £8,963 ICER £/QALY: £11,830
CADTH[85]	2019	-Olaparib -RS	Region: Canada, CAD ($) Perspective: Government Model design: Partitioned survival model with three health states (PFD, PD and death) Time horizon:	Patients with newly diagnosed, advanced, BRCA-mutated (germline or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are	Sponsor submitted: Incremental costs ($): 80,276 EGP reanalysis: Incremental costs ($): 69,501	Sponsor submitted Olaparib vs. RS Incremental QALYs - Overall; PFS; PD; adverse events: 3.73; 5.299; -1.568; -0.000	Sponsor's best estimate: $21,517 per QALY EGP best estimate: $57,784 per QALY

Company evidence submission template for niraparib in patients with newly diagnosed advanced ovarian, fallopian tube or peritoneal cancer.

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
			30 years	in response (complete or partial) to first-line platinum-based chemotherapy.		EGP analysis: Incremental QALYs - Overall; PFS; PD; adverse events: 1.203; 1.836; -0.632; -0.001	
Tan (abstract only) [86]	2019	-Olaparib -RS	Region: Singapore, SGD ($), Perspective: Healthcare payer Model design: Three-state partitioned survival model Time horizon: Lifetime (50 years)	Patients with newly diagnosed advanced ovarian cancer and a BRCA1/2 mutation	NR	NR	17,326 SGD/QALY gained
Chin 2018 (Abstract and poster)[87,88]	2018	-Rucaparib -Placebo	Region, currency: USA, USD ($) Perspective: US health system	Patients with advanced ovarian cancer -BRCAmut	Rucaparib versus placebo was $264,989.	Incremental QALYs for rucaparib versus placebo was 0.73.	$361,535/QALY gained

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
			Model design: Partitioned survival model Health states included: PFD, PD and death Time horizon: Lifetime				
Dottino (Abstract only)[89]	2018	-Observe all -Treat all with niraparib to progression -BRCA germline mutation testing and selective treatment of carriers -BRCA germline and tumor HRD testing and selective treatment of both BRCA carriers and those with HRD + tumors.	Region, currency: USA, USD ($) Perspective: US health system Model design: A decision analysis model which evaluated time in PFD only	Patients with platinum-sensitive recurrent ovarian cancer	Mean cost/patient: Observation - $827 gBRCA testing/selective treatment - $44,221 gBRCA testing + HRD testing/selective treatment - $105,933 Treat all - $165,703	PF-QALY Benefit/patient (years): Observation - 0.29 gBRCA testing/selective treatment - 0.48 gBRCA testing + HRD testing/selective treatment - 0.71 Treat all - 0.74	gBRCA testing/selective treatment - $225,919/PF-QALY gBRCA testing + HRD testing/selective treatment - $262,463/PF-QALY Treat all - $2,377,992/ PF-QALY

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
Dottino 2019[90,91] (Abstract and full paper)	2019	-Observation -BRCA germline mutation testing, followed by selective treatment of only those patients with gBRCAmut with maintenance PARP inhibitor ("gBRCA only") -Both BRCA germline mutation testing and tumor HRD testing, followed by selective treatment of only those patients with either gBRCAmut or HRD+ tumors	Region, currency: USA, USD ($) Perspective: Societal perspective Model design: Decision analysis model which evaluated time in PFD only Time horizon: 24 months	Patients with platinum-sensitive recurrent ovarian cancer (Stage III or IV)	Cost/Patient ($); Additional Annual Cost to U.S. Health System ($) Observation: 827; — gBRCA testing or selective treatment: 46,157 ; 249 million gBRCA testing plus HRD testing or selective treatment: 109,368; 597 million Treat all: 169,127 ; 926 million	PF-QALY Benefit/Patient (mo); PF-QALY Benefit/Patient (y) Observation: 3.4 ; 0.29 ; — gBRCA testing or selective treatment: 5.7 ; 0.48 gBRCA testing plus HRD testing or selective treatment: 8.5 ; 0.71 Treat all: 8.8 ; 0.74	ICER($/PF-QALY) gBRCA testing or selective treatment: 243,092/ PF-QALY gBRCA testing plus HRD testing or selective treatment: 269,883/ PF-QALY Treat all: 2.2 million/ PF-QALY

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
		with maintenance PARP inhibitor ("gBRCA and homologous recombination deficiency only") -Treatment of all patients with maintenance PARP inhibitor ("treat all").					
Fernandez-Santos (Abstract and poster)[92,93]	2017	Pegylated liposomal doxorubicin (PLD), gemcitabine, topotecan, paclitaxel, anti-VEGF therapy (PLD+ bevacizumab), trabectedin + PLD followed by platinum, anti-VEGF therapy (carboplatin +	No model used. Health economics outcomes were calculated by means of dividing median treatment associated direct costs (Euro) by median overall survival (months);	Patients with relapsed ovarian cancer, stratified by type of refractoriness: Platinum resistant or refractory, Early relapse, Late relapse, Late relapse / not suited for platinum.	NR	NR	Early relapse: Trabectedin plus PLD followed by PBC versus PLD alone: 25,299/ LY gained Trabectedin plus PLD followed by PBC versus carboplatin plus PLD:

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
		gemcitabine + bevacizumab followed by bevacizumab), PARP inhibitor maintenance (BRCAm) (carboplatin + paclitaxel followed by olaparib), trabectedin + PLD					59,849/ LY gained Trabectedin plus PLD versus bevacizumab: 82,724/LY gain Trabectedin plus PLD versus PARP maintenance in BRCAmut patients: 52,509/LY gain Late relapse: Carboplatin or paclitaxel plus PLD are the cheapest treatment options, whilst neither bevacizumab nor olaparib-based

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
							schemes appear to be cost-effective (ICER estimates €-74,282 to €-166,280).
Fisher (a) – Abstract only[94]	2018	-Niraparib -RS -Olaparib -Rucaparib	Region, currency: USA, USD ($) Perspective: US payer Model design: Decision-analytic model Health states included: PFD, PD and death Time Horizon: Lifetime (40 years)	Patients with recurrent ovarian cancer, with or without germline BRCA mutation	Incremental costs: Niraparib vs. olaparib = -$57,575 and -$60,400 (niraparib had lower costs) (non-gBRCAmut and gBRCAmut) Niraparib vs. rucaparib= -$117,916 and -$261,950 (non-gBRCAmut and gBRCAmut)	NR	Niraparib vs RS = $94,186 and $58,804, for non-gBRCAmut and gBRCAmut respectively
Fisher (b) - Abstract and poster[95,96]	2018	Non-gBRCAmut population: -Niraparib	Region, currency: USA, USD ($)	Patients with recurrent ovarian cancer -gBRCAmut	Non-gBRCAmut - niraparib vs	Non-gBRCAmut - niraparib vs olaparib: Inc.	Niraparib vs RS - non-gBRCAmut = $94,186

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
		-RS gBRCAmut population: -Niraparib -RS -Olaparib	Perspective: US health payer Model design: Decision-analytic model Health states included: PFD, PD and death Time horizon: Lifetime (40 years)	-non-gBRCAmut	olaparib: Inc. costs; -$55,858 gBRCAmut - niraparib vs. olaparib: Inc. costs; -$60,400 Niraparib vs RS - NR	QALY gain: 1.437 gBRCAmut - niraparib vs. olaparib: similar QALY Niraparib vs RS - NR	Niraparib vs RS - gBRCAmut: $58,804 Niraparib dominated olaparib in both populations
Guy[97]	2018	-Niraparib -Olaparib -Rucaparib -RS	Region, currency: USA, USD ($) Perspective: US payer Model design: Decision analytic model Health states included: PFD, PD and death Time horizon: Lifetime	Patients with platinum-sensitive, recurrent, high-grade, serous epithelial ovarian, fallopian tube, or primary peritoneal cancer -gBRCAmut -non-gBRCAmut	gBRCAmut Intervention: Total costs ($) RS: 95,628 Niraparib: 396,802 Olaparib: 405,601 Rucaparib: 595,510 Non-gBRCAmut Intervention: Total costs ($) RS: 100,724 Niraparib: 333,322	gBRCAmut Intervention: Total LYG; Total QALYs RS: 3.564; 2.801 Niraparib: 8.824; 7.212 Olaparib: 8.824; 6.532 Rucaparib: 7.437; 6.050 Non-gBRCAmut Intervention: Total LYG; Total QALYs	gBRCAmut: ICER vs baseline (RS) RS: - Niraparib: 68,287 Olaparib: 83,078 Rucaparib: 153,866 Non-gBRCAmut: ICER vs baseline (RS) RS: - Niraparib: 108,287

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
					Olaparib: 355,558 Rucaparib: 406,883	RS: 2.816; 2.231 Niraparib: 5.351; 4.379 Olaparib: 3.727; 2.756 Rucaparib: 4.868; 3.948	Olaparib: 485,304 Rucaparib: 178,382 Intervention: ICER vs incremental intervention ($) RS: - Niraparib: 108,287
Liu (Abstract only)[98]	2017	-Olaparib -Niraparib -Rucaparib -Observation	Region, currency: US, USD ($) Perspective: US payer Model design: Decision-analysis model	Patients with platinum-sensitive recurrent epithelial ovarian cancer -gBRCA1/2 -Somatic HRD -wild-type	Population costs. olaparib, $251 million; niraparib, $286 million and rucaparib, $200 million. Observation: approximately $1 million.	NR	For patients with BRCA1/2 mutations: Olaparib vs observation: $195,788 per PF-LYS Niraparib vs observation: $196,117 per PF-LYS Rucaparib vs observation: $290,245 per PF-LYS

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
Mylonas (Abstract only)[99]	2016	-Olaparib -"Watch and Wait"	Region, currency: Greece, Euro (€) Perspective: Third-party payer Model design: Markov model Time horizon: Lifetime	Patients platinum sensitive recurrent ovarian cancer -BRCAmut	Total lifetime cost per patient: Olaparib: 85,716€ Watch and Wait: 12,144€	Olaparib vs. Watch and Wait: Discounted QALYs: 0.89 greater YSFC: 1.34 greater	€63,046/LY gained and €82,799/QALY gained
NICE (TA528)[100]	2018	-Niraparib -RS -Olaparib	Region, currency: UK, GBP Perspective: UK NHS and PSS Model design: A decision analytic model Health state included: PFD, PD and death Time horizon: Lifetime (40 years)	Patients with platinum-sensitive recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer	NR (redacted)	NR (redacted)	Non-gBRCAmut: (Niraparib vs. RS):£29,560/QALY gBRCAmut 2L: (Niraparib vs. RS): £25,837/QALY gBRCAmut 3L+: (Niraparib vs. Olaparib): £14,078/QALY.
NICE (TA620)[101]	2020	-Olaparib -RS	Region, currency: UK, GBP (£)	Patients with platinum-sensitive	NR (redacted)	NR (Redacted)	£46,263/QALY

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
			Perspective: UK NHS and PSS Model design: Partitioned survival model Health states included: PFD, PD and death Time horizon: Lifetime (30 years)	relapsed high-grade epithelial ovarian, fallopian tube, or peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy			
NICE (TA611)[102]	2019	-Rucaparib -Olaparib -RS	Region, currency: U, GBP (£) Perspective: UK NHS and PSS Model design: Partitioned survival model (PFD on and off maintenance, PD and death) Time horizon: 30 years	Patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy -BRCAmut	NR (redacted)	NR (redacted)	ITT: £50,249/ QALY gained BRCA 3L+ Rucaparib dominated olaparib

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
SMC[103]	2018	-Niraparib -Olaparib -RS	Region, currency: Scotland, GBP (£) Perspective: NHS Scotland Model design: Decision analytic model Health states included: PFD, PD and death. Time horizon: Lifetime (40 years)	Patients with high grade serous, recurrent, platinum-sensitive ovarian, fallopian-tube or primary peritoneal cancer -gBRCAmut -non-gBRCAmut	NR (redacted)	NR (redacted)	non-gBRCAmut 2L+: Niraparib vs RS - £47,471 gBRCAmut 2L+: Niraparib vs RS - £27,165 Niraparib vs Olaparib (Olaparib list price) - £19,797
Smith(a)[104]	2015	-Olaparib -Observation	Region, currency: USA, USD ($) Perspective: Third-party payer Model design: Two separate decision analysis models: gBRCA1/2 mutation	Patients with ovarian cancer -gBRCA1/2 mutation -Wild-type BRCA1/2 mutation	Observation - BRCA1/2 mutation (N = 1110): $5.5 million (M) versus $169.2M for maintenance therapy with olaparib (annual). Wild type BRCA1/2 – Observation:	NR	gBRCA1/2: $258,864 per PF-LYS. Wild type BRCA1/2: $600,552 per PF-LYS

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
			Wild-type BRCA1/2 mutation		$22.1M compared to a cost of $444.2M for olaparib maintenance therapy (annual). The cost of olaparib was estimated at $13,440 per month.		
Smith(b) (Abstract only)[105]	2015	-Olaparib -Observation	Region, currency: USA, USD ($) Perspective: NR Model design: Two separate decision analysis models: gBRCA1/2 mutation Wild-type BRCA1/2 mutation	Platinum-sensitive patients with recurrent ovarian cancer	The 1110 patients with a BRCA mutation: Cost of observation: $5.5 million Maintenance therapy with olaparib: $91.3 million The 4449 wild-type BRCA: Maintenance therapy with olaparib: $244.1 Million	NR	BRCA mutation: $135,672 per PF-LYS. Wild-type BRCA: $315,840 per PF-LYS.

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
Wolford[106]	2017	-Olaparib -Rucaparib -IV administered drugs	Region, currency: USA, USD ($) Perspective: NR Model design: Markov model Health states included: response, haematological complications, non-haematological complications, progression, and death.	Patients with recurrent ovarian cancer	Costs prior to progression Olaparib: $114,478 Rucaparib: $137,068	NR	Platinum-based combinations $1,672/PFS mo Non-platinum agents ($6,688/PFS mo) Bevacizumab-containing regimens ($12,482/PFS mo) Olaparib ($13,3731/PFS mo), Rucaparib ($14,034/ PFS mo).
Wolford (Abstract only)[107]	2018	-Paclitaxel (GOG 212) -Bevacizumab (GOG 218, ICON 7, OCEANS, GOG 213); -Niraparib (NOVA) -Olaparib (SOLO-2)	Region, currency: USA, USD ($) Perspective: US Medicare Model design: Markov model Health states included: response, haematological	Patients with advanced ovarian cancer	Expected costs of PARP inhibitors prior to progression: Approx. $471,989 (18.8x paclitaxel, 6.9x pembrolizumab, and 2.2-2.7x bevacizumab).	NR	Paclitaxel was the most cost-effectiveness - $870/PFS month Comparing pembrolizumab to PARPi(s): ICER per month LY gained:

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
		-Rucaparib (ARIEL-3 - Pembrolizumab .	complications, non-haematological complications, progression, and death.				Niraparib - $20,032 Rucaparib - $18,444 Olaparib - $17,520
Wolford (Abstract only)[108]	2019a	-Olaparib -Bevacizumab	Region, currency: USA, USD ($) Perspective: US Medicare Model design: Markov model (response, complications and progression) Time horizon: NR	Patients with advanced ovarian cancer	NR	NR	With an estimated 6-month improvement in PFS, the ICER of bevacizumab was $416,051 PF-LYS. Considering only BRCAmut patients with an expected 20-moth median PFS and similar PFS improvement, the ICER of bevacizumab would be $565,362 PF-LYS.

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
Wolford (b) (Abstract only)[109]	2019	-Olaparib -Recurrent maintenance setting	Region, currency: USA, USD ($) Perspective: US Medicare Model design: Markov model (response, haematological complications, non-haematological complications, progression, and death.) Time horizon: NR	Patient with deleterious or suspected deleterious germline or somatic BRCAmut advanced ovarian carcinoma	NR	NR	SOLO 1 was associated with $312,480 PF-LYS per individual patient, while SOLO2 demonstrated $498,045 PF-LYS. Maintenance olaparib was found to be more cost-effective in the first-line setting, with an ICER of $12,149 per month of life gained when compared directly to SOLO2
Zhong(a)[110]	2018	-Olaparib -Niraparib -Placebo	Region, currency: USA, USD ($)	Patients with recurrent epithelial ovarian,	All patients: Placebo - $1,200	Second model - QA-PFS Life Year All patients:	All patients: Placebo - Olaparib - $287

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
			Perspective: US health care sector Model design: Decision tree model Time horizon: A relatively short time horizon (number of years not reported).	fallopian tube, or primary peritoneal cancer	Olaparib - $123,2000 Niraparib - $138,000 Patients with a BRCA mutation Placebo - $1,600 Olaparib - $256,300 Niraparib - $257,100 Patients without a BRCA mutation Placebo - $1,100 Olaparib - $99,600 Niraparib - $117,100	Placebo - 0.27 Olaparib - 0.60 Niraparib - 0.73	Niraparib - $235 Patients with a BRCA mutation: Placebo - N/A Olaparib - $197 Niraparib - $226 Patients without a BRCA mutation: Placebo - N/A Olaparib - $328 Niraparib - $253
Zhong (b) (Abstract and poster)[111,112]	2018	-Olaparib -Niraparib -Placebo	Region, currency: USA, USD ($) Perspective: US health care sector	Patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in a	NR	NR	The ICERs per PFS life-year (compared to placebo) Niraparib: $235K Olaparib: $287K

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
			Model design: Decision tree model Time horizon: A relatively short time horizon (number of years not reported).	complete or partial response to the most recent chemotherapy			

Abbreviations: BRCA, Breast cancer susceptibility gene; EGP, Economic Guidance Pane; ;IV, intra-venous; GBP, Great British Pound; NHS, National Health Service; NR, not reported; PD, progressed disease; PFD, progression-free disease; PSS, Personal Social Services; UK, United Kingdom; US, United States; USD, US Dollar; YSCF, Years spent chemotherapy free.

B.3.2 Economic analysis

This section describes the company's approach to estimating the cost-effectiveness of niraparib maintenance therapy versus RS in the first-line maintenance setting for patients with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. Key features of the economic analysis are provided in Table 23. Further details are provided in subsequent sections.

Table 23: Summary of the economic analysis

Aspect	Details	Justification
Patient population	Patients with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy	Aligned with anticipated license of niraparib and final NICE scope
Analytical method	Partitioned survival model	The choice of modelling approach was informed by the precedent set by the Committee and review group in TA381 and TA528; and by the approach adopted in ID1296 and TA598. The chosen approach is consistent with the method used in the majority of advanced cancer appraisals reviewed by NICE.
Model structure	Three-health states (progression-free disease, progressed disease, and death) Two 'sub-states' are included for progression-free disease; on-treatment and off-treatment.	A three-health state structure is consistent with approaches accepted in previous NICE technology appraisals in oncology and utilises the key primary (PFS) and secondary (OS) endpoints of the PRIMA trial.
Time horizon	Lifetime (39 years)	As per NICE guidance, a lifetime model (assumed to be 100 years minus the baseline age of 61 in the model) was used. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.[113] This assumption is in line with assumptions made by the ERG and accepted by the Committee in NICE appraisal TA598.
Cycle length	Monthly cycles (30.44 days)	The chosen cycle period allows to capture all relevant costs and health benefits and is consistent with approaches accepted in previous NICE appraisals for maintenance therapies in

Aspect	Details	Justification
		ovarian cancer. Shorter cycle lengths are likely to overcomplicate the model calculation given the use of a lifetime horizon of 39 years and to not meaningfully impact on cost or QALY estimates, while longer cycle lengths increase the risk of over or under predicting costs or QALYs when averaging across cycle times. A half cycle correction was applied.
Discounting options	Costs and health outcomes at 3.5% per annum	In line with NICE reference case[113]
Perspective	NHS and PSS	In line with NICE reference case[113]
Treatment arms within executable model	• Niraparib • RS	In line with final NICE scope and treatment in the PRIMA study
Health effects	Quality-adjusted life-years (QALYs) Life years (LYs)	In line with NICE reference case[113]
Clinical efficacy and safety	Data were sourced from: • PRIMA study • Published clinical evidence • UK population general mortality	The PRIMA study is the primary source of evidence of the efficacy and safety of niraparib maintenance treatment, in the first-line maintenance treatment setting
Costs and resource use	Data were sourced from: • BNF for drug costs • NHS reference costs for disease management unit costs • A systematic review of published studies • Previous HTA appraisals within Ovarian Cancer • Clinical expert opinion	In line with NICE reference case[113]
Utilities	Data were sourced from: • EQ-5D data collected from the PRIMA study	In line with NICE reference case[113]

Abbreviations: BNF, British National Formulary; ERG, Evidence Review Group; EQ-5D-3L, EuroQoL-Five dimensions-Three levels; HTA, health technology appraisal; LY, life years; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OC, ovarian cancer; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; UK, United Kingdom

Patient population

In line with the NICE scope, the economic analysis evaluates the cost-effectiveness of niraparib versus RS in the maintenance treatment of patients with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. This population is in line with the population defined in the NICE scope and decision problem (Table 1) and falls within the anticipated MA for niraparib.

The population in PRIMA included patients with newly diagnosed, histologically confirmed advanced cancer of the ovary, peritoneum, or fallopian tube cancer. All patients had high-grade serous or endometrioid tumours that were classified as Stage III or IV (at diagnosis), according to the criteria of the International Federation of Gynaecology and Obstetrics. The eligibility criteria of the trial included patients with Stage III disease with visible residual tumour after PCS, inoperable Stage III disease, or any stage IV disease, as well as those who had received neoadjuvant chemotherapy (regardless of stage).[114,115] The baseline characteristics of the PRIMA population are summarised in Table 9, Section B.2.3.2 of the submission.

As previously described, Stage III patients with NVRD after PCS were not included in the PRIMA study. The rational for including these patients within a NICE recommendation is set out in Section B.2.14. In summary; clinical advisory board discussions, individual physician interviews (Appendix N: Questionnaire used for clinical interviews), a real-world database analysis (see Appendix L: University of Edinburgh Ovarian Cancer Database study protocol and Section B.2.14) and a targeted literature review (see Appendix M: Targeted literature review for overall survival outcomes in patients with advanced ovarian cancer) confirmed that the clinical need and the extrapolation of the PRIMA trial data to the NVRD population is appropriate for the following reasons:

- NVRD patients constitute about [redacted]% of the whole population.[82,116]
- Patients with NVRD have a better prognosis than those with visible residual disease irrespective of the treatment options received, however they are still at risk of recurrence.[117]

- Clinical evidence suggests that PARP inhibitors demonstrate improved outcomes in patients with NVRD (as observed in the PAOLA-1 phase III trial of olaparib plus bevacizumab versus bevacizumab monotherapy for the maintenance treatment of newly diagnosed advanced ovarian cancer patients[64,82]) and SOLO-1 trials (phase III trial of olaparib monotherapy versus placebo in newly diagnosed advanced ovarian cancer patients[118,119]).

The method used to estimate efficacy outcomes for Stage III patients with NVRD after PCS is detailed in Section B.3.3.

This de novo economic analysis estimates the cost-effectiveness of niraparib compared to RS for the anticipated MA population. In order to support and provide confidence in the MA population results, the results for the PRIMA ITT population are also presented. Complete sets of results are presented for both populations.

Time horizon

In line with the NICE reference case, a lifetime horizon (39 years [100 years - mean age at baseline]) from the date of starting maintenance treatment was used in the base case. This covers the period over which all important differences in costs or outcomes between niraparib and RS would be observed, including those relating to the subset of patients that could be expected to achieve long-term remission after first-line PBC. The impact of shortening the time horizon is explored in scenario analyses.

Discounting

The discount rate used in the base case for both costs and outcomes are 3.5% per annum, as per the NICE reference case. Section 6.2.19 of the 2013 NICE methods guide, recommends that if it is likely that based on the evidence presented, long-term health benefits are likely to be achieved, a discount rate of 1.5% should be considered by the Committee. A discount rate of 1.5% is therefore explored in scenario analysis. Additional discount rates of 0% and 6% were also considered as scenario analyses.

Perspective

The model adopts a National Health Service and Personal Social Services (NHS/PSS) perspective as recommended by the NICE reference case. This includes resource use and costs associated with disease management, treatment acquisition, AEs and end-of-life care.

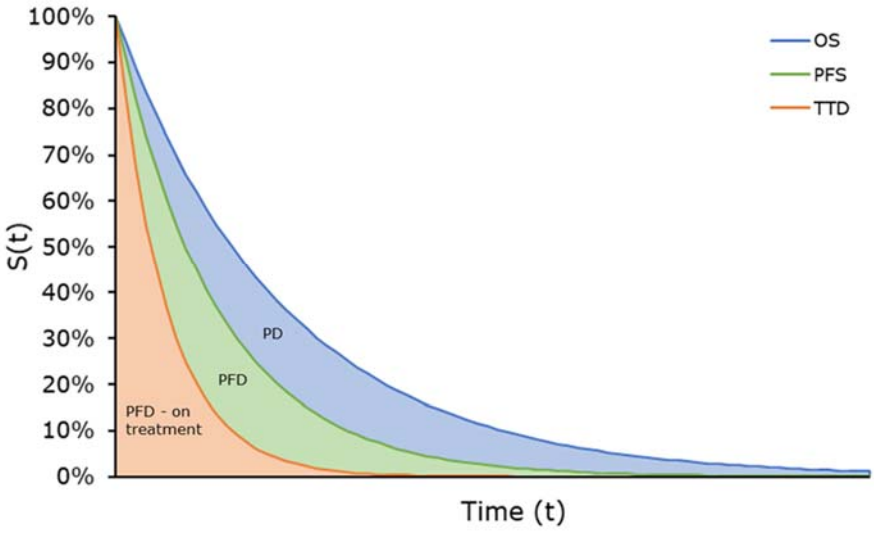
Model structure

A de novo partitioned survival model was developed to assess the cost-effectiveness of niraparib versus RS. The de novo model includes the following three disease specific health states:

- PFD
    - On treatment
    - Off treatment
- PD
- Death, from any cause

The two sub-health states for PFD allow for a split of patients on and off treatment determined by time to treatment discontinuation (TTD) data. An illustration of the model state structure is provided in Figure 16. The model was developed in Microsoft Excel.®

Figure 16: Model schematic



Abbreviations: PD, progressed disease; PFD, progression-free disease; PFS, progression-free survival; OS, overall survival; s(t), survival at time t; TTD, time to treatment discontinuation

This partitioned survival modelling (PSM) approach is consistent with the preferred approaches of Evidence Review Groups and Committees in previous NICE appraisals of maintenance treatment in ovarian cancer (TA381, TA620, TA598), and is consistent with the approaches adopted in the majority of economic evaluations submitted to the NICE for the health technology appraisal (HTA) of treatments for advanced cancer.[120–122] Furthermore, partitioned survival models are extensively and routinely used to model the costs and outcomes of oncology treatments in the UK and globally across HTA bodies. The application of PSMs is well understood by both clinicians and health economists. In a recent review by NICE, it was found that 73% of 30 recent oncology appraisals assessed by NICE used a partitioned survival model.[123]

The three health states in the PSM are mutually exclusive, meaning that patients must occupy one of the states at any given time. The selected health states are consistent with the clinical endpoints assessed in PRIMA, including the primary endpoint of PFS and the secondary endpoint of OS, and capture the disease progression of patients with ovarian cancer. State occupancy is evaluated at monthly intervals equivalent to 30.44 days (365.25/12).

PFD state membership was estimated from the extrapolated PFS KM curve, the state membership of the dead state is estimated using the extrapolated OS Kaplan-Meier curve (Death=1-OS) for the RS arm and the simulated OS curve for the niraparib arm. PD state membership is estimated to be the difference between the OS and PFS curves (PD=OS-PFS).

PFS was assessed by BICR,[114] defined as the time from the date of treatment randomisation to the date of first documentation of progression or death due to any cause; or, in the absence of documented progression, whichever occurred first. Determination of radiological progression was based on imaging assessments according to Response Evaluation Criteria in Solid Tumours v.1.1 (RECIST), and clinical progression was determined through a combination of diagnostic tests and clinical signs and symptoms, plus raised CA-125 levels.

Patients remain in the PD health state, calculated as the difference between the cumulative survival probability of OS and the cumulative survival probability of PFS. The numbers occupying the death state are estimated as one minus the OS curve. OS for RS is calculated from extrapolations of the PRIMA KM data, which have been validated by long-term real-world evidence available from The Edinburgh Ovarian Cancer Database and through discussions with UK key opinion leaders (KOLs).[124] Immaturity of the niraparib OS data and the lack of mature OS data to validate the extrapolations of niraparib, however, inhibit the construction of robust long-term survival extrapolations. Thus similar methods to those adopted in TA528[125], of using a mean ΔPFS:ΔOS relationship, were used within this submission.

The PFD health state reflects disease remission (PFD after response to first-line PBC) whilst PD reflects the return of disease. These states are associated with different morbidity and mortality burden to the patient. The onset of progression in a maintenance setting also marks the transition to a state of progressive disease from stable disease, requiring a change in the follow-up and the management of patients alongside the administration of further treatment, with associated costs to the NHS.

Alongside PFS and OS, the model independently simulates the TTD with niraparib using KM data on the time from randomisation to discontinuation of study treatment in

PRIMA. This ensures that the modelled drug costs for niraparib reflect the actual drug usage in PRIMA, including the time on treatment for those that discontinue therapy early (e.g. prior to progression) due to unacceptable toxicity or any other reason.

The treatment and management costs while on active first-line maintenance treatment is modelled through TTD data. This modelling approach allows different treatment costs and disease management resource use to be assigned to patients on and off first-line maintenance treatment.

Subsequent treatment options (second-line and third-line) are included in the cost-effectiveness analysis. Modelling of subsequent line chemotherapy and PARP therapy were implemented by a one-off sum approach which allows the model to include a range of complex calculations in a simple manner (further details are provided in Section B.3.5). The approach followed the NICE position statement around the inclusion of active therapies available through CDF in the economic evaluations.[126] With this approach subsequent chemotherapy regimens for the platinum sensitive and platinum resistant patients can be estimated for both second- and third-line.

A previous submission in the field considered the development of a four-state model, separating the PD heath state by on second-line treatment or off second-line treatment. This was not considered necessary or suitable for the decision problem at hand for the following reasons:

- Subsequent treatments (second and third-line) are expected to be relatively similar between the two treatment arms with the exception of the proportion of patients receiving chemotherapy treatment options based on their platinum sensitive status, which is captured in the one-off sum approach as well.

- The NICE position statement explicitly states that the economic base case should not consider treatment options that are not available through routine commission.[126] The base case considers the use of subsequent PARP inhibitors available through routine commissioning (i.e. olaparib third-line for platinum-sensitive *BRCA*mut patients for patients who have not previously received a PARP therapy). PARPs available in second line are available

through the CDF only, and are therefore not considered as part of the base case. As such, only a small proportion of RS patients are eligible to receive a PARP (<8%) within the economic analysis; olaparib third-line maintenance for platinum-sensitive patients with a *BRCA* mutation. This means that between niraparib and RS only a minor difference would be observed in third-line subsequent treatment costs. The introduction of the fourth health state would not help to capture the effect of the third-line treatments, only of those received in the second-line line.

- Time to event data from PRIMA to explicitly track subsequent treatments is immature. PFS2 data would be used to define the second-line and further subsequent lines of therapy. PFS2 from PRIMA is only 20% mature[127], which is 11% less mature than that observed in SOLO-1 (31% maturity). Therefore, splitting the PD health state by on or off second-line subsequent treatment would have required making further assumptions about the timing and proportion of patients who receive them. Furthermore, the addition of PFS2 would not alleviate any uncertainty that arise around long-term OS assumptions.

- The evidence elicited from ENGOT-OV16/NOVA and Study 19 suggests that the overall use of platinum and non-platinum chemotherapy in third and subsequent lines of therapy is likely to be similar and therefore have a limited impact on the incremental results.[42,43] (After calculating the drug and administration costs of subsequent platinum and non-platinum therapies, and third-line PARP, they were therefore applied as one-off cost upon progression.)

In order to explore uncertainty around the assumptions made in the present model, extensive scenario analyses were conducted around subsequent treatments, particularly around relaxing the requirement of not considering treatments that are currently in the CDF as subsequent treatments. Some uncertainty remains around the proportion of patients on RS who will receive third-line PARP inhibitors; however it is likely to be a low number (estimated at less than 8%), particularly because in clinical practice is it likely that patients will receive second line PARP through the CDF, if

eligible. More information on the subsequent treatment pathways and underlying uncertainties is available in Section B.3.5

Other costs and health effects captured in the analysis include AEs costs, the costs of routine follow-up, disease and treatment monitoring, and terminal care costs (see Section B.3.5 for additional details).

Consistent with the NICE reference case,[113] the HRQoL impact of treatment was measured in terms of quality adjusted life years (QALYs) using EQ-5D-based health state utility values (HSUVs) evaluated using UK general population preference weights. Using the Van Hout et al. crosswalk algorithm,[128] EQ-5D-5L data collected in PRIMA was mapped to EQ-5D-3L HSUVs, as recommended by NICE. HSUVs were then assigned to the PFD and PD states. The effect of AEs on HRQoL were modelled as a one-off QALY loss applied at the start of the model.

Marketing authorisation adjustment

As outlined in Section B.2.14, the patient population included in the NICE scope and anticipated niraparib European license, is broader than the ITT population in the PRIMA study. In order to implement the extrapolation between the PRIMA ITT and the MA population, three data sources were considered: SOLO-1, PAOLA-1 and PRIMA.[1,32,34,35] For the purpose of the base case analysis, data from the PAOLA-1 study was used, with the other two methods being explored within scenario analyses. Further details on the MA adjustment can be found in Section B.3.3.

Capturing long-term remission

In current clinical practice, and without the use of an effective maintenance therapy, approximately 15% of patients with Stage III–IV epithelial ovarian cancer will be classified as long-term survivors having remained progression-free beyond 7-10 years since diagnosis. In TA598 (olaparib 1L) this ‘exceptional’ responder group is reflected in the model so that after a chosen time, the survival rate for the proportion of patients progression-free was set to all-cause general population mortality. A similar approach was adopted within this analysis. Based on expert advice, a time point of seven years was used in the base case, the same as in TA598[129]. Sensitivity landmarks of 5 and

10 years were explored. The assumptions underpinning the modelling of long-term remission have been validated by a series of KOL interviews and at a UK advisory board. For further details on the long-term remission assumption please refer to Section B.3.3.

Comparison of chosen methods to previous appraisals

A comparison of methods selected for this appraisal and the approaches adopted in previous ovarian cancer appraisals is provided in Table 24. The approaches used in this submission closely match the preferred methods of the Committees and review groups in previous ovarian cancer appraisals.

Table 24: Features of the economic analysis

Factor	Previous appraisals				Current appraisal	
	TA381	TA389	TA528	TA598	Chosen values	Justification
Population and treatment	Recurrent OC – olaparib	Recurrent OC – chemotherapy	Recurrent OC – niraparib	Newly diagnosed OC – olaparib		
Modelling approach	Four-health state, semi-Markov modelling approach (ERG constructed a three-state partitioned survival model in response to the use of Markov modelling)	Three-health state, means based modelling approach	Three-health state, means based modelling approach	Three-health state, partitioned survival subsequently updated to a four-health state approach by the ERG	Three-health state, partitioned survival	Recently conducted for TA598 and aligns with precedent for oncology modelling
Time horizon	10 years	15 years	40 years	50 years	39 years	100 years – baseline age
Starting age	56.7	61.4	56-63	53.5	63	Average population age in PRIMA
Half-cycle correction	Yes	N/A	N/A	Yes	Yes	Prevents under- or over-estimation of costs and QALYs
Health effects measurement	QALYs	QALYs	QALYs	QALYs	QALYs	NICE reference case
Discount rate	3.5%	3.5%	3.5%	3.5% (1.5% in sensitivity analysis)	3.5%	NICE reference case

Factor	Previous appraisals				Current appraisal	
	TA381	**TA389**	**TA528**	**TA598**	**Chosen values**	**Justification**
Perspective (NHS/PSS)	Yes	Yes	Yes	Yes	Yes	NICE reference case
Source of utilities	PF: FACT-O from Study 19 mapped to EQ-5D PD: EQ-5D from OVA-301	EQ-5D from OVA301	EQ-5D from NOVA	EQ-5D from SOLO1	EQ-5D from PRIMA	EQ-5D-5L data from the PRIMA study mapped to EQ-5D-3L utilities as recommended in the NICE reference case
Source of costs	BNF, CMU, NHS reference costs	BNF, NHS reference costs, Unit Costs of Health and Social Care	BNF, NHS reference costs, Unit Costs of Health and Social Care	BNF, CMU, NHS reference costs, Unit Costs of Health and Social Care	BNF, NHS reference costs, Unit Costs of Health and Social Care, UK published literature	NICE reference case

Abbreviations: BNF, British National Formulary; CMU, Commercial Medicines Unit; ERG, evidence review group; EQ-5D,EuroQoL-Five Dimensions; FACT-O, Functional Assessment of Cancer Therapy - Ovarian Cancer; PF, progression-free; PSS, Personal Social Services; QALY, quality-adjusted life year; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; TA, technology appraisal

B.3.3 Clinical parameters and variables

Clinical data used in the analysis were primarily obtained from the PRIMA study and based on the full analysis set (FAS) population. PFS was modelled based on the primary endpoint of modified RECIST v1.1 assessed by BICR, while OS was modelled on the key secondary endpoint of time from randomisation to death from any cause.

The PFS Kaplan Meier data from PRIMA was used to generate survival curves for the ITT population for niraparib and RS. Due to issues with data immaturity, the University of Edinburgh Ovarian Cancer Database was used to clinically validate the choice of standard parametric curve used to extrapolate OS for RS (see Section B.2.14). It should be noted that as the simulated PRIMA population of the Edinburgh dataset included more severe patient in terms of ECOG score, that survival data obtained from the Edinburgh database should be used as a minimum benchmark to the validation of RS survival curves.

External clinical data from the PAOLA-1 study was used to estimate a HR which was applied to the ITT survival curves from PRIMA to estimate the PFS curves for Stage III patients with NVRD. The two curves were then weighted based on real-world evidence on the proportion of patients with NVRD ([redacted]%). The weighted curves are representative of the MA population for niraparib, and the population in the NICE scope.

Further detail on the modelling of PFS and OS is presented in the following sections. The general method of survival analysis is provided below.

General method of survival analysis

The method of survival analysis chosen was based on the guidelines presented in the NICE Decision Support Unit (DSU) technical support document (TSD) 14.[130] This approach included the following:

- An assessment of log-cumulative hazard plots to illustrate the hazards observed in the clinical trial period and allow inspecting if the hazards are likely to be non-monotonic, monotonic or constant. The plots were used to show

whether and where significant changes in the observed hazard occur as a method of considering which parametric models to use. If plots were non-parallel, then separate independent functions were fitted to each arm.

- Standard parametric models, including exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma were fitted to the PRIMA datasets for PFS, TTD and OS. Covariates for patient characteristics were not included in the parametric analysis due to baseline characteristics being balanced across treatment arms in the PRIMA study.

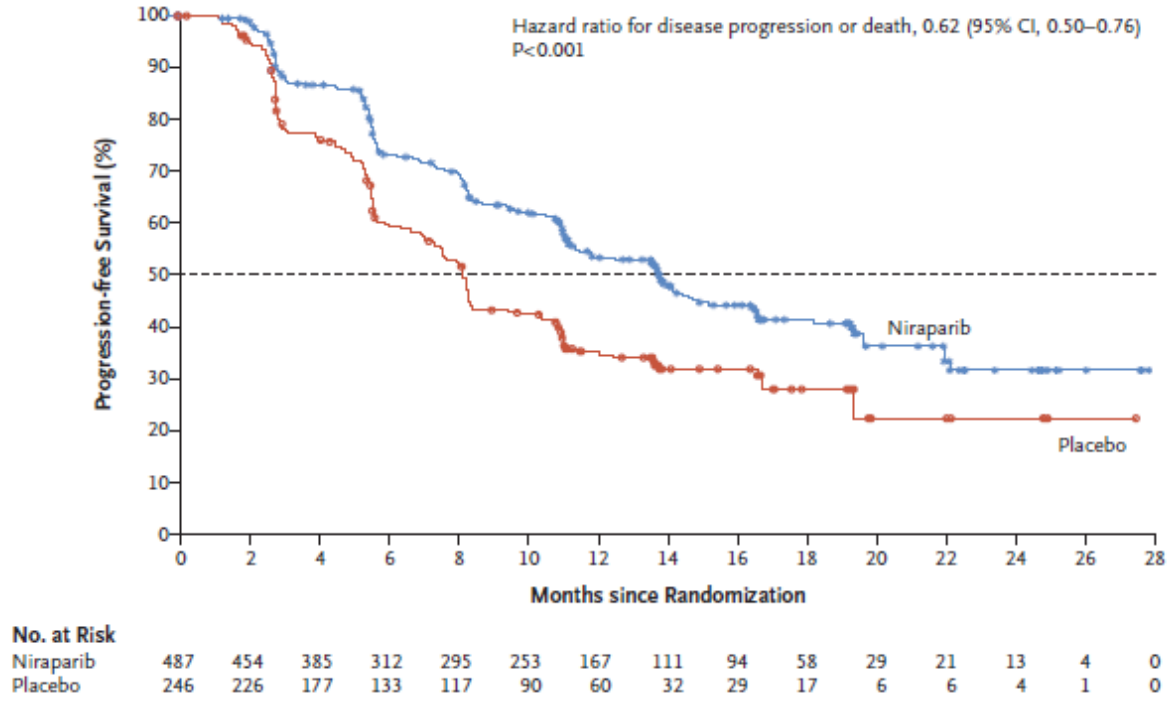
- Curves were then chosen based on statistical fit (Bayesian information criterion (BIC) and Akaike information criterion (AIC) values), visual goodness of fit, expert validation and clinical plausibility (clinician input and comparisons with UK real-world evidence).

ITT population

Progression-free survival

At the time of data cut off (May 17, 2019) there were 232/487 events (47.6% maturity) in the niraparib arm and 155/246 events in the RS arm (63.0% maturity). After a median follow-up of approximately 13.8 months, the median PFS was estimated to be 13.8 months for niraparib, and 8.15 months for RS. The KM curves and cumulative log-log plot for PFS (from randomisation to progression or death) are presented in Figure 17 and Figure 18, respectively.

Figure 17: PRIMA PFS Kaplan Meier data for the ITT dataset



Abbreviations: ITT, intention-to-treat; PFS, progression-free survival

Inspection of the log cumulative hazards (Figure 18) and Schoenfeld residual plot (Figure 19) suggests that the relative hazards are likely to vary over time, and as such it is not possible to conclude that the proportional hazard (PH) assumption holds. In Figure 18 it is clear that the respective lines are not strictly parallel on the log-cumulative hazard plot, however they do not intersect. The residual plot in Figure 19 does not suggest a non-random pattern against time. Therefore, the hypothesis that the PH assumption holds between niraparib and placebo cannot be accepted, meaning that the PH survival models; exponential, Gompertz and Weibull, may be appropriate when selecting a survival curve for extrapolation.

Figure 18: PFS cumulative log-log plot for the ITT data set

Abbreviations: ITT, intention-to-treat; PFS, progression-free survival

Figure 19: PFS Schoenfeld residuals plot for the ITT dataset

Parametric independent models were therefore fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma. An additional weighted curve of generalised gamma and log-logistic was also included as a scenario analysis (detailed below). The goodness of fit statistics (AIC/BIC) for the six standard parametric models are presented in Table 25.

Table 25: AIC and BIC statistical goodness of fit data for PFS ITT dataset (ind. models)

Distribution	Niraparib		RS	
	AIC	BIC	AIC	BIC
Exponential	1878.86	1883.05	1111.39	1114.90
Weibull	1860.31	1868.69	1104.01	1111.02
Gompertz	1877.82	1886.20	1113.39	1120.40
Log-logistic	1843.04	1851.41	1081.11	1088.12
Log-normal	1829.30	1837.68	1073.02	1080.03
Generalised gamma	1820.42	1832.98	1060.46	1070.98

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival; RS, routine surveillance

According to AIC and BIC, the best statistically fitting model to the PFS data was the generalised gamma for both niraparib and RS. In general, the parametric models fitted to the data in Figure 20 and Figure 21 produced reasonable visual predictions for both the niraparib and RS within the observed period.

Figure 20: PFS independent survival curves for niraparib ITT dataset

Abbreviations: KM, Kaplan-Meier; ITT, intention to treat; PFS, progression-free survival

Figure 21: PFS independent survival curves for RS ITT dataset

Abbreviations: KM, Kaplan-Meier; ITT, intention to treat; PFS, progression-free survival; RS, routine surveillance

Landmark PFS rates for niraparib and RS are presented in Table 26 showing that with the generalised gamma distribution a comparatively 'fat' tail is predicted. Four UK clinician interviews were conducted by the company, within which questions on the

expected shape of the curve were posed. The clinicians who were interviewed explained that there is a potential for a significant long-term tail that should be captured by the chosen PFS curve in the first-line ovarian cancer maintenance setting. All four interviewed health care professionals put their choice between the log-logistic and the generalised gamma curves for RS and agreed that the 'fat tail' observed in these distributions are clinically plausible in the first-line setting. Long-term TFST data is available in the University of Edinburgh Ovarian Cancer Database at 5 and 10 years. In lieu of PFS data from a real-world evidence (RWE) setting, the TSFT data were used as a proxy to predict progression-free survival, albeit with limitations. The log-logistic and generalised gamma curves lie on either side of the long-term real-world data, aligning with the feedback obtained from the clinicians: at 5 (10) years the RWE data show [redacted] of the patients are progression free. This compares with [redacted]% ([redacted]%) using the generalised gamma and [redacted]% ([redacted]%) with the log-logistic. Given this evidence, the generalised gamma curve was chosen (Figure 22) as the base case distribution for RS for the following reasons:

- Clinicians agree that PFS should exhibit a 'fat tail' within the first-line setting
- Superior statistical fit compared to the log-logistic curve (Table 25)

Table 26: <u>Landmark PFS survival rates ITT dataset</u>

Distribution	Tx	Proportion progression-free at			
		1 year	5 years	10 years	30 years
KM data	Niraparib	53.20%	-	-	-
	RS	34.80%	-	-	-
Exponential	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]

Distribution	Tx	Proportion progression-free at			
		1 year	5 years	10 years	30 years
Generalised gamma	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; Tx, treatment; RS, routine surveillance; RWE, real world evidence. **Selected based case curve**

Figure 22: Niraparib and RS PFS KM and generalised gamma curve ITT dataset (base case)

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; RS, routine surveillance

In order to address the uncertainty around the choice of distribution for PFS, the impact of alternative PFS distributions was explored in detail within the economic analysis. Scenario analyses were performed which considered:

- Weighted generalised gamma and log-logistic distributions based on the methods reported in Jackson et al. 2009.[51]
- Log-logistic curve

For the weighted method, generalised gamma and log-logistic distributions based on the methods reported in Jackson et al. 2009[131] were used. As recommended by Jackson et al., the generalised gamma and log-logistic PFS curves for niraparib and RS were weighted based on their measure of predictive ability (AIC criterion). Figure

23 presents the resultant weighted curves for niraparib and RS. As expected, the curves lie in between the log-logistic and the generalised gamma distribution and provide a good visual fit to the KM curves. Please note that the limitation of this approach is that using a weighted curve does not allow for the use of probabilistic sensitivity analyses (PSA).

Figure 23: Niraparib and RS PFS KM and weighted curve of the generalised gamma curve and log-logistic curve – ITT dataset (scenario analysis)

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; RS, routine surveillance

Overall survival

At the time of the last data cut off from PRIMA (May 17, 2019) there were 48/487 events (deaths) (9.9% maturity) in the niraparib arm and 31/246 events in the RS arm (12.6% maturity), over a median follow-up of approximately [redacted] months.[114] Due to the immaturity of the overall survival data in PRIMA (particularly in the niraparib group), the extrapolated survival curves estimated from the KM data have a wide range of long-term survival predictions. As discussed, the University of Edinburgh Ovarian Cancer Database provides long-term clinical data to help aid the selection of an appropriate OS curve for RS. However, there are no such mature data available for first-line PARP maintenance therapies. It was therefore deemed inappropriate to use the highly immature PRIMA OS data as a means of estimating OS for niraparib within the model.

Table 27 presents OS landmark survival rates for the six standard parametric distributions for RS and real-world data. The Weibull and the Gompertz curves substantially underestimate OS at 10 years when compared to the real-world data. In addition, the exponential, log-normal and generalised gamma curves substantially over estimated OS at 10 years compared to real world data. As such these curves were not considered any further in this economic analysis. The remaining log-logistic curve closely aligns with the real-world data at 10 years with [redacted]% alive at 10 years compared with [redacted]% in the RWE study. Visual inspection of the log-logistic curve indicates that it fits the observed KM data well for the RS ITT dataset (Figure 24 and Figure 25).

Table 27: Landmark survival rates for OS with RS ITT dataset

Distribution	Proportion alive at				
	1 year	5 years	10 years	15 years	30 years
KM	[redacted]	-	-	-	-
RWE	[redacted]	[redacted]	[redacted]	[redacted]	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan-Meier; OS, overall survival; RWE, real world evidence

Figure 24: OS independent survival curves for RS ITT dataset

Abbreviations: KM, Kaplan Meier; ITT, intention to treat; OS, overall survival; RS, routine surveillance

Figure 25: RS OS KM and log-logistic curve ITT dataset

Abbreviations: KM, Kaplan Meier; ITT, intention to treat; OS, overall survival; RS, routine surveillance

In order to estimate OS for niraparib, a relationship between the PFS benefit between RS and niraparib was used. This method of OS elicitation has been adopted in past submissions (TA528 and TA611) and was used as evidence in a recent ovarian cancer appraisal (TA598). Within TA528, a mean ΔPFS:ΔOS relationship of 1:2 based on

mature OS data from Study 19 was originally presented as part of the appraisal. As the submission evolved, a range of magnitudes between 1:1 and 1:2 were explored in the second-line setting of ovarian cancer. The Committee agreed that the PFS benefit observed with PARP inhibitors in platinum-sensitive relapsed ovarian cancer setting will translate into an OS benefit at a ratio of 1:>1 (i.e. 1 month of incremental PFS translates to more than 1 month of incremental OS).[100] Within TA611 (rucaparib 2L), the submission used a similar method to that adopted in TA528 in a range of scenario analyses (referencing the methods used in TA528).

An additional data cut from Study 19, offering the only available long-term OS data on PARPs, has since been published. The data cut provides long-term OS follow-up (median 78.0 months) for patients treated with olaparib and RS. The OS Kaplan-Meier data were digitised to generate patient level data, subsequently analysed in R studio to produce a restricted KM mean OS for Table 28PFS:ΔOS relationship observed in Study 19 has been updated (Table 28). This new data cut increased the mean ΔPFS:ΔOS relationship from 1:2.4 to 1:3.01, which further suggests that the mean ΔPFS:ΔOS should be 1:2 as a minimum in the relapsed setting.

Table 28: Mean OS benefit compared to the mean PFS benefit from Study 19 within the ITT population

Endpoint	RS	Olaparib	Difference	Mean OS difference / Mean PFS difference
Restricted mean PFS	0.42	0.58	0.16	3.01
Restricted mean OS	2.99	3.47	0.48	

Abbreviations: KM, Kaplan Meier; ITT, intention to treat; PFS, progression-free survival; OS, overall survival; RS, routine surveillance

First-line maintenance therapy is of curative intent and therefore any mean ΔPFS:ΔOS relationship expected to be achieved in the second-line maintenance setting should be reflected at a minimum (or greater) within the first-line maintenance setting.

In line with the evidence presented in Table 28 above, it would be reasonable to suggest a relationship of 1:>3. However, due to the limitations of applying phase II trial data to phase III data, and drawing comparisons between trials, a conservative mean ΔPFS:ΔOS relationship of 1:2 was therefore selected for the base case. A range of

mean ΔPFS:ΔOS relationships below that of the base case were explored in scenario analyses (1:1, 1:1.25, 1:1.5, 1:1.75, 1:2.5 and 1:3).

In order to model this relationship, the mean PFS difference between the niraparib and RS arms was used to estimate a HR which would extend the RS OS extrapolation with 2 times the mean PFS difference between niraparib and RS, so that:

Niraparib mean OS = (RS mean OS + [Mean PFS difference x 2])

OS for all treatments was then implemented such that the mortality risk of the modelled population was never below the mortality risk observed in the age and gender matched general population. This adjustment comes into effect at approximately the 20-year mark for niraparib and 25-year mark for RS. The mortality risk of the general population was derived from UK life tables published by the Office for National Statistics.

Table 29 presents the mean PFS and OS outputs for niraparib and RS calculated as a result of a mean ΔPFS:ΔOS = 1:2. Niraparib is associated with [redacted] additional years of survival compared to RS, which is two times the mean PFS gain observed for niraparib when modelling the generalised gamma curve for PFS ([redacted] years).

Table 29: Mean ΔPFS:ΔOS relationship between niraparib and RS (undiscounted)

Intervention	Mean PFS*	Mean OS	Incremental PFS	Incremental OS	Mean ΔPFS:ΔOS
RS	[redacted]	[redacted]	[redacted]	[redacted]	1:2
Niraparib					

Abbreviations: PFS, progression-free survival; OS, overall survival; RS, routine surveillance
*PFS distribution for niraparib and RS – generalised gamma

The resultant niraparib and RS OS curves for the ITT dataset are presented in Figure 26.

Figure 26: Niraparib and RS OS KM and survival curves for the ITT dataset

Abbreviations: ITT, intention to treat; KM, Kaplan Meier; OS, overall survival; RS, routine surveillance

Time-to-treatment discontinuation

At the time of data cut off (May 16, 2019) there were 310/487 (64%) niraparib patients who had discontinued treatment within the niraparib ITT dataset; three did not receive treatment, 58 discontinued due to adverse events, 218 discontinued due to disease progression, 12 withdrew and 19 discontinued for unknown reasons. After a median follow-up of approximately 13.8 months, the median time to treatment discontinuation (TTD) was estimated to be [redacted] months in the niraparib arm (Figure 27). In order to extrapolate TTD for use in the economic model, six standard parametric models were fit to the observed trial data: exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma.

Figure 27: TTD Kaplan Meier for niraparib ITT population

Abbreviations: ITT, intention to treatment; TTD, time to treatment discontinuation

Table 30: Summary of AIC and BIC goodness of fit for TTD with niraparib ITT dataset

Distribution	Niraparib	
	AIC	BIC
Exponential	2320.63	2324.82
Weibull	2319.29	2327.67
Gompertz	2322.47	2330.85
Log-logistic	**2313.93**	**2322.31**
Lognormal	2323.88	2332.25
Generalised Gamma	N/A	N/A

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ITT, intention to treatment; TTD, time to treatment discontinuation; N/A, not applicable

According to AIC and BIC, the best fitting models statistically to the data were the log-logistic and the Weibull (Table 30). Figure 28 presents five parametric survival curves for niraparib TTD; the generalised gamma distribution did not converge for the available data and so it could not be plotted. Although the log-logistic distribution had the best statistical fit of the five distributions (Table 30), the Weibull appears to have a better visual fit (Figure 28). Clinicians consulted during a UK advisory board considered the Weibull distribution to be more realistic when modelling TTD for niraparib. Therefore, the Weibull distribution was selected as the base case TTD curve for niraparib.

Figure 28: Niraparib TTD independent survival analysis curves for the ITT dataset

Abbreviations: KM, Kaplan Meier; TTD, time to treatment discontinuation

As highlighted in Section B.2.3.1, completed treatment in the PRIMA trial protocol (dated 2019) was defined as three years. The trial protocol indicated that patients should discontinue treatment at that time unless their consulting physician deemed that the patient would continue to receive benefit by remaining on the treatment beyond three years. To capture this within the economic model a three-year stopping rule was implemented. Of the [redacted]% of patients that were on treatment at three years according to the TTD extrapolated curve, [redacted]% of these would be assumed to continue treatment beyond three years, with the remaining [redacted]% discontinuing treatment. The [redacted]% of the [redacted]% on treatment after three years continue to follow the Weibull extrapolation (capped at OS) and patients continued to incur the cost of niraparib treatment. If patients are assumed to remain progression-free beyond the defined long-term remission time point (see page 138), they are assumed to discontinue treatment. The efficacy (PFS and OS) of niraparib were not altered as a result of this stopping rule. Clinical expert opinion and evidence from the SOLO-1 trial indicate that the treatment effect of a PARP inhibitor is likely to be maintained once a patient discontinues treatment.[43]

Figure 29 presents the base case niraparib TTD curve with the three-year stopping rule in which only [redacted]% of the [redacted]% of patients continue treatment at three years. The

impact of removing the stopping rule or assuming that [redacted]% of patients discontinue treatment at three years were explored in scenario analyses.

Figure 29: Niraparib TTD KM and the Weibull distribution for the ITT population

Abbreviations: KM, Kaplan Meier; TTD, time to treatment discontinuation

Long-term remission assumption

As highlighted in Section B.1.3, first-line treatment of ovarian cancer is of curative intent and the RWE study from the University of Edinburgh Ovarian Cancer database showed that within the population of interest, there are a proportion of patients who will remain progression free for an extended period of time. In order to capture this long-term remission, the following assumption was applied in the model. Patients who are classed as long-term responders are those who remain progression-free for a prolonged period. Within the NICE submission for olaparib in first-line maintenance (TA598) a seven-year cure point was adopted based on data from the University of Edinburgh Ovarian Cancer Database.[132] Following clinical feedback from key opinion leader interviews and obtained from UK advisory board, the same time point was deemed appropriate for this economic analysis.

For the base-case time point of 7 years, patients still progression-free are assumed to stay progression-free subject to all-cause mortality for the remainder of the time horizon. For this group of patients, survival was modelled based on the mortality risk

of the general population elicited from the UK National Statistics life tables.[133] The long-term remission assumption was applied to both niraparib and RS. Scenario analyses were conducted assuming long-term remission occurs at 5 and 10 years.

MA population

As highlighted previously, the PRIMA ITT population did not include Stage III NVRD patients. However, the anticipated licensed population for niraparib includes these patients. For reasons set out in Section B.2.14 it is important to include these patients within a NICE recommendation. Therefore, in order to estimate survival outcomes and costs in NVRD patients, an adjustment method was employed to extrapolate from the ITT population to the MA population.

As previously described in Section B.2.14, a targeted literature review was conducted to determine the PFS and OS associated with NVRD among people with advanced (Stage III/IV) ovarian cancer receiving first-line treatment. The following data sources were identified:

1. PAOLA-1[64,82]

- Stage III patients following partial debulking surgery (PDS) with residual disease who have receive NACT or Stage IV patients (n=196)
- Stage III with no visible residual disease (n=73)

2. SOLO-1[83,118]

- ITT population (includes NVRD) (n=391)
    - Stage III with no visible residual disease (n=172)

3. PRIMA[114]

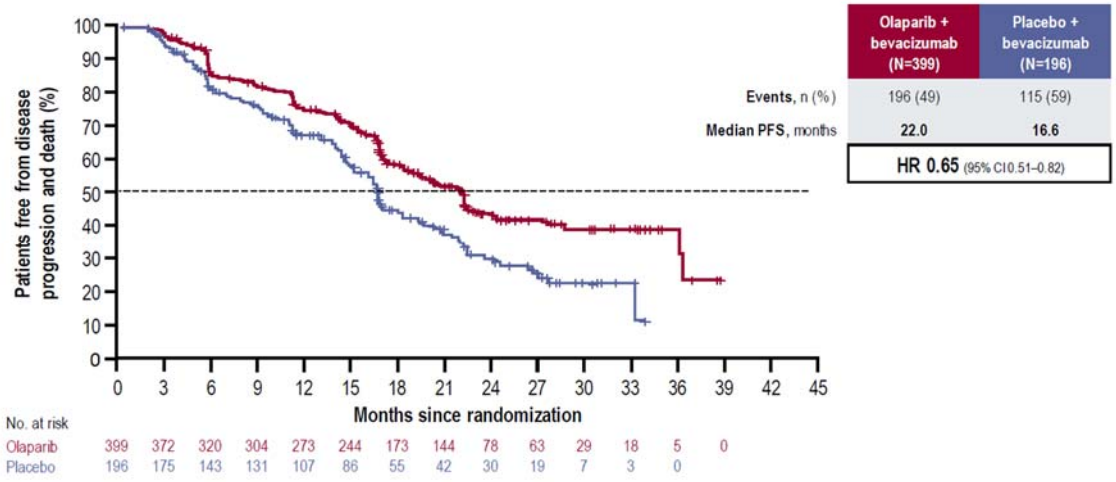
- ITT population (n=733)
    - Stage III disease at initial diagnosis (with visible disease) (n=476)
    - Stage IV disease at initial diagnosis (n=257)

The methods used to perform the adjustment are described below for each dataset, followed by a discussion justifying the base-case selection (with the others being explored in scenario analyses).

PAOLA-1

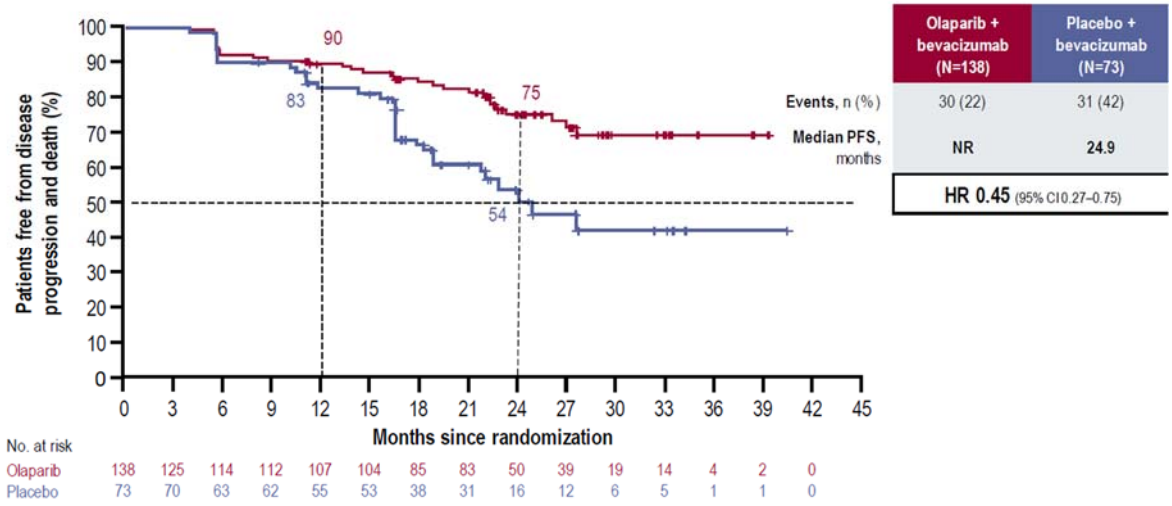
KM data from the PAOLA-1 ITT population (Figure 30) and a subgroup of Stage III patients with NVRD (Figure 31) were digitised to produce reclaimed PLD. Compared with the ITT population, the NVRD patients can be seen to have an improved prognosis (as seen through comparing the placebo curves) and there is also an improved treatment effect (HR of 0.45 compared with HR of 0.65)

Figure 30: PAOLA-1 Kaplan-Meier estimate of Stage III patients with PDS and residual disease, patients who had received NACT, Stage IV patients[82]



Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan Meier; PDS, partial debulking surgery; PFS, progression-free survival; NACT neoadjuvant chemotherapy

Figure 31: PAOLA-1 Kaplan-Meier estimate of Stage III patients with PDS and no visible residual disease[82]



Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan Meier; PDS, partial debulking surgery; PFS, progression-free survival

In order to apply these two observed idiosyncrasies, this data was subsequently analysed in R Studio using a simple Cox to model to produce two HRs:

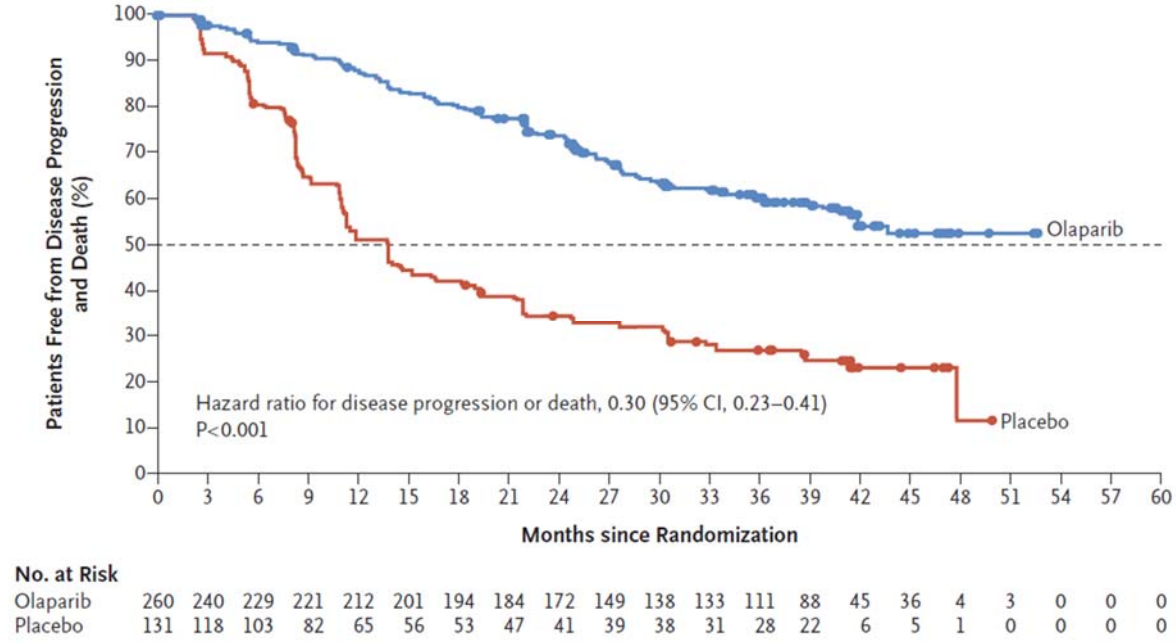
- A “NVRD effect” hazard ratio of 0.490 (0.329-0.723) was estimated between the two placebo curves.
- A “treatment effect” hazard ratio of 0.340 (0.233-0.497) was also estimated between the two treatment curves.

In order to predict survival curves for PFS within the economic model the ‘NVRD effect’ HR and ‘treatment effect’ HR were applied to the RS and niraparib base case PFS ITT curves, respectively.

SOLO-1

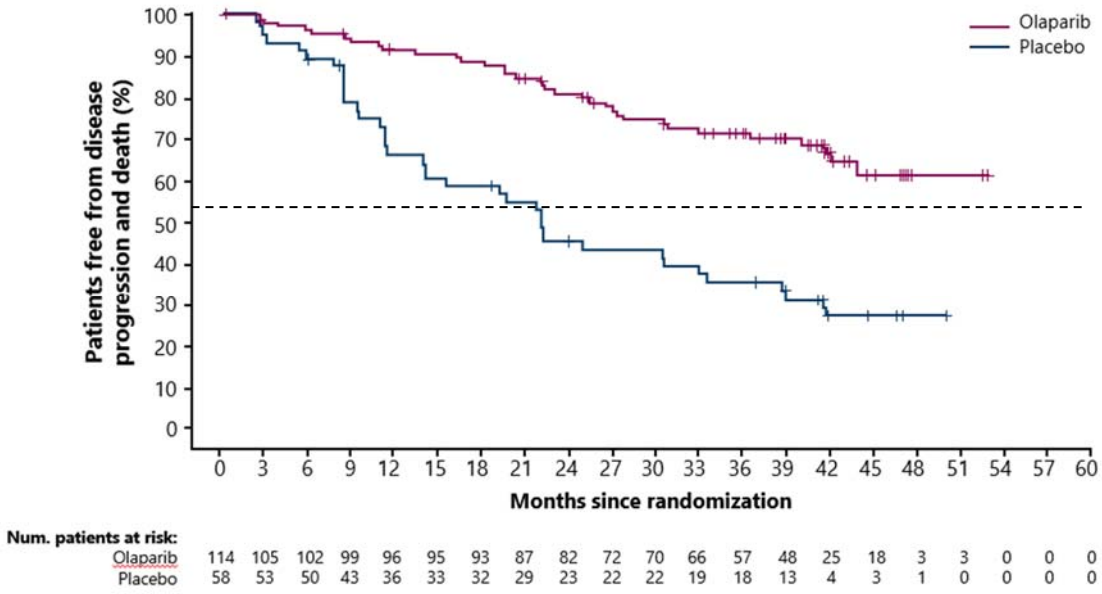
The same methods used to analyse the PAOLA-1 data were used to produce NVRD curves, instead using data from SOLO-1 shown in Figure 32 and Figure 33. As can be seen from these curves, compared with the ITT population, patients with NVRD have an improved prognosis (as seen through comparing the RS curves) as well as an improved treatment effect.

Figure 32: SOLO-1 Kaplan-Meier estimate of investigator-assessed PFS in the ITT population[83]



Abbreviations: CI, confidence interval; ITT, intention to treat; KM, Kaplan Meier; PFS, progression-free survival

Figure 33: SOLO-1 Kaplan-Meier estimate of investigator-assessed PFS in Stage III patients who underwent upfront surgery and had no visible residual disease[83]



As above, in order to apply these two observed idiosyncrasies, the SOLO-1 data was analysed in R Studio using a simple Cox to model to produce two HRs:

- A “NVRD effect” hazard ratio of 0.753 (0.521 - 1.327) was estimated between the RS ITT curve and the RS NVRD curve.

- A “treatment effect” hazard ratio of 0.718 (0.491 - 1.393) was estimated from the olaparib ITT and olaparib NVRD curves.

The ‘NVRD effect’ HR and ‘treatment effect’ HR were applied to the RS and niraparib base case PFS curves, respectively, to generalise the ITT PFS curves to reflect the anticipated MA population.

PRIMA

A third option considered the niraparib treatment effect observed between Stage III and IV patients within the PRIMA trial. Subgroup analyses indicated that niraparib was more efficacious in Stage III (HR: 0.54 [CI 0.42 – 0.70]) patients than in stage IV patients (HR: 0.79 [0.55 – 1.12]).[114] At a minimum it could be assumed that the efficacy of niraparib observed in Stage III with VRD would be as good as in patients with NVRD. To model this within the analysis, the RS ITT efficacy was first lifted using the PAOLA-1 ‘NVRD effect’ HR, and then the Stage III HR of 0.54 observed in PRIMA was applied to achieve the niraparib NVRD efficacy.

Method applied in base case

In order to decide which data source was the most appropriate for use within the economic model, UK clinicians were consulted at a UK advisory board and through a series of four KOL interviews. Feedback from clinicians was that the data from the PAOLA-1 trial were more relevant than the SOLO-1 trial because:

- In the PAOLA-1 trial, the two groups (non-NVRD and NVRD groups) were mutually exclusive. Conversely, in SOLO-1, 44% (n=114) of the ITT population were Stage III patients with NVRD. There is therefore considerable overlap between the NVRD subgroup and the ITT population, which means the prognostic effect of being NVRD on PFS is potentially underestimated.

- The PAOLA-1 trial included patients with and without a *BRCA* mutation whereas the SOLO-1 trial included only *BRCA*mut patients, which make up only 25%[10] of the MA population for niraparib.

While the PAOLA-1 trial treatment arms both included bevacizumab and so a true NVRD effect with placebo only cannot be observed, clinicians advised that PAOLA- 1 is still the most appropriate data source as the relative effect is modelled as opposed to an absolute effect. Furthermore, given the NVRD effect described above, the PRIMA trial data is likely to underestimate the survival for Stage III patients with NVRD because the HRs obtained from PRIMA included Stage III patients with visible disease at study entry, rather than those with NVRD.

Therefore, the HRs derived from the PAOLA-1 study were selected for use within the base case of the economic analyses. Scenario analyses were conducted to explore the impact of using HRs derived from PRIMA and SOLO-1.

Progression-free survival

Using the 'NVRD effect' and 'treatment effect' HRs obtained from PAOLA-1, the base case ITT PFS curves for niraparib and RS were adjusted to generate curves representative of NVRD patients. The overall MA curves were then produced by weighting the ITT and the NVRD curves (assuming [redacted]% of patients are NVRD [based on evidence from the Edinburgh database and the PAOLA-1 trial])[116] for both niraparib and RS. Although clinician interviews confirmed the use of the [redacted]% in the base case, it was highlighted as a relatively conservative estimate, as there are areas in England where this ratio is higher. Therefore, in scenario analyses the impact of changing the proportion of Stage III patients with NVRD to 30% and to 40% was explored. Figure 34 presents the resultant MA PFS curves (with the ITT curves for reference) for niraparib and RS.

Figure 34: Niraparib and RS PFS curves for the MA population

Abbreviations: ITT, intention to treat; KM, Kaplan Meier; PFS, progression-free survival; MA, marketing authorisation; RS, routine surveillance

Overall survival

OS for niraparib and RS was not adjusted explicitly to the MA population due to lack of published OS data for Stage III patients with NVRD after PCS. As such, OS is only partially adjusted through the mean ΔPFS:ΔOS relationship applied to the niraparib arm and through the long-term remission effect to both arms (as more patients achieve long-term remission through the improved PFS). This, however, is anchored to the OS RS. Figure 37 presents the resultant MA OS curves (with the ITT curves for reference) for niraparib and RS.

Figure 35: Niraparib and RS OS curves for the MA population

Abbreviations: ITT, intention to treat; KM, Kaplan Meier; OS, overall survival; MA, marketing authorisation; RS, routine surveillance

Time-to-treatment discontinuation

In line with improved PFS in the MA population, it is likely that patients would also be on treatment for a similarly extended time. Therefore, to extrapolate TTD between the PRIMA ITT population and the anticipated MA population for niraparib, the 'treatment effect' estimated from PAOLA-1 for PFS was applied to the niraparib TTD curves. Subsequently, the NVRD and ITT curves were weighted to produce an MA curve for niraparib TTD. Figure 36 presents the resultant MA TTD curves (with the ITT curves for reference) for niraparib.

Figure 36: Niraparib TTD curve for the MA population

Abbreviations: ITT, intention to treat; KM, Kaplan Meier; MA, marketing authorisation; TTD, time to treatment discontinuation

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

Within the PRIMA trial, EQ-5D data were collected using the EQ-5D-5L instrument. The EQ-5D-5L descriptive system of health states comprises 5 dimensions ('5D'): (1) mobility; (2) self-care; (3) usual activities; (4) pain/discomfort and (5) anxiety/depression. Those are rated by a verbal 5-point rating scale allowing for distinction of five levels ('5L') of severity: Level 1: no problems; Level 2: slight problems; Level 3: moderate problems; Level 4: severe problems; Level 5: extreme problems per dimension and providing a 1-digit number for each dimension. The digits for the 5 dimensions can be combined in a 5-digit code describing the patient's health state. A total of 3,125 combinations and therewith different health states are possible.

EQ-5D-5L data were collected every 8 weeks (± 7 days) for 56 weeks beginning on the first day of the first cycle, then every 12 weeks (± 7 days) while on study treatment. During the follow-up period, if a patient discontinued study treatment, assessments occurred at 4 weeks, 8 weeks, 12 weeks and 24 weeks (± 1 week for each timepoint) after EOT, regardless of the status of subsequent treatment.

Mapping (EQ-5D-5L to EQ-5D-3L)

The 3-level version (EQ-5D-3L) and the UK time trade-off values set are the reference case for HTA submissions, as defined by NICE. If EQ-5D-5L is collected, NICE recommend applying the mapping function developed by van Hout et al.[128] to convert it to the EQ-5D-3L for the reference-case analysis. All completed EQ-5D-5L questionnaires that contained responses to all five health domains were mapped to EQ-5D-3L utilities using the crosswalk method by van Hout et al. Following this, a simple descriptive analysis was conducted on the data to estimate the mean utilities for PFD and PD. The results of the EQ-5D analysis are presented in Table 31. The mean utility values for patients receiving niraparib was marginally higher than for RS.

Table 31: EQ-5D-3L values from the PRIMA study for the ITT population

Parameter	Observations (n)	HSUV
Niraparib		
PFD	[redacted]	[redacted]
PD	[redacted]	[redacted]
RS		
PFD	[redacted]	[redacted]
PD	[redacted]	[redacted]
Overall		
PFD	[redacted]	[redacted]
PD	[redacted]	[redacted]

Abbreviations: EQ-5D-3L, EuroQoL Five Dimensions Three Levels; HSUV, health state utility value; ITT, intention to treat; PFD, progression-free disease; RS, routine surveillance

Health-related quality-of-life studies

Published health-related quality-of-life for patients with advanced ovarian cancer were identified through a SLR. This review intended to identity HSUV and disutilities associated with advanced ovarian cancer. A de novo SLR was first conducted up to 13th February 2019, with an update performed on the 27th February 2020. Please see Appendix H for the methods used to identify relevant studies and for full results. A total of 23 quality-of-life references were identified.

Of the 23 quality-of-life references included in this SLR, three included patients within the first-line maintenance setting; Friedlander 2018, CADTH 2019 and NICE 2019 (TA598).[84,85,134] CADTH reported utility values for patients with newly diagnosed ovarian cancer, PFS, recurrent/progressive ovarian cancer and stage 3 and 4 ovarian cancer using data from US and Canadian published literature. Friedlander reported

utility scores for patients who were treated with pazopanib or placebo in the AGO-OVAR16 trial. This trial elicited utility scores using the EQ-5D-3L questionnaire. NICE 2019 (TA598), a technology appraisal of olaparib, reported utility scores for patients who were treated with olaparib or RS in the SOLO-1 clinical trial which were measured using the EQ-5D-5L questionnaire. Consistent with the NICE reference case, utility values were evaluated using UK general population preference weights. Utilities were reported for PFD and PD health states. NICE 2019 (TA598) also reported disutilities associated with specific AEs. TA598 included a one-off QALY adjustment for an AE, modelled based on its disutility (loss of utility) multiplied by its assumed duration. The economic analysis only included AEs that were ≥ grade 3, as only these AEs are likely to have a significant impact on the decision-making process in term of costs, and/or an impact on the quality-of-life of patients. A summary of utility values reported in CADTH, 2019, NICE 2019 (TA598) and Friedlander 2018 is presented in Table 32.

In addition to the three first-line studies identified in the SLR three HTA appraisals for second-line maintenance therapies were identified as being of relevance to the Company submission (TA528 [niraparib 2L][100], TA620 [olaparib 2L][101] and TA611 [rucaparib 2L] [102]). A summary of the utility values identified are present in Table 33.

NICE 2018a (TA528) reported utility scores included in a 2018 technology appraisal submission to NICE for niraparib as monotherapy for the maintenance treatment of ovarian cancer in the relapsed setting. This submission reports treatment specific utility scores for niraparib, olaparib, RS and a non-treatment specific scores for PFD. Only niraparib, RS and non-treatment specific utility values are reported for PD. The submission mapped utility values from treatment specific EQ-5D-5L to EQ-5D-3L using a 'cross-walk' algorithm published by van Hout et al. Base-case utilities adopted in the submission for PFD were 0.858, 0.848 and 0.769 for niraparib, RS and olaparib, respectively. Base-case utilities adopted in the submission for PD were 0.821, 0.815 and 0.718 for niraparib, RS and olaparib, respectively. However, it should be noted that the Committee disagreed with the use of treatment-specific utilities.[100]

NICE 2020 (TA620) reported utility scores included in a technology appraisal submission to NICE for olaparib as monotherapy for the maintenance treatment of

ovarian cancer in a relapsed setting. This study reports three non-treatment specific utility value sets for olaparib and placebo. These include the base-case values which were taken from NICE 2018a (TA528) and two sensitivity analysis sets obtained from SOLO-2 mapped EQ-5D-5L and mapped values from the results of the Study 19 FACT-O questionnaire.

NICE 2019 (TA611) reported utility values for PFS and PD sourced from the ARIEL3 trial comparing rucaparib maintenance treatment against placebo for patients with platinum sensitive, recurrent ovarian cancer. Base case scores adopted for PFS and PD were 0.830 and -0.074 (utility decrement) respectively with values elicited using the EQ-5D-3L.[102]

In addition to the health state utilities, disutilities per adverse event were also identified in the three second-line maintenance studies. Disutilities were reported for anaemia, thrombocytopenia, neutropenia, fatigue, hypertension, and abdominal pain, and are summarised in Table 34.

For the base case, following the systematic review of published literature and the analysis of the PRIMA trial EQ-5D data described above, it was concluded that the mapped PRIMA EQ-5D-3L utility values obtained through descriptive analyses of PRIMA data would be used. These data were considered the most robust and applicable source of utility data, as they were directly collected in patients newly diagnosed advanced ovarian cancer following response to PBC. Additionally, non-treatment specific utilities were used in the base case, following review of the previous submissions and responses from NICE which indicated that non-treatment specific utilities were preferred to treatment specific utilities.

Table 32: Utility values associated with specific disease states within the first-line maintenance setting

Category	Interventions and comparators	Patient population	Utility score	Method of elicitation/valuation	Source
Health states					
PFD	Pazopanib and placebo	Patients who have not progressed after first-line chemotherapy for epithelial ovarian, fallopian tube, or primary peritoneal cancer	0.850	EQ-5D	Friedlander 2018[134] (AGO-OVAR16 clinical trial)
PFD	Olaparib and RS	Patients with platinum sensitive serous ovarian cancer with a BRCA mutation following first-line chemotherapy	0.79	Utilities capped at general population	TA598[84]
PFD			0.872	EQ-5D-5L	
PD			0.649	Sourced from the OVA-301 trial	
PD			0.828	SOLO-2 EQ-5D-5L	
PFD	-	-	0.86	NR	CADTH
PD	-	Recurrent/progressive ovarian cancer	0.43	US literature (visual analogue scale) [135]	
NR	-	Stage 3 and 4 ovarian cancer	0.77	Canadian literature (EQ-5D)[136]	
PFD	-	Newly diagnosed ovarian cancer	0.55	US literature (time trade -off score)[135]	
Adverse events grade ≥ 3					
Anaemia			-0.119 (7 days - duration of event)	Published literature	TA598
Neutropenia			-0.090 (7 days - duration of event)		
Diarrhoea			-0.047 (5 days - duration of event)		

Abbreviations: EQ-5D-5L, EuroQoL-Five Dimensions-Five Levels; NICE, National Institute for Health and Care Excellence; PD, progressed disease; PFD, progression-free disease; US, United States

Company evidence submission template for niraparib in patients with newly diagnosed advanced ovarian, fallopian tube or peritoneal cancer.

Table 33: Summary of utility values reported in patients who had received two or more prior lines of chemotherapy (2L+) identified in the SLR

Health state	Intervention	Patient population	Utility score	Method of elicitation	Source
PFD	Independent of treatment arm	Patients with recurrent platinum sensitive serous ovarian cancer	0.801	Mapped EQ-5D-5L from ENGOT-OV16/NOVA	NICE 2020 (TA620)– base-case
	Independent of treatment arm	Patients with recurrent platinum sensitive serous ovarian cancer with a BRCA mutation	0.802	SOLO-2 mapped EQ-5D-5L	NICE 2020 (TA620)– SOLO-2
	Independent of treatment arm	Patients with recurrent platinum sensitive serous ovarian cancer with a BRCA mutation	0.77	Study 19 FACT-O mapped	NICE 2020 (TA620)– Study 19 FACTO mapped
	Independent of treatment arm	Patients with recurrent platinum sensitive serous ovarian cancer	0.831	Mapped EQ-5D-5L from ENGOT-OV16/NOVA	NICE 2018a (TA528))
	Niraparib		0.858	Mapped EQ-5D-5L from ENGOT-OV16/NOVA	

Company evidence submission template for niraparib in patients with newly diagnosed advanced ovarian, fallopian tube or peritoneal cancer.

Health state	Intervention	Patient population	Utility score	Method of elicitation	Source
	Placebo		0.848	Mapped EQ-5D-5L from ENGOT-OV16/NOVA	
	Olaparib		0.769	Study 19 EQ-5D-3L	
	Independent of treatment arm (mapped from EQ-5D-5L to EQ-5D-3L)		0.801	Mapped EQ-5D-5L from ENGOT-OV16/NOVA	
	Niraparib (mapped from EQ-5D-5L to EQ-5D-3L)		0.812	Mapped EQ-5D-5L from ENGOT-OV16/NOVA	
	Placebo (mapped from EQ-5D-5L to EQ-5D-3L)		0.770	Mapped EQ-5D-5L from ENGOT-OV16/NOVA	
	Independent of treatment arm	Patients with recurrent platinum sensitive serous ovarian cancer	0.830	EQ-5D-3L	NICE 2019 (TA611)
PD	Independent of treatment arm	Patients with recurrent platinum sensitive serous ovarian cancer with a BRCA mutation	0.719	Mapped EQ-5D-5L from ENGOT-OV16/NOVA	NICE 2020 (TA620)– base-case

Health state	Intervention	Patient population	Utility score	Method of elicitation	Source
	Independent of treatment arm	Patients with recurrent platinum sensitive serous ovarian cancer with a BRCA mutation	0.739	SOLO-2 mapped EQ-5D-5L	NICE 2020 (TA620)– SOLO-2
	Independent of treatment arm	Patients with recurrent platinum sensitive serous ovarian cancer with a BRCA mutation	0.68	Study 19 FACTO mapped	NICE 2020 (TA620)– Study 19 FACT-O mapped
	Independent of treatment arm	Patients with recurrent platinum sensitive serous ovarian cancer	0.799	Mapped EQ-5D-5L from ENGOT-OV16/NOVA	NICE 2018a (TA528)
	Niraparib		0.821	Mapped EQ-5D-5L from ENGOT-OV16/NOVA	
	Placebo		0.815	Mapped EQ-5D-5L from ENGOT-OV16/NOVA	
	Olaparib		0.718	Mapped EQ-5D-5L from ENGOT-OV16/NOVA	

Health state	Intervention	Patient population	Utility score	Method of elicitation	Source
	Independent of treatment arm (mapped from EQ-5D-5L to EQ-5D-3L)		0.719	Mapped EQ-5D-5L from ENGOT-OV16/NOVA	
	Niraparib (mapped from EQ-5D-5L to EQ-5D-3L)		0.728	Mapped EQ-5D-5L from ENGOT-OV16/NOVA	
	Placebo (mapped from EQ-5D-5L to EQ-5D-3L)		0.705	Mapped EQ-5D-5L from ENGOT-OV16/NOVA	
	Independent of treatment arm	Patients with recurrent platinum sensitive serous ovarian cancer	-0.074 (decrement)	EQ-5D-3L	NICE 2019 (TA611)

Abbreviations: BRCA, breast cancer susceptibility gene; PFD, progression-free disease; PD, progressed disease; SLR, systematic literature review; TA, technology appraisal

Table 34. Summary of disutility values reported in patients who had received two or more prior lines of chemotherapy (2L+) identified in the SLR

Health state	Intervention	Patient population	Disutility score	Method of elicitation	Source
Anaemia	-	Patients with recurrent platinum sensitive serous ovarian cancer	0.00	Collected in the ENGOT-OV16/NOVA trial	NICE 2018a (TA528)
	-	Patients with recurrent platinum sensitive serous ovarian cancer	-0.119 (duration of 7 days)	Published literature	NICE 2020 (TA620)
Thrombocytopenia	-	Patients with recurrent platinum sensitive serous ovarian cancer	0.00	Collected in the ENGOT-OV16/NOVA trial	NICE 2018a (TA528)[100]
Neutropenia	-	Patients with recurrent platinum sensitive serous ovarian cancer	0.00	Collected in the ENGOT-OV16/NOVA trial	NICE 2018a (TA528)[100]
		Patients with recurrent platinum sensitive serous ovarian cancer with a BRCA mutation	-0.090 (duration of 7 days)	Published literature	NICE 2020 (TA620)[137]
Fatigue	-	Patients with recurrent platinum sensitive serous ovarian cancer	-0.084	Collected in the ENGOT-OV16/NOVA trial	NICE 2018a (TA528)[100]
Hypertension	-	Patients with recurrent platinum	-0.02	Published literature	NICE 2016 (TA381)[35]

Health state	Intervention	Patient population	Disutility score	Method of elicitation	Source
		sensitive serous ovarian cancer			
	-	Patients with recurrent platinum sensitive serous ovarian cancer with a BRCA mutation	0.00	Collected in the ENGOT-OV16/NOVA trial	NICE 2018a (TA528)[100]
Abdominal pain	-	Patients with recurrent platinum sensitive serous ovarian cancer with a BRCA mutation	-0.069 (duration of 17 days)	Published literature	NICE 2020 (TA620)[137]

Abbreviations: TA, technology appraisal

Adverse reactions

The safety profile for niraparib as a first-line maintenance is consistent with other PARP inhibitors within ovarian cancer (see Section B.2.10). The costs and impact of AEs on patient's quality-of-life are included within this analysis, which aligns with previous maintenance therapy submissions in ovarian cancer. The NICE submission for niraparib as a second-line maintenance therapy (TA528) considered treatment-related AEs of grade ≥3 as these were expected to have the largest impact on quality of life.[138] The olaparib first-line NICE submission (TA598) also considered treatment-related grade ≥3 AEs, modelled via the incidence of grade ≥3 AEs.[139] In line with existing cost-effectiveness analyses, this economic analysis considered grade ≥3 treatment related AEs that are reported in ≥5% of patients in either treatment group of the PRIMA trial.

AEs were incorporated as one-off events and the impact was attributed to the first cycle of the model, under the assumption that AEs are likely to occur very soon after treatment initiation and require acute care. This is consistent with the modelling approaches adopted in NICE TA528 and NICE TA598.[138,139] The cost and QALY impact of AEs were calculated as the sum product of the AEs for each treatment and the cost per treatment/disutility for each event. For the base case, disutilities obtained through the published literature discussed above were used to model the impact of grade ≥ 3 AEs.

Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of base case utility values for the cost-effectiveness analyses is presented in Table 35. Note, the utility values applied for the PRIMA ITT population and the anticipated MA population were equivalent.

Table 35: Summary of base case utility values for cost-effectiveness analysis

State	Utility value: mean (standard deviation)	95% confidence interval	Reference in submission (section and page number)	Justification
PFD	[redacted]	[redacted]	Measurement and valuation of health effects Health-related quality-of-life data from clinical trials, page 147	In line with the NICE reference case and reflective of the patient population considered in this submission
PD	[redacted]	[redacted]	Measurement and valuation of health effects Health-related quality-of-life data from clinical trials, page 147	
Grade ≥ 3 adverse events				
Anaemia	-0.12	-0.08, 0.17	Adverse reactions, page 148 Sourced from TA598[84]	Reflective of the patient population considered in this submission
Thrombocytopenia	-0.09	-0.06, -0.13	Adverse reactions, page 148 Assumed equivalent to neutropenia	
Platelet count decreased	-0.09	-0.06, -0.13	Adverse reactions, page 148 Assumed equivalent to neutropenia	
Neutropenia	-0.09	-0.06, -0.13	Adverse reactions, page 148 Sourced from TA598[84]	
Hypertension	-0.02	-0,01, -0.13	Adverse reactions, page 148	
Neutrophil count decrease	-0.09	-0.06, -0.13	Assumed equivalent to neutropenia	

Abbreviations: PD, progressed disease; PFD, progression-free disease; NICE, National Institute for Health and Care Excellence

B.3.5 Cost and healthcare resource use identification, measurement and valuation

A SLR was conducted to identify cost and resource use data associated with the treatment and management of patients with advanced high grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded (completely or partially) to first-line PBC. See Appendix I for extended detail of how cost and resource use data were reviewed and identified.

The costs included in the model consist of:

1. Treatment-related costs (including subsequent treatment costs)
    - Acquisition costs
    - Administration costs
2. Disease management costs
3. Adverse-event costs
4. End-of-life care costs

Equivalent cost and healthcare resource use are applied for the PRIMA ITT population and the anticipated MA population.

Intervention and comparators' costs and resource use

Drug related costs considered include the acquisition and administration cost of niraparib and subsequent treatments (chemotherapy and subsequent maintenance therapy).

Drug acquisition costs

Niraparib

Niraparib is available in 100mg capsules and comes in pack sizes of 56. The list price for 56 x 100 mg capsules is £4,500.

A simple discount of [redacted] is applied in the economic analysis, resulting in a price of £[redacted] for 56 x 100 mg capsules, specific to the first-line setting.

Niraparib is an oral monotherapy with a recommended starting dose of 200 mg (two 100 mg capsules), taken once daily. For patients who weigh ≥ 77 kg and have baseline platelet count ≥ 150,000/μL, the recommended starting dose of niraparib is 300 mg (three 100 mg capsules), taken once daily.

Within the PRIMA trial, the original protocol initially started patients on 300 mg once daily (OD), however a subsequent protocol amendment (February 2018) allowed patients who weigh <77 kg and/or have a baseline platelet count < 150,000/μL, to initiate on 200 mg OD and the anticipated marketing authorization is in line with this amendment. The dose intensity recorded in the PRIMA trial was [redacted] mg.[68]

To understand how the dose changed over time, two analyses were carried out, one looking at an average dose per cycle and the second looking at actual dose received.

1. Average dose: An analysis of patient level data by cycle demonstrates [redacted] (Figure 37).

Figure 37: Average starting dose by cycle for the niraparib ITT dataset of the PRIMA trial

Cycle	2	4	6	8	10	12
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2. Actual dose: An analysis of the niraparib starting dose received for months 1 to 12 in the PRIMA ITT was conducted. Figure 38 demonstrates how the dose received quickly reduces over the first few cycles before stabilising. It also shows an increasing proportion of patients receiving a 100 mg daily dose over time (47% of patients with a dose of 100 mg by month 12).

Figure 38: Niraparib dose level by month on treatment

The efficacy data behind this economic analysis is driven by the actual dose received in the PRIMA trial, which is assumed to be in line with what can be anticipated in a real-life setting. As such, and given the data presented above, it was considered appropriate to use the actual dose level by month on treatment to model the niraparib dose for cycles 1 through to 11, and then to assume a last observation carried forward (LCOF) approach for cycles 12+ until treatment discontinuation. This approach of modelling actual dose received mitigates the need to capture wastage, but it is acknowledged that over the course of the entire treatment, there may be some wastage on the final pack received, as with any treatment. Scenario analyses were conducted to explore the impact of modelling the observed dose intensity ( ) and a fixed daily dose of 200 mg.

Based on this dose level by month, the base case monthly (30.44 days) treatment cost with niraparib was calculated for cycles 1 through to 11, and 12+ (Table 36). As niraparib is an oral treatment, no administration costs were applied.

Acquisition costs were applied in line with how the treatment was received in the ITT population of the PRIMA study. TTD extrapolations (outlined in Section B.3.3) were used directly in the model to estimate duration of treatment with niraparib, and therefore to estimate total acquisition costs per patient.

Table 36: Total acquisition costs for niraparib per cycle (month=30.44 days)

Model cycle	Proportion of patients across dose (mg) categories			Frequency of administration per cycle	Total acquisition cost per cycle
	100	200	300		
1	[redacted]	[redacted]	[redacted]	30.44	[redacted]
2	[redacted]	[redacted]	[redacted]	30.44	[redacted]
3	[redacted]	[redacted]	[redacted]	30.44	[redacted]
4	[redacted]	[redacted]	[redacted]	30.44	[redacted]
5	[redacted]	[redacted]	[redacted]	30.44	[redacted]
6	[redacted]	[redacted]	[redacted]	30.44	[redacted]
7	[redacted]	[redacted]	[redacted]	30.44	[redacted]
8	[redacted]	[redacted]	[redacted]	30.44	[redacted]
9	[redacted]	[redacted]	[redacted]	30.44	[redacted]
10	[redacted]	[redacted]	[redacted]	30.44	[redacted]
11	[redacted]	[redacted]	[redacted]	30.44	[redacted]
12	[redacted]	[redacted]	[redacted]	30.44	[redacted]
12+	[redacted]	[redacted]	[redacted]	30.44	[redacted]

Abbreviations: mg, milligram

Routine surveillance

The comparator in the analysis (and defined by the final NICE scope) is RS, comprising patient observation, follow-up, and general supportive or symptomatic care. The analysis assumes no drug acquisition for RS.

Concomitant medications

No concomitant medications are included within the proposed label for niraparib (Appendix C). Drug related costs associated with concomitant drugs received during treatment have therefore not been considered in this analysis. These costs are also unlikely to substantially differ between treatment arms, and the impact on the results and decision making is thus assumed to be insignificant.

Administration costs

The analysis assumes there is no administration cost for niraparib (oral treatment), or RS.

Table 37: Summary of drug related costs

Items	Niraparib	Rationale	RS
Protocol dosing per administration	200mg (2x100mg capsules)	Draft SmPC (Appendix C)	N/A
Frequency of administration	Once daily	Draft SmPC (Appendix C)	NA
List price treatment cost: 100mg (56 capsule packet)	£4,500	List price per pack	£0
CA treatment cost: 100mg (56 capsule packet)	£[redacted]	Simple discount of [redacted]%	
Average daily dose	See Table 36	PRIMA trial daily dose intensity	-
Monthly treatment cost (30.44 days)			
1	[redacted]	Monthly dose observed in PRIMA	£0
2	[redacted]	Monthly dose observed in PRIMA	£0
3	[redacted]	Monthly dose observed in PRIMA	£0
4	[redacted]	Monthly dose observed in PRIMA	£0
5	[redacted]	Monthly dose observed in PRIMA	£0

Items	Niraparib	Rationale	RS
6	[redacted]	Monthly dose observed in PRIMA	£0
7	[redacted]	Monthly dose observed in PRIMA	£0
8	[redacted]	Monthly dose observed in PRIMA	£0
9	[redacted]	Monthly dose observed in PRIMA	£0
10	[redacted]	Monthly dose observed in PRIMA	£0
11	[redacted]	Monthly dose observed in PRIMA	£0
12+	[redacted]	Monthly dose observed in PRIMA	£0
Total mean treatment cost per patient over lifetime horizon with a stopping rule of 3 years for the MA population	[redacted]	Monthly treatment cost applied in line with TTD curve and 3 year stopping rule ([redacted] of patients discontinue)	£0
Administration cost	£0	Oral administration	-

Abbreviations: CA; Commercial arrangement; mg, milligram; N/A, not applicable; SmPC, Summary of product characteristics; TTD, time to treatment discontinuation

Subsequent treatment costs

Treatment regimen

Following progression on a first-line maintenance therapy, patients can receive several subsequent treatment regimens. The anticipated treatment pathway for patients with newly diagnosed ovarian cancer is presented in Figure 5, Section B.1.3.4. Immediate subsequent therapy would include a second-line chemotherapy regimen, of either PBC (for patients who are platinum-sensitive) or non-platinum-based chemotherapy (platinum-resistant patients). The definition of platinum-sensitive is evolving as highlighted by Colombo et al 2019, which makes defining a clear cut off for platinum-sensitivity more challenging.[36]

Following second-line chemotherapy, patients who are platinum-sensitive and have not yet received a PARP are eligible for treatment with a second-line PARP. Within the UK setting, patients' access to a PARP is restricted such that they may only receive one once - no PARP following a PARP is permitted, and as such only patients who have undergone RS in the first-line maintenance setting would be eligible for second-

line PARP therapy. However, in the relapsed second-line setting the PARP inhibitors available in the UK are reimbursed through the CDF. Due to the NICE position statement on comparators in the CDF[126], these cannot be considered in the analysis, Therefore second-line PARP use has not been incorporated in the treatment pathway for the base case, as per instructions from NICE .

After second-line chemotherapy (and second-line PARP maintenance therapy on the RS arm) patients may then receive a third-line chemotherapy regimen. As before, the regimens may be platinum or non-platinum-based chemotherapy dependent on whether the patient is platinum-sensitive or resistant. Following third-line chemotherapy, olaparib maintenance therapy is available via routine commissioning for platinum-sensitive patients with a *BRCA* mutation (~25% of patients with ovarian cancer) who have not had a PARP maintenance treatment option before. As this treatment option has routine commissioning, this subsequent treatment option is used as the base case in the analysis, albeit for the very small number of patients who have not previously received a PARP at second or first-line and who have a *BRCA* mutation.

The subsequent treatment options for patients progressing from first-line maintenance therapy are variable and hence there will always be a degree of uncertainty when attempting to capture them within an economic model. In order to try and reduce uncertainty, this economic analysis explored several options to model subsequent treatments.

Options for modelling subsequent treatment:

1. KOL feedback obtained through a series of KOL interviews – CDF rule applied
    a. No allowance of second-line PARP
    b. Patients receive third-line PARP (olaparib *BRCA*mut only)
2. KOL feedback obtained through a series of KOL interviews
    a. Allowance of second-line PARP

b. No patient receives third-line PARP (as patients receive PARP inhibitors in second-line)

3. Clinical trial 'next anticancer therapy' data collected in PRIMA for niraparib and RS

As described, option 1 was modelled as the base case within this economic analysis. In order to model this, KOLs were asked questions on the second and third-line chemotherapy regimens given to patients in clinical practice split by platinum-sensitivity. The data were supplemented with the proportion of RS patients who are expected to be eligible to receive a PARP inhibitor in subsequent lines of treatment.

For completeness, to further assess the uncertainty in subsequent therapies, options 2 and 3 were explored within the scenario analyses. Table 38 to Table 40 present the subsequent therapy regimens for options 1-3.

Table 38: Base case subsequent treatment regimens (Option 1 - KOL feedback with no second-line PARPi as a comparator– CDF rule applied)

Treatment class	Second-line treatment		Third-line treatment	
	Niraparib	RS	Niraparib	RS
Carboplatin	44.37%	44.37%	30.45%	30.45%
Cisplatin	4.12%	4.12%	4.22%	4.22%
Taxane	38.06%	38.06%	44.82%	44.82%
Doxorubicin	4.57%	4.57%	9.42%	9.42%
Docetaxel	5.09%	5.09%	6.37%	6.37%
Gemcitabine	0.00%	0.00%	0.00%	0.00%
Bevacizumab	0.00%	0.00%	0.00%	0.00%
Cyclophosphamide	3.78%	3.78%	4.73%	4.73%
PARP inhibitor	0.00%	0.00%	0.00%	7.81%
PD(L)-1 inhibitor	0.00%	0.00%	0.00%	0.00%

Abbreviations: KOL, key opinion leader; PARP, Poly (ADP-ribose) polymerase; PDL-1, Programmed death-ligand 1; RS, routine surveillance

Table 39: Scenario analyses subsequent treatment regimens (Option 3 – PRIMA next anticancer therapy data)

Treatment class	Second and subsequent line treatment		Third-line treatment	
	Niraparib	RS	Niraparib	RS
Carboplatin	[redacted]	[redacted]	N/A	N/A
Cisplatin	[redacted]	[redacted]	N/A	N/A
Taxane	[redacted]	[redacted]	N/A	N/A

Treatment class	Second and subsequent line treatment		Third-line treatment	
	Niraparib	RS	Niraparib	RS
Doxorubicin	[redacted]	[redacted]	N/A	N/A
Docetaxel	[redacted]	[redacted]	N/A	N/A
Gemcitabine	[redacted]	[redacted]	N/A	N/A
Bevacizumab	[redacted]	[redacted]	N/A	N/A
Cyclophosphamide	[redacted]	[redacted]	N/A	N/A
PARP inhibitor	[redacted]	[redacted]	N/A	N/A
PD(L)-1 inhibitor	[redacted]	[redacted]	N/A	N/A

Abbreviations: KOL, key opinion leader; PARP, Poly (ADP-ribose) polymerase; PDL-1, Programmed death-ligand 1; RS, routine surveillance

Table 40: Scenario analyses subsequent treatment regimens (Option 2 - KOL feedback allowing for second-line PARPi to be a comparator)

Treatment class	Second-line treatment		Third-line treatment	
	Niraparib	RS	Niraparib	RS
Carboplatin	44.37%	44.37%	N/A	N/A
Cisplatin	4.12%	4.12%	N/A	N/A
Taxane	38.06%	38.06%	N/A	N/A
Doxorubicin	4.57%	4.57%	N/A	N/A
Docetaxel	5.09%	5.09%	N/A	N/A
Gemcitabine	0.00%	0.00%	N/A	N/A
Bevacizumab	0.00%	0.00%	N/A	N/A
Cyclophosphamide	3.78%	3.78%	N/A	N/A
PARP inhibitor	0.00%	45.00%	N/A	N/A
PD(L)-1 inhibitor	0.00%	0.00%	N/A	N/A

Abbreviations: KOL, key opinion leader; PARP, Poly (ADP-ribose) polymerase; PDL-1, Programmed death-ligand 1; RS, routine surveillance

Treatment costs

Subsequent treatment drug costs were calculated based on available formulations: recommended dose and duration, pack sizes, unit costs and price per mg for each treatment from the BNF.[140] The recommended dose of subsequent treatment was based on: TA528, NICE CDF criteria and relevant trial protocol doses and SmPCs.[27,138] A cost of £332.13 (NHS 2018/19 reference costs - SB15Z) and £195.44 (NHS 2018/19 reference costs - SB11Z) were applied for chemotherapies administered intravenously and orally, respectively.[141] Subsequent PARP use incurred no administration costs. Treatment costs and dosing regimens are presented in Table 41 and Table 42, respectively.

The cost of subsequent treatments is applied as a one-off cost upon progression, which is consistent with modelling approaches adopted in TA528 (niraparib 2L), Guy 2018, TA611 (rucaparib 2L) and SMC 2018.[97,142–144] A limitation of the partitioned survival model structure is that it does not allow specific tracking of patients once they progress. Therefore, ongoing subsequent treatment options could not be applied to throughout the model time horizon. Furthermore, the evidence elicited from ENGOT-OV16/NOVA and Study 19 suggest that chemotherapy regimens are not expected to differ largely between treatment arms.[42,43] This is highlighted in the feedback obtained from UK clinicians. (Table 38)

For the base case only the cost of for third-line olaparib in platinum sensitive *BRCA*mut patients are included. It is estimated that only 7.81% (proportion *BRCA*mut [25%] * proportion platinum-sensitive after third-line chemotherapy [31%]) of patients within the RS arm will be eligible to receive olaparib as a third-line treatment option. In clinical practice this proportion is likely to be even smaller as feedback obtained at an advisory board indicated that clinicians are allowing patients to receive second-line PARP inhibitor treatment if eligible despite the CDF restrictions. As only a small proportion of patients will receive third-line olaparib within the economic model and as the chemotherapy regimens are aligned between the two treatment arms, no major differences are expected in terms of costs between the two treatment arms within the base case analysis. As such a simple one-off approach of applying subsequent treatment costs was deemed more appropriate than a method that explicitly tracks when patients would receive subsequent treatment.

Table 41: Subsequent treatment drug costs (sourced from the BNF).[140] N.B All drug costs are as per the BNF list price

Subsequent treatment class	Subsequent treatment combination	Treatment	Pack size	Price per pack	Unit size
Carboplatin	Carboplatin only	Carboplatin	1	18.73	450
	Carboplatin w/gemcitabine	Carboplatin	1	18.73	450
	Carboplatin w/gemcitabine	Gemcitabine	1	13.09	1000
	Carboplatin w/paclitaxel	Carboplatin	1	18.73	450
	Carboplatin w/paclitaxel	Paclitaxel	1	19.68	150
Cisplatin	Cisplatin	Cisplatin	1	4.48	50
	Cisplatin/gemcitabine	Cisplatin	1	4.48	50
	Cisplatin/gemcitabine	Gemcitabine	1	13.09	1000
Taxane	Carboplatin w/paclitaxel	Carboplatin	1	18.73	450
	Carboplatin w/paclitaxel	Paclitaxel	1	19.68	150
	Docetaxel	Docetaxel	1	14.74	80
	Paclitaxel	Paclitaxel	1	19.68	150
	Paclitaxel albumin	Paclitaxel albumin	1	19.68	150
Doxorubicin	Doxorubicin	Doxorubicin	1	19.57	10
	Doxorubicin hydrochloride	Doxorubicin hydrochloride	1	19.57	10
	Liposomal doxorubicin hydrochloride	Liposomal doxorubicin hydrochloride	1	19.57	10
	Pegylated liposomal doxorubicin	Pegylated liposomal doxorubicin	1	19.57	10

Subsequent treatment class	Subsequent treatment combination	Treatment	Pack size	Price per pack	Unit size
	Pegylated liposomal doxorubicin hydrochloride	Pegylated liposomal doxorubicin hydrochloride	1	19.57	10
Gemcitabine	Carboplatin w/gemcitabine	Carboplatin	1	18.73	450
	Carboplatin w/gemcitabine	Gemcitabine	1	13.09	1000
	Gemcitabine	Gemcitabine	1	13.09	1000
	Gemcitabine hydrochloride	Gemcitabine hydrochloride	1	13.09	1000
Bevacizumab	Bevacizumab	Bevacizumab	1	242.66	100
	Bevacizumab	Bevacizumab	1	924.40	400
Cyclophosphamide	Cyclophosphamide	Cyclophosphamide	100	139.00	50
PARP inhibitor*	Niraparib	Niraparib	56	[redacted]	100
	Olaparib	Olaparib	56	[redacted]	100
	Rucaparib	Rucaparib	60	[redacted]	300
PD(L) inhibitor	Atezolizumab	Atezolizumab	1	3807.69	1200
	Pembrolizumab	Pembrolizumab	1	2630.00	100

Abbreviations: BNF, British National Formulary; PARP, Poly (ADP-ribose) polymerase; PDL-1, Programmed death-ligand 1. *A discount assumed for all second-line PARPs equivalent to niraparib [redacted]% discount applied in the second-line setting

Table 42: Subsequent chemotherapy dosing regimens

Treatment	Dose	Frequency of cycle	Source
Carboplatin	Dose based on creatinine clearance rates plus twenty-five	Repeated every 21 days for up to 6 cycles	TA528[138]

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Treatment	Dose	Frequency of cycle	Source
	multiplied by the AUC (5mg/mL/min		
Gemcitabine	Dose based on body surface area and calculated as 1000mg/m^2	Repeated twice every 21 days for up to 6 cycles	TA528[138]
Paclitaxel	Dose based on body surface area of patient population and calculated as 175 mg/m^2	Repeated every 21 days for up to 6 cycles	TA528[138]
Cisplatin	Based on body surface area of patient population and calculated as 100 mg/m^2	Repeated every 21 days for up to 6 cycles	TA528[138]
Docetaxel	Based on body surface area of patient population and calculated as 100 mg/m^2	Repeated every 21 days for up to 6 cycles	TA528[138]
Doxorubicin	Based on body surface area of patient population and calculated as 70 mg/m^2	Repeated every 21 days for up to 6 cycles	TA528[138]
Bevacizumab	7.5 mg per kg	Repeated every 21 days for up to 12 cycles	NICE CDF criteria and ICON-7 protocol maintenance dose[145,146]
Cyclophosphamide	Fixed 50 mg dose	Repeated twice every 28 days for up to 6 cycles	TA528[138]
Niraparib	300 mg OD	Daily for up to [redacted][147]	[redacted] and ENGOT-OV16/NOVA protocol dose[148]
Olaparib	600 mg OD	Daily for up to [redacted][147]	[redacted] and SOLO-1 protocol dose[118]
Rucaparib	1200 mg OD	Daily for up to [redacted][147]	[redacted] and ARIEL-3 protocol dose[149]
Atezolizumab	Fixed dose of 840 mg	Every 3 weeks until progression. Assumed [redacted] months to align with PARPi	[redacted] and SmPC[150]
Pembrolizumab	Fixed dose of 200 mg	Every 3 weeks until progression. Assumed [redacted] months to align with PARPi	[redacted] and SmPC[151]

Abbreviations: AUC, area under the curve; CDF, Cancer Drugs Fund; kg, kilogram; mg, milligram; m, meter; NICE, National Institute for Health and Care Excellence; OD, once daily; TA, technology appraisal

Disease management unit costs and resource use

Disease management resource use was primarily based on the olaparib first-line NICE submission (TA598) (which in turn was based on BGCS guidelines), the niraparib draft SmPC and UK clinical expert opinion.[30]

Disease management resource use costs in this economic analysis were calculated by multiplying the resource use by the unit cost of each respective resource use item. Resource use and associated unit costs are presented in Table 43. Costs were source from the NHS 2018/19 reference costs.[141]

For the base case inputs, the model assumes that while on treatment, patients in the RS arm are assessed by a consulting physician once every month and undergo a CT scan and a complete blood count test every three months. Outpatient visits decrease to every three months once a patient discontinued treatment. Patients in the niraparib treatment arm undergo the same monitoring as RS with the addition of weekly complete blood count tests in the first month of treatment. While the niraparib draft SmPC recommends additional heart rate and blood pressure monitoring, feedback from UK KOLs is that patients will be able to do this within the home setting. It also anticipated that the final SmPC will recommend that patients perform heart rate and blood pressure monitoring at home. Therefore, these additional requirements for niraparib are not included in the model.

Following progression, patients treated with niraparib or RS are assumed to visit a consulting physician monthly and to undergo a CT scan and complete blood count test every three months. A scenario analyses was conducted in resource use which was informed by a series of UK KOL interviews. Clinical opinion was that a patient would not be expected to undergo regular CT scans as they would receive one upon progression. Therefore, as part of the scenario analyses, a conservative approach was taken whereby patients undergo a CT every 6 months.

Disease management cost and resource use inputs modelled in the base case and as part of a scenario analyses are presented in Table 43 and Table 44, respectively.

Table 43: Base case disease management resource use and unit costs

Intervention	Health state	Outpatient visit Oncology – consultant led (503; Gynaecological Oncology)	CT scan (RD20A)	Complete blood count (DAPS05)	Outpatient visit Oncology – non consultant led (503; Gynaecological Oncology)	Total cost per cycle (£)
Unit cost (£)		£126.91	£83.23	£2.79	£131.01	--
Niraparib	PFD on treatment (cycle 1)	1.0	0.3	4.0	0.0	£163
	PFD on treatment (cycle 2)	1.0	0.3	1.0	0.0	£155
	PFD on treatment (cycle 3+)	1.0	0.3	1.0	0.0	£155
	PFD off treatment	0.3	0.3	0.3	0.0	£64
	PD	1.0	0.3	0.3	0.0	£153
RS	PFD on treatment	0.3	0.3	0.3	0.0	£64
	PFD off treatment	0.3	0.3	0.3	0.0	£64
	PD	1.0	0.3	0.3	0.0	£153

Abbreviations: CT, computerised tomography; PD, progressed disease; PFD, progression-free disease; RS, routine surveillance

Table 44: Scenario analysis disease management resource use and unit costs

Intervention	Health state	Outpatient visit Oncology – consultant led (503; Gynaecological Oncology)	CT scan (RD20A)	Complete blood count (DAPS05)	Outpatient visit Oncology – non consultant led (503; Gynaecological Oncology)	Total cost per cycle (£)
Unit cost (£)		£126.91	£83.23	£2.79	£131.01	--
Niraparib	PFD on treatment (cycle 1)	0.5	0.2	0.5	0.7	£174
	PFD on treatment (cycle 2)	0.5	0.2	0.5	0.7	£174
	PFD on treatment (cycle 3+)	0.5	0.2	0.5	0.7	£174
	PFD off treatment	0.3	0.2	0.3	0.3	£100
	PD	0.5	0.3	0.3	0.7	£177
RS	PFD on treatment	0.5	0.2	0.5	0.7	£174
	PFD off treatment	0.3	0.2	0.3	0.3	£100
	PD	0.5	0.3	0.3	0.7	£177

Abbreviations: CT, computerised tomography; PD, progressed disease; PFD, progression-free disease; RS, routine surveillance

Adverse reaction unit costs and resource use

The health effects of treatment-related AEs were included in the evaluation and modelled via the incidence of grade ≥ 3 AEs. Grade ≥ 3 AEs were included in the evaluation as they are likely to be associated with costs that will affect decision making. The base case costs associated with treating and managing AEs used in the model are presented in Table 45. Costs were sourced from the 2018/19 NHS reference costs.[141] KOL input suggested that most of these adverse events are usually managed in an outpatient setting, therefore to explore the impact of different assumptions around the costing of AEs, a scenario analysis was conducted in which patients were treated in an outpatient setting. "Day case" NHS reference costs (for anaemia, thrombocytopenia and hypertension) aligned with the codes used for the base case AE costs were modelled. The costs adopted in this scenario analysis are presented in Table 46. Treatment-related grade 3 AE rates were obtained directly from the PRIMA trial.[114] Table 47 presents the AE rates applied in the model.

Table 45: Base case costs per grade ≥ 3 AE

Grade ≥ 3 AE	Cost per event	NHS Reference Costs, year 2018/19 currency description[141]
Anaemia	£668.83	Non-elective long stay, short stay, day case, regular day or night admission weighted average of the following codes: • SA04G • SA04H • SA04J • SA04K • SA04L
Thrombocytopenia	£714.57	Non-elective long stay, short stay, day case, regular day or night admission weighted average of the following codes: • SA12G • SA12H • SA12J
Platelet count decreased	£0.00	Assumed to equal £0. Platelet count decrease is generally asymptomatic and so does not attribute cost.
Neutropoenia	£123.07	Neutropenia Drugs, Band 1; XZD25Z
Hypertension	£595.34	Non-elective long stay, short stay, day case, regular day or night admission weighted average of the following codes:

Grade ≥ 3 AE	Cost per event	NHS Reference Costs, year 2018/19 currency description[141]
		• EB04Z
Neutrophil count decreased	£391.90	Neutropenia Drugs, Band 1; XZD25Z

Abbreviations: AE, adverse event; NHS, National Health Service

Table 46: Scenario analyses costs per grade ≥ 3 AE

Grade ≥ 3 AE	Cost per event	NHS Reference Costs, year 2018/19 currency description [141]
Anaemia	£274.68	Day case weighted average of the following codes: • SA04G • SA04H • SA04J • SA04K • SA04L
Thrombocytopenia	£315.05	Day case weighted average of the following codes: • SA12G • SA12H • SA12J
Platelet count decreased	£0	Assumed to equal £0. Platelet count decrease is generally asymptomatic and so does not attribute cost.
Neutropoenia	£123.67	Neutropenia Drugs, Band 1; XZD25Z
Hypertension	£324.57	Day case of the following code: • EB04Z
Neutrophil count decreased	£391.90	Neutropenia Drugs, Band 1; XZD25Z

Abbreviations: AE, adverse event; NHS, National Health Service

Table 47: Treatment-related grade ≥ 3 AE rates applied in the economic analysis sourced from the PRIMA trial[114]

Grade ≥ 3 AE	Niraparib (%)	RS (%)
Anaemia	31%	2%
Thrombocytopenia	29%	0%
Platelet count decreased	13%	0%
Neutropenia	13%	1%
Hypertension	6%	1%
Neutrophil count decrease	8%	0%

Abbreviations: AE, adverse event

Miscellaneous unit costs and resource use

A one-off cost of £7,576 upon death was applied to reflect the costs of terminal care (transitions to the death state). This cost was sourced from a UK study by Guest *et al*.,[152] and has been accepted in previous NICE appraisals (TA528 and TA598).[138,139]

The cost reported in Guest *et al.* was inflated to a 2018/19 cost year using Personal

Social Services Research Unit (PSSRU) inflation indices.[153] In Guest *et al.* the study calculated the total end-of-life care cost using patient-level primary care records sourced from general practices in the UK, and the dataset comprised records for patients with advanced cancer including ovarian cancer. The model assumes that 51.28% of patients will receive end-of-life care within a NHS setting, based on data from a UK study by Gao *et al.*[154] This approach is aligned with that adopted in TA589 for olaparib as a first-line maintenance setting.[139]

B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

A summary of variables applied in the economic analysis is presented in Table 48.

Table 48: Summary of base case model inputs

Parameter	Value	OWSA		Within PSA varied by	Reference to location in submission
		Upper bound	Lower bound		
Model setup					
Time horizon	39 years	N/A – varied in scenario analyses		Fixed	Page 112
Discount rate costs	3.5%	N/A		Fixed	Page 109
Discount rate outcomes	3.5%	N/A		Fixed	
Clinical inputs					
Niraparib PFS distribution	G. gamma	95% CI		G. gamma	Page 123
RS PFS	G. gamma	95% CI		G. gamma	
RS OS	Log-logistic	95% CI		Log-logistic	Page 130
Niraparib OS	Mean ΔPFS:ΔOS = 1:2	N/A – varied in scenario analyses		Beta	
Niraparib TTD distribution	Weibull	95% CI		Weibull	Page 138
Niraparib stopping rule	3 years	N/A – varied in scenario analyses		Fixed	
Proportional of patients discontinuing at stopping rule	[redacted]%	N/A – varied in scenario analyses		Fixed	
Long-term remission	7 years	N/A – varied in scenario analyses		Fixed	Page 138
MA extrapolation approach 'NVRD effect'; HR	0.49	0.40	0.59	Gamma	Page 143
MA extrapolation approach 'treatment effect; HR	0.34	0.28	0.59	Gamma	
Incidence of adverse events					
Niraparib - Anaemia	31.0%	19.6%	43.7%	Beta	Page 178

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Parameter	Value	OWSA		Within PSA varied by	Reference to location in submission
		Upper bound	Lower bound		
Niraparib - Thrombocytopenia	28.7%	18.2%	40.6%	Beta	
Niraparib - Platelet count decreased	13.0%	8.3%	18.5%	Beta	
Niraparib - Neutropenia	12.8%	8.2%	18.2%	Beta	
Niraparib - Hypertension	6.0%	3.9%	8.6%		
Niraparib - Neutrophil count decrease	7.6%	4.9%	10.8%	Beta	
RS - Anaemia	1.6%	1.0%	2.3%	Beta	Page 178
RS - Thrombocytopenia	0.4%	0.3%	0.6%	Beta	
RS - Platelet count decreased	0.0%	0.0%	0.0%	Beta	
RS - Neutropenia	1.2%	0.8%	1.7%	Beta	
RS - Hypertension	1.2%	0.8%	1.7%		
RS - Neutrophil count decrease	0.0%	0.0%	0.0%	Beta	
Utilities					
PFD health state	[redacted]	[redacted]	[redacted]	Beta	Page 158
PD health state	[redacted]	[redacted]	[redacted]	Beta	
Disutilities					
Anaemia	0.12	0.08	0.17	Beta	Page 158
Thrombocytopenia	0.09	0.06	0.13	Beta	
Platelet count decreased	0.09	0.06	0.13	Beta	
Neutropenia	0.09	0.06	0.13	Beta	
Hypertension	0.02	0.01	0.03	Beta	
Neutrophil count decrease	0.09	0.06	0.13	Beta	
Technology costs (£)					
Niraparib - cycle 1	[redacted]	N/A		Fixed	Page 160
Niraparib - cycle 2	[redacted]	N/A		Fixed	
Niraparib - cycle 3	[redacted]	N/A		Fixed	
Niraparib - cycle 4	[redacted]	N/A		Fixed	
Niraparib - cycle 5	[redacted]	N/A		Fixed	

Parameter	Value	OWSA		Within PSA varied by	Reference to location in submission
		Upper bound	Lower bound		
Niraparib - cycle 7	[redacted]	N/A		Fixed	
Niraparib - cycle 7	[redacted]	N/A		Fixed	
Niraparib - cycle 8	[redacted]	N/A		Fixed	
Niraparib - cycle 9	[redacted]	N/A		Fixed	
Niraparib - cycle 10	[redacted]	N/A		Fixed	
Niraparib - cycle 11	[redacted]	N/A		Fixed	
Niraparib - cycle 12+	[redacted]	N/A		Fixed	
RS - all cycles	0	N/A		Fixed	
Administration costs (£)					
Niraparib - all cycles	0	0	0	Fixed	Page 160
RS - all cycles	0	0	0	Fixed	
Monitoring costs (£)					
Outpatient visit (consultant oncologist)	126.91	82.13	181.28	Gamma	Page 175
CT scan	83.23	53.87	118.89	Gamma	
Blood test	2.79	1.80	3.98	Gamma	
Outpatient visit (non-consultant lead oncologist)	131.01	84.78	187.14	Gamma	
Monitoring resource use					
Niraparib - outpatient visit (consultant oncologist) - PFD cycle 1	1.0	0.65	1.43	Gamma	Page 175
Niraparib - outpatient visit (consultant oncologist) - PFD cycle 2	1.0	0.65	1.43	Gamma	
Niraparib - outpatient visit (consultant oncologist) - PFD cycle 3+	1.0	0.65	1.43	Gamma	

Parameter	Value	OWSA		Within PSA varied by	Reference to location in submission
		Upper bound	Lower bound		
Niraparib - outpatient visit (consultant oncologist) - PFD off treatment	0.3	0.19	0.43	Gamma	
Niraparib - outpatient visit (consultant oncologist) - PD all cycles	1.0	0.65	1.43	Gamma	
Niraparib - CT scan - PFD cycle 1	0.3	0.19	0.43	Gamma	
Niraparib - CT scan - PFD cycle 2	0.3	0.19	0.43	Gamma	
Niraparib - CT scan - PFD cycle 3+	0.3	0.19	0.43	Gamma	
Niraparib - CT scan - PFD off treatment	0.3	0.19	0.43	Gamma	
Niraparib - CT scan - PD (all cycles)	0.3	0.19	0.43	Gamma	
Niraparib - Complete blood count - PFD cycle 1	4.0	2.59	5.71	Gamma	
Niraparib - Complete blood count - PFD cycle 2	1.0	0.65	1.43	Gamma	
Niraparib - Complete blood count - PFD cycle 3+	1.0	0.65	1.43	Gamma	
Niraparib - Complete blood count - PFD off treatment	0.3	0.19	0.43	Gamma	
Niraparib - Complete blood count - PD (all cycles)	0.3	0.19	0.43	Gamma	
Niraparib - outpatient visit (non-consultant lead) - PFD cycle 1	0.0	0.0	0.0	Gamma	

Parameter	Value	OWSA		Within PSA varied by	Reference to location in submission
		Upper bound	Lower bound		
Niraparib - outpatient visit (non-consultant lead) - PFD cycle 2	0.0	0.0	0.0	Gamma	
Niraparib - outpatient visit (non-consultant lead) - PFD cycle 3+	0.0	0.0	0.0	Gamma	
Niraparib - outpatient visit (non-consultant lead) - PFD cycle off treatment	0.0	0.0	0.0	Gamma	
Niraparib - outpatient visit (non-consultant lead) - PD all cycles	0.0	0.0	0.0	Gamma	
RS - outpatient visit (consultant lead) - PFD all cycles	0.3	0.18	0.43	Gamma	
RS - outpatient visit (consultant lead) - PD all cycles	1.0	0.65	1.43	Gamma	
RS - CT scan - PFD all cycles	0.3	0.18	0.43	Gamma	
RS - CT scan - PD all cycles	0.3	0.18	0.43	Gamma	
RS - complete blood count- PFD all cycles	0.3	0.18	0.43	Gamma	
RS - complete blood count scan - PD all cycles	0.3	0.18	0.43	Gamma	
RS - outpatient visit (non-consultant lead) - PFD all cycles	0.0	0.0	0.0	Gamma	
RS - outpatient visit (non-consultant lead) - PD all cycles	0.0	0.0	0.0	Gamma	
Adverse event costs (£) - Cost per event					
Anaemia	669	433	955	Gamma	Page 178
Thrombocytopenia	715	462	1021	Gamma	
Platelet count decreased	0	0	0	Gamma	
Neutropenia	124	80	177	Gamma	
Hypertension	595	385	850	Gamma	

Parameter	Value	OWSA		Within PSA varied by	Reference to location in submission
		Upper bound	Lower bound		
Neutrophil count decrease	392	254	560	Gamma	
Subsequent chemotherapy technology costs (£)					
Rate of administration for all subsequent regimens	See Table 38			Beta	Page 166
Unit costs of subsequent treatment	See Table 41	N/A		Fixed	
Dosing of subsequent treatment	See Table 42	N/A		Fixed	
Niraparib - Total cost of subsequent treatment costs	[redacted]	[redacted]	[redacted]	Gamma	
RS - Total cost of subsequent treatment costs	[redacted]	[redacted]	[redacted]	Gamma	
Terminal care costs (£)					
End of life unit costs	7,798	4,903	10,822	Gamma	
Proportion of patients receiving end of life care in NHS setting	51.3%	31.3%	71.1%	Beta	Page 179

Abbreviations: CI, confidence interval; CT, computerised tomography; N/A, not applicable; NHS, National Health Service; OWSA, one-way sensitivity analyses; PFD, progression-free disease; PFD, progression-free survival; PD, progressed disease; PSA, probabilistic sensitivity analyses; RS, routine surveillance;

Assumptions

A summary of the model assumptions is provided in Table 49.

Table 49: Model assumptions

Category	Assumption	Justification
Population and comparators	The PRIMA trial is representative of patient population receiving first-line maintenance treatment with niraparib and RS for patients in the UK population. The PAOLA-1 study is suitable to inform extrapolation between the ITT and the MA population. The PRIMA trial can be extrapolated to predict efficacy in the MA population, which includes a group of patients who are at lower risk of recurrence due to their surgical outcomes.	The clinical trial population for PRIMA compared maintenance therapy with niraparib versus placebo in patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer who had previously received one platinum-based regimens and were responsive (partial or complete) to their last platinum-based chemotherapy. Clinical expert opinion indicated that the PRIMA trial can be extrapolated to predict the efficacy of the MA population and that the PAOLA-1 trial is the best available body of evidence to inform this.
	RS is an appropriate comparator for niraparib	RS was considered for all populations as per the PRIMA clinical trial and is in line with the NICE scope

Category	Assumption	Justification
Model structure and settings	Partitioned survival model	Reflective of the natural history of the disease and a well-accepted model structure in oncology.
	UK NHS and PPS perspective	In line with NICE reference case.
	Lifetime horizon	In line with the NICE reference and with previous NICE appraisals in OC.
	3.5% per annum discount rate for costs and outcomes	In line with NICE reference case.
	Half cycle correction applied	Assuming a cost or outcome is incurred on average mid-way through a cycle.
Clinical effectiveness	Treatment effect is not impacted by treatment stopping rules.	Aligned with clinical expert opinion and clinical evidence observed in PARPi first-line trials (SOLO-1).
	Active treatment OS is estimated based on the following relationship: mean ΔPFS:ΔOS = 1:2	Niraparib OS data is highly immature and there is no long-term first-line survival treatment to validate extrapolations. As such a mean ΔPFS:ΔOS relationship was adopted; this is based on external clinical trial evidence within maintenance treatments for ovarian cancer and the method has been adopted in existing ovarian cancer HTA submissions.
	The generalised gamma distribution provides an appropriate PFS extrapolation for niraparib and RS.	The generalised gamma distribution for PFS is the best statistically fitting curve and was selected by clinicians as clinically plausible.
	The log-logistic distribution provides an appropriate OS extrapolation for RS.	The log-logistic distribution is the second best statistically fitting curve. Its choice was driven by the help of real-world evidence data and was selected by clinicians as clinically plausible.
Quality-of-life inputs	Grade ≥ 3 AEs are included and assumed occur in the first cycle of the model time horizon.	AE are likely to occur very soon after treatment and only require acute care. This is consistent to the modelling approaches adopted in NICE TA528 and NICE TA598.
Cost and resource use inputs	Treatment discontinuation for niraparib is in line with the trial discontinuation criteria (3 years)	As per PRIMA study protocol and as expected to be provided in clinical practice.
	No wastage of doses	Dosage was based on actual dose taken in the PRIMA trial

Category	Assumption	Justification
	No administration costs for oral maintenance or subsequent chemotherapy treatments.	Oral treatments
	Subsequent treatment is applied as a one-off cost upon disease progression.	In line with previous HTA appraisals, and not expected to impact results as subsequent treatment is similar between treatments.
	Patients are not allowed to receive a PARPi after a PARPi.	In line with NICE CDF criteria for second-line PARPi treatment.
	Subsequent treatment regimens are based on UK clinical expert opinion.	Assumed to be more aligned with clinical practice that PRIMA trial data.
	Costs for subsequent chemotherapy regimens classes are calculated based on a straight average as opposed to a weighted average	Subsequent chemotherapy costs have a minor impact on cost-effectiveness results; hence a straight average calculation is sufficient.
	No indirect costs are applied in the model.	In line with the NICE reference case

Abbreviations: AE, adverse events; NICE, National Institute for Health and Excellence; NHS, National Health Service; OC, ovarian cancer; PSS, Personal Social Services; RCT, randomised controlled trials; UK, United Kingdom; RS, routine surveillance.

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

MA population

Total costs, life years (LYs), QALYs, and incremental cost per QALY gained for niraparib versus RS for the anticipated MA population for niraparib are presented in Table 50. In the base case analysis, niraparib generates [redacted] incremental QALYs and £[redacted] incremental costs over a lifetime horizon compared with RS, resulting in an ICER of £13,870 per QALY gained. Disaggregated base case results are presented in Appendix J: Clinical outcomes and disaggregated results.

ITT population

The results from the ITT population offer confidence in decision making in the MA population results, as the ICER for the MA population was seen to be more cost effective than for the ITT population. The total costs, LYs, QALYs, and incremental cost per QALY gained for niraparib versus RS for the ITT are presented in Table 51. In the base case analysis, niraparib generates [redacted] incremental QALYs and £[redacted] incremental costs over a lifetime horizon compared with RS, resulting in an ICER of £18,856 per QALY gained. Disaggregated base case results are presented in Appendix J: Clinical outcomes and disaggregated results..

The fact that niraparib is more cost-effective in the MA population than in the ITT population is in line with evidence on the prognosis and treatment effect on patients with NVRD, who are excluded from the ITT population (please refer to Section B.2.14 for further details).

Table 50: Base-case results for niraparib versus RS for the anticipated MA population

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER versus baseline (£/QALY)
RS	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,870

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance.

Table 51: Base-case results for niraparib versus RS for the ITT population

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER versus baseline (£/QALY)
RS	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,856

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention to treat; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance.

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

Probabilistic sensitive analyses (PSA) was conducted to explore the impact of model parameters uncertainty on the results. PSA involves drawing a value at random for each variable from its uncertainty distribution. This is performed for each parameter simultaneously and the resulting incremental results are recorded. This constitutes one 'simulation'. Ten thousand simulations were performed, which each gave a distribution of incremental results, and consequently, an assessment of the robustness of the cost-effectiveness results. PFS and OS remained independent within the PSA as per a standard PSM. However, the sum of the proportion of patients in each health state will not be able to exceed 100% of the patient population. For event rates and utilities, a beta distribution was used to restrict draws to between 0 and 1. For costs and resource use estimates, and hazard ratios a gamma distribution was fitted to prevent values less than zero. Treatment costs remained fixed. An incremental cost-effectiveness plane (ICEP) scatter plot, cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) were produced to graphically illustrate the level of variability and uncertainty in the results.

MA population

Total costs, LYs, QALYs, and incremental cost per QALY gained for niraparib versus RS for the anticipated MA population for niraparib generated through a PSA are presented in Table 52. In the PSA, niraparib generates [redacted] incremental QALYs and £[redacted] incremental costs over a lifetime horizon compared with RS, resulting in an ICER of £13,792 per QALY gained. The corresponding ICEP, CEAC and CEAF are presented in Figure 39 to Figure 41, respectively. At a WTP threshold of £30,000 niraparib had a 100% probability of being cost-effectiveness compared to RS in the MA population.

ITT population

Total costs, LYs, QALYs, and incremental cost per QALY gained for niraparib versus RS for the ITT generated through a PSA are presented in Table 53. In the PSA,

niraparib generates [redacted] incremental QALYs and £[redacted] incremental costs over a lifetime horizon compared with RS, resulting in an ICER of £18,559 per QALY gained. The corresponding ICEP, CEAC and CEAF are presented in Figure 42 to Figure 44, respectively. At a WTP threshold of £30,000 niraparib had a 96.1% probability of being cost-effectiveness compared to RS in the ITT population.

Table 52: PSA results for niraparib versus RS for the anticipated MA population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£) (SD)	Incremental QALYs (SD)	ICER versus baseline (£/QALY)
RS	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	13,792

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analyses; QALYs, quality-adjusted life years; RS, routine surveillance.

Table 53: PSA results for niraparib versus RS for the ITT population

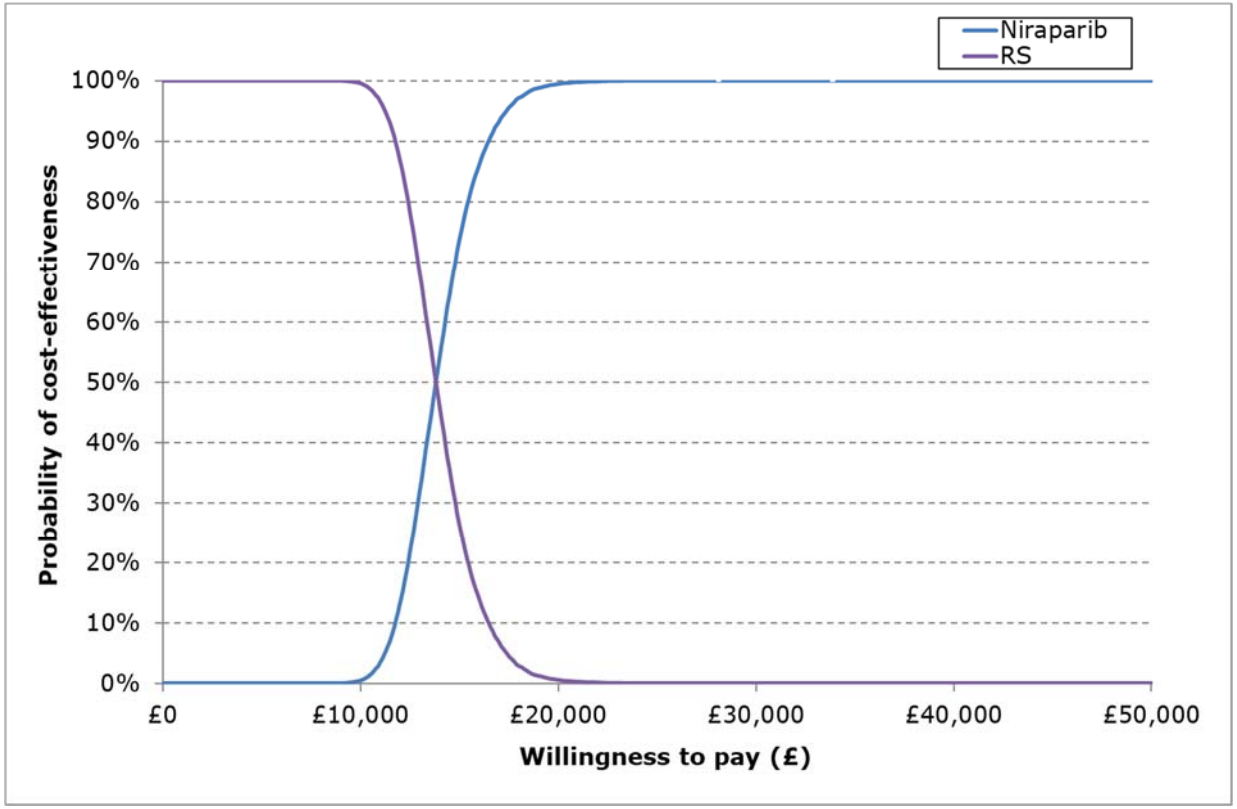
Technologies	Total costs (£)	Total QALYs	Incremental costs (£) (SD)	Incremental QALYs (SD)	ICER versus baseline (£/QALY)
RS	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	18,559

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention to treat; LYG, life years gained; PSA, probabilistic sensitivity analyses; QALYs, quality-adjusted life years; RS, routine surveillance.

Figure 39: Incremental cost-effectiveness plane for niraparib versus RS for the anticipated MA population (10,000 iterations)

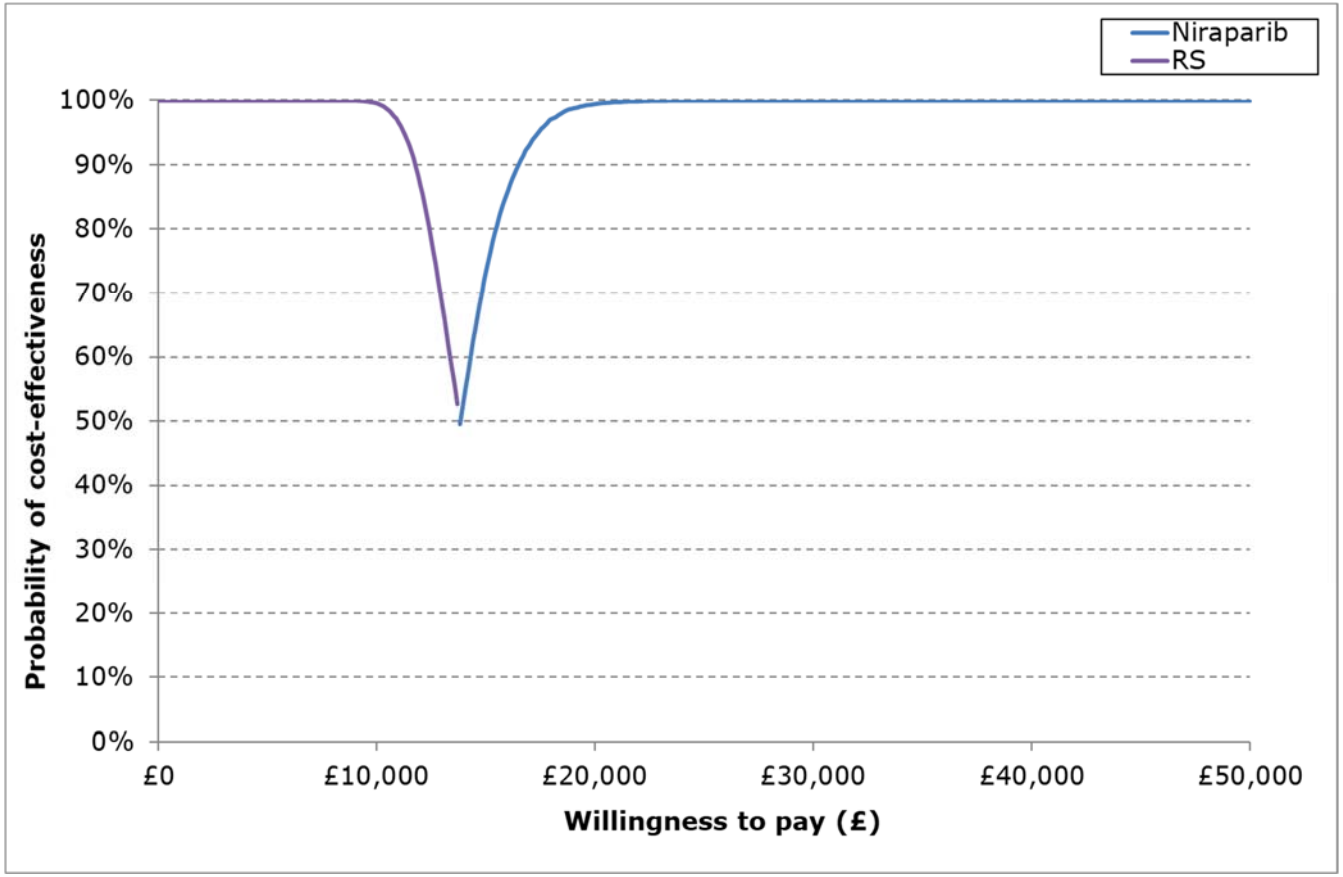
Abbreviations: QALYs, quality-adjusted life years; RS, routine surveillance

Figure 40: Cost-effectiveness acceptability curve for niraparib versus RS for the anticipated MA population (10,000 iterations)



Abbreviation: RS, routine surveillance

Figure 41: Cost-effectiveness acceptability frontier for niraparib versus RS for the anticipated MA population (10,000 iterations)

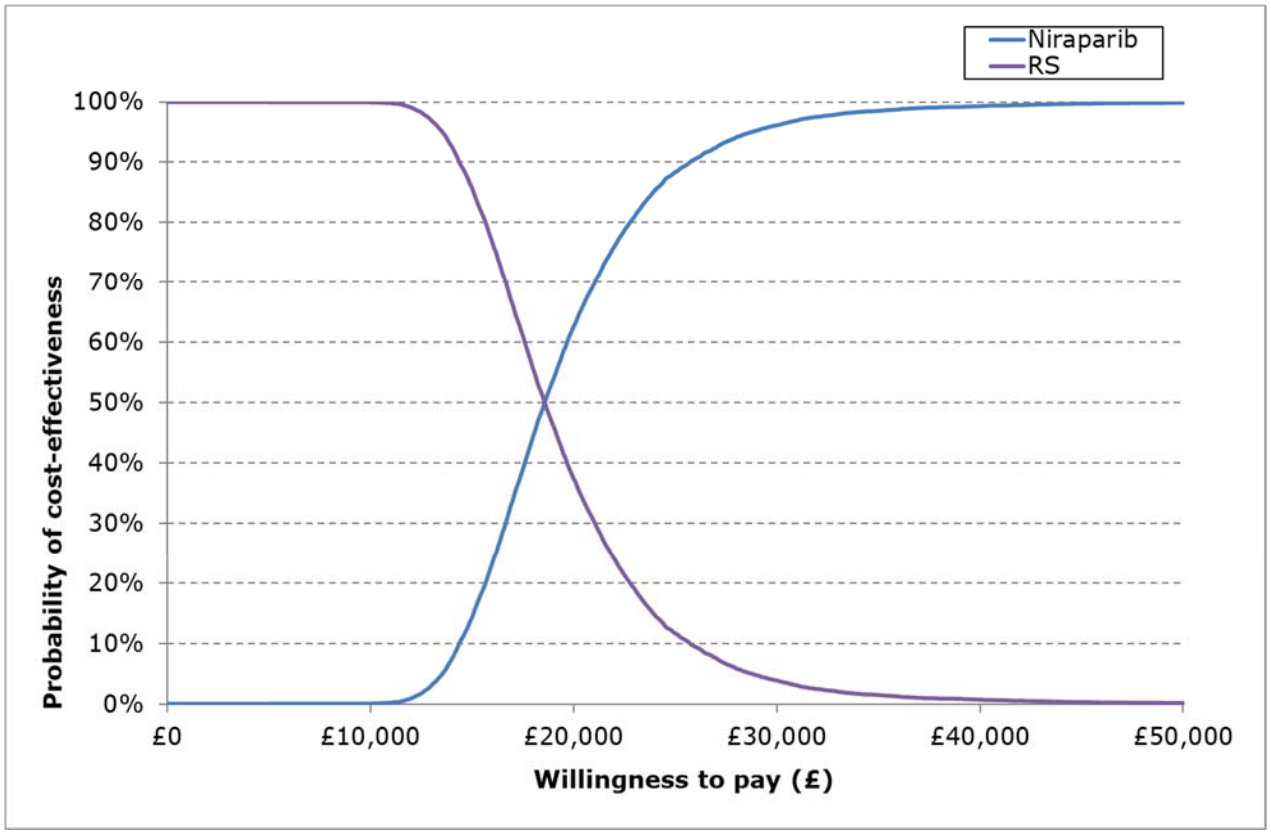


Abbreviations: RS, routine surveillance

Figure 42: Incremental cost-effectiveness plane for niraparib versus RS for the ITT population (10,000 iterations)

Abbreviations: QALYs, quality-adjusted life years; RS, routine surveillance

Figure 43: Cost-effectiveness acceptability curve for niraparib versus RS for the ITT population (10,000 iterations)



Abbreviation: RS, routine surveillance

Figure 44: Cost-effectiveness acceptability frontier for niraparib versus RS for the ITT population (10,000 iterations)

Abbreviations: RS, routine surveillance

Deterministic sensitivity analysis

Deterministic one-way sensitivity analysis (OWSA) was conducted to explore the level of uncertainty in the model results. The OWSA involved varying one parameter at a time and assessing the subsequent impact on the incremental QALYs and incremental costs. By adjusting each parameter individually, the sensitivity of the model results to that parameter can be assessed. The OWSA was conducted by allocating a 'low' value and a 'high' value to each parameter; the low value is the lower bound of the 95% confidence interval (CI), the high value is the upper bound of the 95% CI. In the absence of CI data, the variable will be altered by +/- 20%, with the exception of HRs which are varied by 10%. A tornado diagram was developed to graphically present the parameters which have the greatest effect on the ICER.

MA population

A OWSA tornado diagram presenting the top 20 most sensitive parameters for the MA population is presented in Figure 45, with tabulated results presented in Table 54. Within the OWSA all ICERs remained below £18,000 per QALY gained. The model was most sensitive to the shape and scale of the niraparib PFS distribution, the percentage of patients with Stage III NVRD at baseline, the shape and scale of the RS PFS distribution, the proportion of ITT patients progression free at the cure year, and the hazard ratio estimating stage III NVRD patients from the ITT patients for niraparib.

ITT population

A OWSA tornado diagram presenting the top 20 most sensitive parameters for the ITT population is presented in Figure 46, with tabulated results presented in Table 55. Within the OWSA all ICERs remained below £30,000 per QALY gained. The model was most sensitive to the shape and scale of the niraparib PFS distribution, the shape and scale of the RS PFS distribution, RS subsequent treatment total costs, the shape and scale of the niraparib TTD distribution and the niraparib arm resource use (PD) for outpatient visits.

Figure 45: OWSA tornado diagram for the MA population

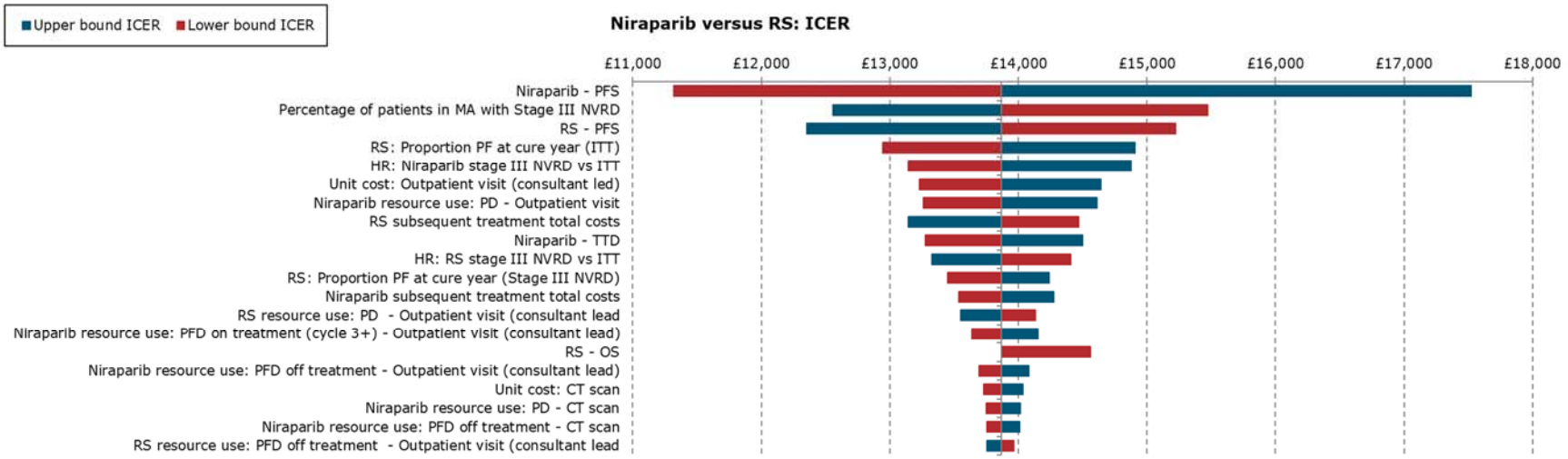


Table 54: Tabulated OWSA results for the MA population

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Niraparib - PFS	[redacted]	[redacted]	[redacted]	11,318	17,524	6,206
Percentage of patients in MA with Stage III NVRD	0.25	0.16	0.35	15,475	12,558	2,918
RS - PFS	[redacted]	[redacted]	[redacted]	15,221	12,356	2,865
RS: Proportion PF at cure year (ITT)	[redacted]	[redacted]	[redacted]	12,944	14,910	1,966

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
HR: Niraparib stage III NVRD vs ITT	[redacted]	[redacted]	[redacted]	13,142	14,877	1,735
Unit cost: Outpatient visit (consultant led)	126.91	82.13	181.28	13,232	14,644	1,413
Niraparib resource use: PD - Outpatient visit	1.00	0.65	1.43	13,260	14,610	1,351
RS subsequent treatment total costs	10,694.86	6,921.15	15,276.58	14,468	13,144	1,324
Niraparib – TTD	[redacted]	[redacted]	[redacted]	13,274	14,500	1,226
HR: RS stage III NVRD vs ITT	[redacted]	[redacted]	[redacted]	14,408	13,325	1,082
RS: Proportion PF at cure year (Stage III NVRD)	[redacted]	[redacted]	[redacted]	13,448	14,237	789
Niraparib subsequent treatment total costs	6,738.85	4,361.03	9,625.80	13,537	14,274	736
RS resource use: PD - Outpatient visit (consultant lead	1.00	0.65	1.43	14,131	13,553	578
Niraparib resource use: PFD on treatment (cycle 3+) -	1.00	0.65	1.43	13,636	14,154	518

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Outpatient visit (consultant lead)						
RS - OS	[redacted]	[redacted]	[redacted]	14,561	14,115	446
Niraparib resource use: PFD off treatment - Outpatient visit (consultant lead)	0.30	0.19	0.43	13,696	14,080	384
Unit cost: CT scan	83.23	53.87	118.89	13,732	14,037	306
Niraparib resource use: PD - CT scan	0.30	0.19	0.43	13,750	14,015	266
Niraparib resource use: PFD off treatment - CT scan	0.30	0.19	0.43	13,756	14,008	252
RS resource use: PFD off treatment - Outpatient visit (consultant lead	0.30	0.19	0.43	13,966	13,753	213

Figure 46: OWSA tornado diagram for the ITT population

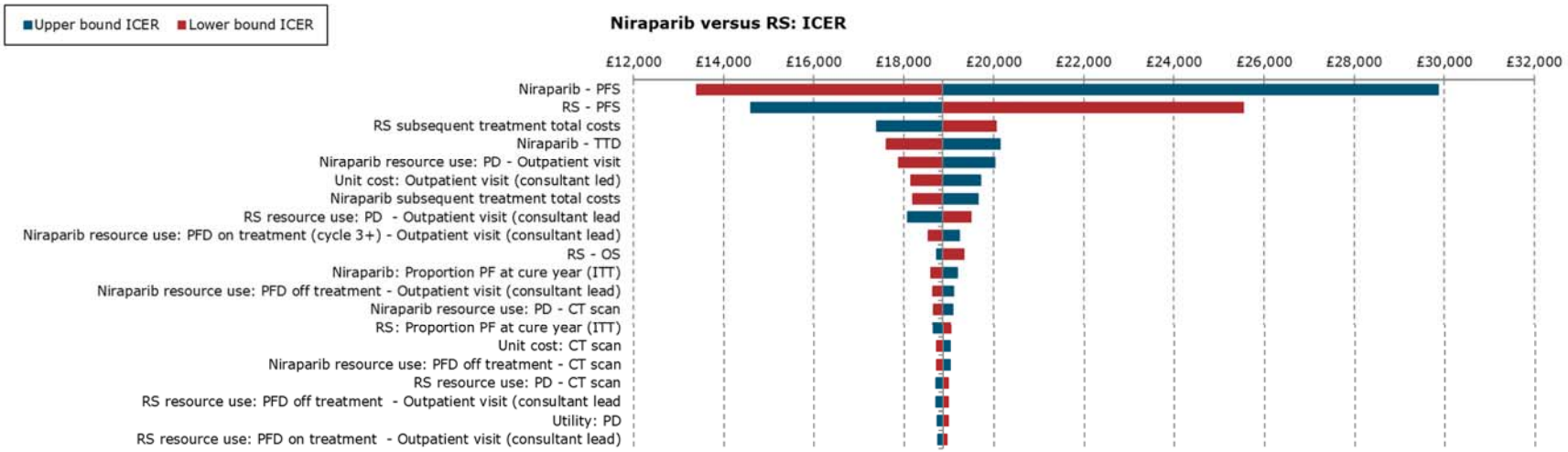


Table 55: Tabulated OWSA results for the ITT population

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Niraparib - PFS	[redacted]	[redacted]	[redacted]	13,396	29,866	16,470
RS - PFS	[redacted]	[redacted]	[redacted]	25,536	14,605	10,930
RS subsequent treatment total costs	10,695	6,921	15,277	20,055	17,402	2,653
Niraparib - TTD	[redacted]	[redacted]	[redacted]	17,622	20,133	2,511
Niraparib resource use: PD - Outpatient visit	1.00	0.65	1.43	17,890	20,030	2,140

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Unit cost: Outpatient visit (consultant led)	126.91	82.13	181.28	18,160	19,703	1,543
Niraparib subsequent treatment total costs	6,739	4,361	9,626	18,206	19,646	1,440
RS resource use: PD - Outpatient visit (consultant lead	1.00	0.65	1.43	19,492	18,085	1,407
Niraparib resource use: PFD on treatment (cycle 3+) - Outpatient visit (consultant lead)	1.00	0.65	1.43	18,542	19,238	696
Niraparib: Proportion PF at cure year (ITT)	[redacted]	[redacted]	[redacted]	18,597	19,190	593
RS - OS	[redacted]	[redacted]	[redacted]	19,332	18,740	592
RS: Proportion PF at cure year (ITT)	[redacted]	[redacted]	[redacted]	18,162	18,642	480
Niraparib resource use: PFD off treatment - Outpatient visit (consultant lead)	0.30	0.19	0.43	18,647	19,111	464

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Niraparib resource use: PD - CT scan	0.30	0.19	0.43	18,666	19,087	421
Unit cost: CT scan	83.23	53.87	118.89	18,718	19,024	306
Niraparib resource use: PFD off treatment - CT scan	0.30	0.19	0.43	18,719	19,023	304
RS resource use: PD - CT scan	0.30	0.19	0.43	18,981	18,705	277
RS resource use: PFD off treatment - Outpatient visit (consultant lead	0.30	0.19	0.43	18,977	18,710	266
Utility: PD	[redacted]	[redacted]	[redacted]	18,982	18,734	248
RS resource use: PFD on treatment - Outpatient visit (consultant lead)	0.30	0.19	0.43	18,944	18,751	193

Scenario analysis

Table 56 details scenario analyses results versus RS for the MA and ITT population. Across both populations results were most sensitive to varying the mean ΔPFS:ΔOS relationship, varying the PFS distribution for niraparib and RS and applying a 0% or 6% discount rate. The ICER remained below £26,000 and £35,000 across all scenarios explored for the MA and ITT population, respectively.

Table 56: Scenario analyses for the anticipated MA and ITT population for niraparib versus and RS

		Population →	Marketing authorisation population				ITT population			
Category	**Base case**	**Scenario**	**Inc. costs (£)**	**Inc. LYs**	**Inc. QALYs**	**ICER (£)**	**Inc. costs (£)**	**Inc. LYs**	**Inc. QALYs**	**ICER (£)**
Base case			[redacted]	[redacted]	[redacted]	13,870	[redacted]	[redacted]	[redacted]	18,856
Discount rate	3.5%	0.0%	[redacted]	[redacted]	[redacted]	9,901	[redacted]	[redacted]	[redacted]	13,421
		1.5%	[redacted]	[redacted]	[redacted]	11,508	[redacted]	[redacted]	[redacted]	15,636
		6.0%	[redacted]	[redacted]	[redacted]	17,126	[redacted]	[redacted]	[redacted]	23,243
Weight	PRIMA	UK data	[redacted]	[redacted]	[redacted]	13,870	[redacted]	[redacted]	[redacted]	18,856
Time horizon	39 years	35 years	[redacted]	[redacted]	[redacted]	13,928	[redacted]	[redacted]	[redacted]	18,912
		30 years	[redacted]	[redacted]	[redacted]	14,216	[redacted]	[redacted]	[redacted]	19,191
		25 years	[redacted]	[redacted]	[redacted]	15,028	[redacted]	[redacted]	[redacted]	19,966
PFS	G. gamma	Log-log for both niraparib and RS	[redacted]	[redacted]	[redacted]	19,211	[redacted]	[redacted]	[redacted]	27,941
		Weighted LLG/GG	[redacted]	[redacted]	[redacted]	16,168	[redacted]	[redacted]	[redacted]	22,433
Label population	PAOLA-1 approach	SOLO-1 approach	[redacted]	[redacted]	[redacted]	18,030	N/A	N/A	N/A	N/A
		PRIMA	[redacted]	[redacted]	[redacted]	13,960	N/A	N/A	N/A	N/A
Long- term remission (LTR)	LTR at 7-years	LTR at 10 years	[redacted]	[redacted]	[redacted]	13,830	[redacted]	[redacted]	[redacted]	20,812
		LTR at 5 years	[redacted]	[redacted]	[redacted]	13,529	[redacted]	[redacted]	[redacted]	16,685

Company evidence submission template for niraparib in patients with newly diagnosed advanced ovarian, fallopian tube or peritoneal cancer.

Population →			Marketing authorisation population				ITT population			
Category	**Base case**	**Scenario**	**Inc. costs (£)**	**Inc. LYs**	**Inc. QALYs**	**ICER (£)**	**Inc. costs (£)**	**Inc. LYs**	**Inc. QALYs**	**ICER (£)**
Base case			[redacted]	[redacted]	[redacted]	13,870	[redacted]	[redacted]	[redacted]	18,856
NVRD (MA population)	[redacted]%	[redacted]%	[redacted]	[redacted]	[redacted]	13,183	N/A	N/A	N/A	N/A
		[redacted]%	[redacted]	[redacted]	[redacted]	12,105	N/A	N/A	N/A	N/A
Mean ΔPFS:ΔOS relationship	1:2	1:1	[redacted]	[redacted]	[redacted]	25,581	[redacted]	[redacted]	[redacted]	34,606
		1:1.25	[redacted]	[redacted]	[redacted]	19,984	[redacted]	[redacted]	[redacted]	28,204
		1:1.5	[redacted]	[redacted]	[redacted]	17,296	[redacted]	[redacted]	[redacted]	24,022
		1:1.75	[redacted]	[redacted]	[redacted]	15,348	[redacted]	[redacted]	[redacted]	21,065
		1:2.5	[redacted]	[redacted]	[redacted]	11,766	[redacted]	[redacted]	[redacted]	15,767
		1:3	[redacted]	[redacted]	[redacted]	10,337	[redacted]	[redacted]	[redacted]	13,697
OS	Log-logistic for RS	Lognormal for RS	[redacted]	[redacted]	[redacted]	13,870	[redacted]	[redacted]	[redacted]	18,856
TTD	Weibull for niraparib	Log-logistic for niraparib	[redacted]	[redacted]	[redacted]	15,430	[redacted]	[redacted]	[redacted]	20,250
Treatment costs	Monthly dosing	Fixed niraparib dose	[redacted]	[redacted]	[redacted]	15,490	[redacted]	[redacted]	[redacted]	20,844
Treatment costs	Monthly dosing Wastage	Dose intensity	[redacted]	[redacted]	[redacted]	15,490	[redacted]	[redacted]	[redacted]	20,844
		No wastage	[redacted]	[redacted]	[redacted]	13,873	[redacted]	[redacted]	[redacted]	18,865
	[redacted]% discontinue at 3 years	No stopping rule	[redacted]	[redacted]	[redacted]	14,952	[redacted]	[redacted]	[redacted]	19,664
	[redacted]% discontinue at 3 years	[redacted]% discontinue at 3 years	[redacted]	[redacted]	[redacted]	12,991	[redacted]	[redacted]	[redacted]	18,714
Resource use	Literature	KOL	[redacted]	[redacted]	[redacted]	13,968	[redacted]	[redacted]	[redacted]	18,716

Population →			Marketing authorisation population				ITT population			
Category	**Base case**	**Scenario**	**Inc. costs (£)**	**Inc. LYs**	**Inc. QALYs**	**ICER (£)**	**Inc. costs (£)**	**Inc. LYs**	**Inc. QALYs**	**ICER (£)**
Base case			[redacted]	[redacted]	[redacted]	13,870	[redacted]	[redacted]	[redacted]	18,856
Subsequent treatment	KOL with second-line and third-line chemotherapy, and third-line PARPi	PRIMA in second-line; no third-line costs applied	[redacted]	[redacted]	[redacted]	14,295	[redacted]	[redacted]	[redacted]	19,712
		KOL with second-line PARPi; no third-line costs applied	[redacted]	[redacted]	[redacted]	13,278	[redacted]	[redacted]	[redacted]	17,694
		No subsequent treatment cost	[redacted]	[redacted]	[redacted]	14,622	[redacted]	[redacted]	[redacted]	20,409
Quality of life	PRIMA descriptive analysis Published disutilities	TA598 - PFD capped at general population, PD from OVA-301	[redacted]	[redacted]	[redacted]	14,794	[redacted]	[redacted]	[redacted]	20,057
		TA528 - EQ-5D-3L ENGOT-OV16/NOVA	[redacted]	[redacted]	[redacted]	14,007	[redacted]	[redacted]	[redacted]	19,030

Abbreviations: AE, adverse event; HTS, health technology appraisal; HR-d, homologous recombinant deficient; ICER. Incremental cost-effectiveness ratio; Inc. incremental; ITT, intention to treat; KOL, key opinion leader; MA, marketing authorisation, N/A, not applicable; OS, overall survival; PD, progressed disease; PFD, progression-free disease; QALY, quality-adjusted life year; RS, routine surveillance; TA, technology appraisal; TTD, time to treatment discontinuation; UK, United Kingdom

Summary of sensitivity analyses results

MA population

Within the MA population and across all scenarios and sensitivity analyses conducted, the ICER remained below £26,000 per QALY. Mean PSA results lay close to the deterministic base-case results, and niraparib was 100% cost-effective at a willingness to pay of £30,000 per QALY or more. These results highlight the robustness of the model to parameter and structural uncertainty. A particular point should be noted that all three MA modelling approaches produce consistent ICERs.

Within the OWSA all ICERs remained below £18,000 per QALY gained. The model was most sensitive to the shape and scale of the niraparib PFS distribution, the percentage of patients with Stage III NVRD at baseline, the shape and scale of the RS PFS distribution, the proportion of ITT patients progression free at the cure year, and the hazard ratio estimating stage III NVRD patients from the ITT patients for niraparib. Scenario analyses were most sensitive to varying the mean ΔPFS:ΔOS relationship, varying the PFS distribution for niraparib and RS, the approach for modelling the MA population, and applying a 0% or 6% annual discount rate.

ITT population

The results from the ITT population can be used to give increased confidence in the MA population results. Across all scenario analyses, the ICERs for the MA population were seen to be more cost effective than for the ITT population. Within the ITT population and across all scenarios and sensitivity analyses conducted the ICER remained below £35,000 per QALY. Mean PSA results lay close to the deterministic base-case results, and niraparib was more than 96.1% cost-effective at a willingness to pay of £30,000 per QALY or more.

Within the OWSA all ICERs remained below £30,000 per QALY gained. The model was most sensitive to the shape and scale of the niraparib PFS distribution, the shape and scale of the RS PFS distribution, RS subsequent treatment total costs, the shape and scale of the niraparib TTD distribution, and the niraparib arm resource use (PD) for outpatient visits. Scenario analyses were also most sensitive to varying the mean

ΔPFS:ΔOS relationship, varying the PFS distribution for niraparib and RS, and applying a 0% or 6% discount rate.

Overall, it should be noted that across the MA and ITT populations all the analyses conducted produced cost-effectiveness that fall under £26,000 and £35,000 per QALY gained, respectively. This highlights that niraparib can be considered a cost-effective treatment for all patients with advanced ovarian cancer that are in response to first-line PBC.

B.3.9 Subgroup analysis

N/A

B.3.10 Validation

Validation of cost-effectiveness analysis

The cost-effectiveness analysis conducted for use within this submission has been through rigorous internal and external validation. The model was developed by two independent health economists (FIECON). The model has been subject to rigorous internal (FIECON and GSK) reviews to ensure the model has been produced to the highest standards, with additional external technical reviews from two third parties (Evidera and EcoStat). A series of KOL interviews and two UK advisory boards (one clinical, one economic) were conducted to ensure all modelling inputs and assumptions were reflective of the decision problem at hand and were clinically valid and plausible. All comments and feedback have been incorporated into the final analyses, where appropriate. Clinical interviews were carried out using the methods described in Table 57.

Table 57: Clinical expert interview methods

Method description	Response
Criteria for selection	Leading OC experts in England
Number of experts approached	Four
Number of experts who participated	Four
Declaration of potential conflict(s) of interest from each expert	Standard GSK process • Prior to engagement, all advisors are requested to complete a Red Flag survey documenting any committee they are part of, their role on that committee and the influence of any decisions made, which is reviewed by an independent GSK committee to ensure no conflicts with GSK activities. • A contract is also signed requesting that the advisor declares their engagement with GSK at any external activity (i.e. speaker meeting, HTA committee meetings) for the next 2 years.
Background information provided and consistency with all the evidence provided in the submission	See Appendix N

Method description	Response
Method used to collect the clinician input	Two of the clinicians were interviewed in person, and two were interviewed by telephone.
Medium used to collect clinician input	Questionnaire
Questions asked	See Appendix N
Whether iteration was used in the collation of opinions	Review and summary of opinions

Abbreviations: OC, ovarian cancer

In order to validate the analysis, the median PFS and TTD predicted by the model were compared against the clinical trial data. The predicted undiscounted median (in months) PFS and TTD for niraparib and RS for the ITT population are presented in Table 58. In addition, predicted landmark survival rates compared to clinical trial KM are presented in Table 59. The comparison demonstrates that the model closely predicts the clinical data for niraparib and RS for the ITT population.

Table 58: Summary of model predicted PFS outcomes compared with clinical data, ITT population (median)

Outcome	Clinical trial	Clinical trial result, median months	Model result, median months
Niraparib			
PFS	PRIMA[9]	13.8 (CI: 11.5,14.9)	13.6
TTD	PRIMA[9]	[redacted]	11.0
RS			
PFS	PRIMA[9]	8.2 (CI: 7.3,8.5)	8.0
TTD	PRIMA[9]	N/A	N/A

Table 59. Summary of model predicted PFS outcomes compared with clinical data, ITT population (landmark rates)

Distribution	Years				
	1	2	3	4	5
Niraparib					
PFS KM data[9]	53%	32%	-	-	-
PFS extrapolated data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD KM data[9]	[redacted]	[redacted]	-	-	-
TTD extrapolated data	[redacted]	[redacted]	[redacted]	-	-
RS					
PFS KM data[9]	35%	23%	-	-	-
PFS extrapolated data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; TTD, time to treatment discontinuation; RS, routine surveillance.

In order to validate the OS model outputs, the long-term extrapolations for RS (ITT) were compared with external real world data, via the Edinburgh study as previously described and also with published 5-year survival rates from Cancer Research UK (Stage III and IV) data in Table 60.

Whilst the fit of the OS curve using the chosen model was the best fit overall, it is acknowledged that the survival rates for RS predicted by the model are higher than those observed in the RWE study. As highlighted in Section B.3.3, this may be due to the patient population in the relevant subset of the Edinburgh database having more severe disease (in terms of ECOG) than the PRIMA patient population, and so mortality is expected to be higher. As such this data serves as a benchmark for the RS OS to be validated against, and the model estimates can be considered appropriate.

Table 60: Comparison of RS OS predictions with real world evidence in ITT

Distribution	Years					
	1	2	3	5	10	15
PRIMA KM data	[redacted]	[redacted]	-	-	-	-
CRUK (weighted average of Stage III/IV survival)	-	-	-	21.1%	-	-
Edinburgh RWE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RS model output	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CRUK, Cancer Research United Kingdom; KM, Kaplan-Meier; OS, overall survival; RS, routine surveillance; RWE, real world evidence

In order to validate the survival extrapolations for the MA population the modelled median OS for RS was compared against the median OS data obtained from the University of Edinburgh Ovarian Cancer database. Figure 15 shows that the median survival for the MA cohort in the University of Edinburgh Ovarian Cancer database was approximately [redacted]. This closely aligns with the modelled median OS of [redacted] years for RS in the MA population.

Table 61: Comparison of real world evidence and modelled OS for RS (median [years])

Treatment arm	University of Edinburgh Ovarian Cancer database	Modelled median*
RS OS	~[redacted]	[redacted]

Abbreviations: OS, overall survival; RS, routine surveillance. *undiscounted

B.3.11 Interpretation and conclusions of economic evidence

MA population

In the base case analysis, niraparib was associated with [redacted] incremental QALYs, and £[redacted] incremental costs per patient, compared with RS. The corresponding ICER was £13,870 per QALY gained and would therefore be considered a cost-effective use of NHS resources. Results are robust to changes in key model parameters. Mean PSA results lay close to the deterministic base-case results, and niraparib was 100% cost-effective at a willingness to pay of £30,000 per QALY or more.

The results from the ITT population provide additional confidence in the MA population results, as the ICER for the MA population was seen to be more cost effective than for the ITT population for the base case and across all scenario analyses. In the base case analysis, niraparib was associated with [redacted] incremental QALYs, and £[redacted] incremental costs per patient, compared with RS. The corresponding ICER was £18,856 per QALY gained and would therefore be considered a cost-effective use of NHS resources. Results are robust to changes in key model parameters. Mean PSA results lay close to the deterministic base-case results, and niraparib was approximately 96% cost-effective at a willingness to pay of £30,000 per QALY or more. Niraparib can therefore be considered a cost-effective treatment option regardless of a patient's *BRCA* status in the first-line maintenance setting, where patients currently have no licensed treatment options following response to first-line PBC.

Strengths and weaknesses

The main strengths of the analyses are:

- As well as presenting results for the ITT population of the PRIMA trial, the model population includes the anticipated MA population for niraparib. The extrapolation from the ITT population to the MA population is underpinned by extensive evidence from published literature and UK real world data, validated by UK clinical expert opinion.

- The model efficacy data is primarily sourced from the PRIMA trial which included UK patients with advanced Stage III-IV ovarian cancer. As such the clinical evidence can be considered representative of UK patients with advance ovarian cancer who have received and responded (partial or complete) to first-line PBC.

- The clinical outcomes predicted by the model and the assumptions underpinning it were ratified by UK clinical expert opinion and real-world evidence from patients with OC in the UK.

- All costs and resource use in the model have been sourced from UK sources and where inflated to a 2019 cost year where necessary. Resource use estimates were validated by UK KOLs.

While the model has many strengths, some limitations remain:

- The MA population is estimated based upon an extrapolation of the PRIMA ITT efficacy. As a result, there remains uncertainty surrounding the efficacy of niraparib in the broader population. However, the model indicates that the cost-effectiveness results remain relatively stable between the two populations and the evidence that the extrapolation was based upon was validated by clinical expert opinion. Scenario analyses using alternative extrapolation approaches (SOLO-1 and PRIMA, instead of PAOLA-1) generate ICERs that lie below the base case ICER for the ITT population without extrapolation to the MA population.

- The immaturity of niraparib OS from PRIMA lead to implausible long-term extrapolations when based on parametric survival curves. To alleviate this issue, a mean ΔPFS:ΔOS relationship of 1:2 was modelled based on external data from the second-line maintenance setting. The lack of mature OS data from the first-line setting to validate this assumption raises a level of uncertainty within the results, however extensive sensitivity analyses have been conducted. Additionally, results are driven by the shape and scale of the RS OS in both the MA and ITT population. Although UK specific RWE and UK

clinician input were used to strengthen the robustness of the RS extrapolation, this still serves as a source of uncertainty.

- Clinical benefits beyond the duration of the trials were estimated through the fitting of parametric distributions to patient level data to estimate PFS, OS, and TTD over a lifetime horizon. This assumption may have led to uncertainty in the efficacy results, but it is appropriate due to the inherent limitation of short-term trial durations. The methods for survival extrapolation follow the NICE DSU guidelines and the extrapolations were validated by an external ovarian cancer clinical expert.[155] To explore uncertainty in the results, scenario analyses considered alternative parametric distributions for which results were found to not have a significant impact.

In conclusion, this submission demonstrates the clinical and cost-effectiveness of niraparib relative to RS within its expected marketing authorisation.

The economic evaluation confirms a robust and favourable cost-effectiveness profile; the anticipated MA population is expected to be more cost-effective than the ITT population compared with RS, with a base case ICER of £13,870, in the presence of a simple discount.

B.4 References

1. Office for National Statistics. Cancer registration statistics 2017, England - Office for National Statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland.
2. Cortez A.J., Tudrej P., Kujawa K.A. & Lisowska K.M. Advances in ovarian cancer therapy. *Cancer Chemother. Pharmacol.* **81**, 17–38 (2018).
3. Jonsson, B., Hofmarcher, T., Lindgren, P., Moen, F. & Wilken, N. *Comparator report on patient access to cancer medicines in Europe revisitied - A UK perspective*. https://www.abpi.org.uk/media/3459/report-access-cancer-medicines-in-europe-revisited-uk-perspective.pdf (2017).
4. Office for National Statistics. Cancer survival in England 2013 - 2017, followed up 2018- Office for National Statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinengland/latest (2019).
5. Hanker, L. C. *et al.* The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. *Ann. Oncol.* **23**, 2605–2612 (2012).
6. Coleman, R. L., Monk, B. J., Sood, A. K. & Herzog, T. J. Latest research and treatment of advanced-stage epithelial ovarian cancer. *Nat Rev Clin Oncol* **10**, 211–224 (2013).
7. Birrer, M. J. & Fujiwara, K. Medical treatment for relapsed epithelial ovarian, fallopian tubal, or peritoneal cancer: Platinum-resistant disease.

http://www.uptodate.com/contents/medical-treatment-for-relapsed-epithelial-ovarian-fallopian-tubal-or-peritoneal-cancer-platinum-resistant-disease.

8. Lorusso, D., Mancini, M., Di Rocco, R., Fontanelli, R. & Raspagliesi, F. The Role of Secondary Surgery in Recurrent Ovarian Cancer. *International Journal of Surgical Oncology* https://www.hindawi.com/journals/ijso/2012/613980/ (2012) doi:10.1155/2012/613980.
9. González-Martín, A. *et al.* Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *New England Journal of Medicine* **381**, 2391–2402 (2019).
10. Hollis, R. L., Churchman, M. & Gourley, C. Distinct implications of different BRCA mutations: efficacy of cytotoxic chemotherapy, PARP inhibition and clinical outcome in ovarian cancer. *Onco Targets Ther* **10**, 2539–2551 (2017).
11. Martín-Cameán, M. *et al.* The role of surgery in advanced epithelial ovarian cancer. *Ecancermedicalscience* **10**, (2016).
12. Murai, J. *et al.* Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. *Cancer Res.* **72**, 5588–5599 (2012).
13. Sonnenblick A., De Azambuja E., Azim H.A. & Piccart M. An update on PARP inhibitors - Moving to the adjuvant setting. *Nat. Rev. Clin. Oncol.* **12**, 27–41 (2015).
14. Konstantinopoulos, P. A., Ceccaldi, R., Shapiro, G. I. & D'Andrea, A. D. Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. *Cancer Discov* **5**, 1137–1154 (2015).
15. Ledermann, J. A. *et al.* Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **24 Suppl 6**, vi24-32 (2013).

16. European Society for Medical Oncology. Ovarian Cancer Treatment Recommendations | ESMO. (2020).
17. Fong, P. C. *et al.* Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N. Engl. J. Med.* **361**, 123–134 (2009).
18. Audeh, M. W. *et al.* Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet* **376**, 245–251 (2010).
19. Mirza, M. *et al.* Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *New england journal of medicine* **375**, 2154-2164 (2016).
20. Matulonis U.A. *et al.* Long-term benefit of niraparib treatment of recurrent ovarian cancer (OC). *J. Clin. Oncol.* **35**, (2017).
21. Mikule K., Wang S., Weroha S.J., Nakashima J. & Wilcoxen K. A preclinical evaluation of niraparib efficacy as monotherapy, maintenance and after olaparib treatment (PARP inhibitor after PARP inhibitor) in patient-derived ovarian xenograft tumor models. *Eur. J. Cancer* **72**, S96 (2017).
22. Zhang, Z et al. Biotransformation and Disposition of Niraparib, an Investigational, Selective Human PARP-1 and PARP-2 Antagonist, In Vitro. 20th North American ISSX 2015.
23. Vaidyanathan, A. *et al.* ABCB1 (MDR1) induction defines a common resistance mechanism in paclitaxel- and olaparib-resistant ovarian cancer cells. *Br. J. Cancer* **115**, 431–441 (2016).
24. NICE. Ovarian cancer: recognition and initial management |Clinical guideline [CG122].

25. Khalique, S., Hook, J. & Ledermann, J. Maintenance therapy in ovarian cancer. *Current Opinion in Oncology* **26**, 521–528 (2014).
26. NICE. Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy | Guidance TA598 | NICE. https://www.nice.org.uk/guidance/ta598 (2019).
27. NHS England Cancer Drugs Fund Team. National Cancer Drugs Fund List v1.158. (2020).
28. EMC. Lynparza 100mg Film-Coated Tablets - Summary of Product Characteristics (SmPC). *Electronic Medicines Compendium* https://www.medicines.org.uk/emc/product/9204/smpc (2019).
29. NICE. Ovarian cancer: recognition and initial management (CG122). (2011).
30. Ledermann, J. A. *et al.* Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **24 Suppl 6**, vi24-32 (2013).
31. Fotopoulou, C. *et al.* British Gynaecological Cancer Society (BGCS) epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **213**, 123–139 (2017).
32. Prat, J. FIGO's staging classification for cancer of the ovary, fallopian tube, and peritoneum: abridged republication. *J Gynecol Oncol* **26**, 87–89 (2015).
33. NICE. Guidance on the use of paclitaxel in the treatment of ovarian cancer (TA55). Available at: https://www.nice.org.uk/guidance/ta55 [accessed May 2017].

34. NICE. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (TA389). Available at: https://www.nice.org.uk/guidance/ta389 [May 2017].
35. NICE. Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy (TA381). Available at: https://www.nice.org.uk/guidance/ta381 [accessed May 2017].
36. Colombo, N. *et al.* ESMO–ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Annals of Oncology* **30**, 672–705 (2019).
37. NICE. Managing advanced (stage II-IV) ovarian cancer - NICE Pathways. https://pathways.nice.org.uk/pathways/ovarian-cancer#path=view%3A/pathways/ovarian-cancer/managing-advanced-stage-ii-iv-ovarian-cancer.xml&content=view-index.
38. Rutten, M., Sonke, G. S. & Westermann, A. Prognostic Value of Residual Disease after Interval Debulking Surgery for FIGO Stage IIIC and IV Epithelial Ovarian Cancer. *International Journal of Gynecology & Obstetrics* (2015).
39. Janssen-Cilag. Caelyx 2mg/ml concentrate for solution for infusion - Summary of Product Characteristics. 2017. Available at: https://www.medicines.org.uk/emc/medicine/15842 [accessed June 2017].
40. Pujade-Lauraine E. *et al.* Oreo phase IIIB trial: Olaparib maintenance retreatment in platinum-sensitive, relapsed epithelial ovarian cancer patients

previously treated with a parp inhibitor (PARPI). *Int. J. Gynecol. Cancer* **27**, 1634–1635 (2017).

41. Mirza, M. *et al.* Engot-ov16/nova: a phase 3 randomized double-blind trial of maintenance with PARP-inhibitor niraparib versus placebo in patients with platinum-sensitive ovarian cancer. *International journal of gynecological cancer* **24**, 33-34 (2014).
42. Coleman, R. *et al.* Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet (london, england)* **390**, 1949-1961 (2017).
43. Moore K. *et al.* Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *New Engl. J. Med.* **379**, 2495–2505 (2018).
44. Colombo N. *et al.* ESMO-ESGO-ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up. *Ann. Oncol.* **27**, 16–41 (2016).
45. NICE. Managed Access Agreement: Data collection arrangement for the single technology appraisal of olaparib for newly diagnosed advanced BRCA-mutated ovarian, fallopian tube or primary peritoneal cancer, after response to first-line platinum-based chemotherapy. (2019).
46. Tew, W. P., Muss, H. B., Kimmick, G. G., Von Gruenigen, V. E. & Lichtman, S. M. Breast and ovarian cancer in the older woman. *J. Clin. Oncol.* **32**, 2553–2561 (2014).
47. Oskay-Ozcelik, G. & Sehouli, J. Pros and cons for systemic therapy in recurrent ovarian cancer. *Anticancer Res.* **29**, 2831–2836 (2009).
48. Lynparza (olaparib). Summary of product characteristics.

49. EMC. Rubraca 300mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc). https://www.medicines.org.uk/emc/product/10028/smpc (2019).
50. NICE. Bevacizumab with carboplatin, gemcitabine and paclitaxel for treating the first recurrence of platinum-sensitive advanced ovarian cancer (terminated appraisal) | Guidance | NICE. https://www.nice.org.uk/guidance/ta560.
51. Ledermann, J. *et al.* Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol.* **15**, 852–861 (2014).
52. EMA. Roche. Avastin 25mg/ml concentrate for solution for infusion - Summary of Product Characteristics. 2017. (2017).
53. NICE. Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (TA284). Available at: https://www.nice.org.uk/guidance/ta284 [accessed May 2017].
54. Zejula 100 mg hard capsules - Summary of Product Characteristics (SmPC) - (eMC). https://www.medicines.org.uk/emc/product/8828/smpc.
55. ESMO. Relapsed Epithelial Ovarian Carcinoma Treatment Recommendations. https://www.esmo.org/guidelines/gynaecological-cancers/newly-diagnosed-and-relapsed-epithelial-ovarian-carcinoma/eupdate-ovarian-cancer-treatment-recommendations.
56. Ovarian cancer overview - NICE Pathways. https://pathways.nice.org.uk/pathways/ovarian-cancer.
57. Tesaro/GSK. Clinical Study Report PR-5017-C: A Phase 3, randomized, double-blind, placebo-controlled, mutlicenter study of niraparib maintenance

treatment in patients with advanced ovarian cancer following response on front-line platinum-based chemotherapy. (2019).

58. Gonzalez-Martin, A. *et al.* A randomized, double-blind phase III trial of niraparib maintenance treatment in patients with HRD+ advanced ovarian cancer after response to front-line platinum-based chemotherapy. *Journal of clinical oncology* **34**, (2016).
59. Martín-Cameán, M. *et al.* The role of surgery in advanced epithelial ovarian cancer. *Ecancermedicalscience* **10**, (2016).
60. Nick, A. M., Coleman, R. L., Ramirez, P. T. & Sood, A. K. A framework for a personalized surgical approach to ovarian cancer. *Nat Rev Clin Oncol* **12**, 239–245 (2015).
61. Moore, K. N. *et al.* Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. *The Lancet Oncology* **20**, 636–648 (2019).
62. Moore, K. *et al.* Food effect substudy of a phase 3 randomized double-blind trial of maintenance with niraparib (MK4827), a poly(ADP)ribose polymerase (PARP) inhibitor versus placebo in patients with platinum-sensitive ovarian cancer. *Journal of clinical oncology* **32**, (2014).
63. Pakneshan, S., Safarpour, D., Tavassoli, F. & Jabbari, B. Brain metastasis from ovarian cancer: a systematic review. *J. Neurooncol.* **119**, 1–6 (2014).
64. Ray-Coquard, I. L. *et al.* PAOLA-1/ENGOT-ov25 trial: Phase III Olaparib plus bevacizumab (bev) as maintenance therapy in patients with newly diagnosed, advanced ovarian cancer (OC) treated with platinum-based chemotherapy (PCh) plus bev. *Ann Oncol* **30**, (2019).

65. Eskander, R. N. *et al.* Correlation between Surgeon's assessment and radiographic evaluation of residual disease in women with advanced stage ovarian cancer reported to have undergone optimal surgical cytoreduction: An NRG Oncology/Gynecologic Oncology Group study. *Gynecologic Oncology* **149**, 525–530 (2018).
66. *UK Advisory Board for niraparib in first-line maintenance treatent for ovarian cancer. 2019*.
67. Delga, B. *et al.* 30 Years of Experience in the Management of Stage III and IV Epithelial Ovarian Cancer: Impact of Surgical Strategies on Survival. *Cancers (Basel)* **12**, (2020).
68. Ghirardi, V. *et al.* Minimal residual disease at primary debulking surgery versus complete tumor resection at interval debulking surgery in advanced epithelial ovarian cancer: A survival analysis. *Gynecol. Oncol.* **157**, 209–213 (2020).
69. Liang, M. I. *et al.* Prognostic role of pathologic response and cytoreductive status at interval debulking surgery after neoadjuvant chemotherapy for advanced epithelial ovarian cancer. *J Surg Oncol* **120**, 779–785 (2019).
70. Babayeva, A. *et al.* Clinical Outcome After Completion Surgery in Patients With Ovarian Cancer: The Charite Experience. *Int. J. Gynecol. Cancer* **28**, 1491–1497 (2018).
71. Kobal, B. *et al.* Primary debulking surgery versus primary neoadjuvant chemotherapy for high grade advanced stage ovarian cancer: comparison of survivals. *Radiol Oncol* **52**, 307–319 (2018).

72. Phillips, A. *et al.* Complete cytoreduction after five or more cycles of neo-adjuvant chemotherapy confers a survival benefit in advanced ovarian cancer. *Eur J Surg Oncol* **44**, 760–765 (2018).
73. Torres, D. *et al.* Factors that influence survival in high-grade serous ovarian cancer: A complex relationship between molecular subtype, disease dissemination, and operability. *Gynecol. Oncol.* **150**, 227–232 (2018).
74. Sørensen, S. M., Schnack, T. H. & Høgdall, C. Impact of residual disease on overall survival in women with Federation of Gynecology and Obstetrics stage IIIB-IIIC vs stage IV epithelial ovarian cancer after primary surgery. *Acta Obstet Gynecol Scand* **98**, 34–43 (2019).
75. Sioulas, V. D. *et al.* Optimal primary management of bulky stage IIIC ovarian, fallopian tube and peritoneal carcinoma: Are the only options complete gross resection at primary debulking surgery or neoadjuvant chemotherapy? *Gynecol. Oncol.* **145**, 15–20 (2017).
76. Ataseven, B. *et al.* Prognostic impact of debulking surgery and residual tumor in patients with epithelial ovarian cancer FIGO stage IV. *Gynecologic Oncology* **140**, 215–220 (2016).
77. Horowitz, N. S. *et al.* Does aggressive surgery improve outcomes? Interaction between preoperative disease burden and complex surgery in patients with advanced-stage ovarian cancer: an analysis of GOG 182. *J. Clin. Oncol.* **33**, 937–943 (2015).
78. Vergote I. *et al.* Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials. *Lancet Oncol.* **19**, 1680–1687 (2018).

79. Wimberger, P. *et al.* Influence of residual tumor on outcome in ovarian cancer patients with FIGO stage IV disease: an exploratory analysis of the AGO-OVAR (Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group). *Ann. Surg. Oncol.* **17**, 1642–1648 (2010).
80. du Bois, A. *et al.* Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). *Cancer* **115**, 1234–1244 (2009).
81. Chang, S.-J. & Bristow, R. E. Evolution of surgical treatment paradigms for advanced-stage ovarian cancer: redefining 'optimal' residual disease. *Gynecol. Oncol.* **125**, 483–492 (2012).
82. Harter, P., Mouret-Reynier, M.-A. & Pignata, S. Phase III PAOLA-1/ENGOT-ov25: maintenance olaparib with bevacizumab in patients with newly diagnosed, advanced ovarian cancer treated with platinum-based chemotherapy and bevacizumab as standard of care. (2019).
83. Mathews, C. A. *et al.* Maintenance olaparib after platinum-based chemotherapy in patients (pts) with newly diagnosed advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): Efficacy by surgical and tumor status in the Phase III SOLO1 trial. Poster presented at the ASCO Annual Meeting, Chicago, USA on May 31–June 4, 2019. *JCO* **37**, 5541–5541 (2019).
84. Overview | Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line

platinum-based chemotherapy | Guidance | NICE. https://www.nice.org.uk/guidance/ta598.

85. CADTH. Lynparza for Newly Diagnosed Ovarian Cancer – Details | CADTH.ca. https://www.cadth.ca/lynparza-newly-diagnosed-ovarian-cancer-details (2019).
86. Tan D.S. *et al.* Cost-effectiveness of olaparib vs routine surveillance in the maintenance setting for patients with BRCA-mutated advanced ovarian cancer after response to first-line platinum-based chemotherapy in Singapore. *Ann. Oncol.* **30**, ix79–ix80 (2019).
87. Chin L. & Carlson J.J. Cost-effectiveness analysis of rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy. *Value Health* **21**, S30 (2018).
88. Chin, L. & Carlson, J. COST-EFFECTIVENESS ANALYSIS OF RUCAPARIB MAINTENANCE TREATMENT FOR RECURRENT OVARIAN CARCINOMA AFTER RESPONSE TO PLATINUM THERAPY. *ISPOR | International Society For Pharmacoeconomics and Outcomes Research* https://www.ispor.org/heor-resources/presentations-database/presentation/ispor-2018/cost-effectiveness-analysis-of-rucaparib-maintenance-treatment-for-recurrent-ovarian-carcinoma-after-response-to-platinum-therapy (2018).
89. Dottino, J., Moss, H. A., Lu, K. H., Secord, A. A. & Havrilesky, L. J. Are FDA-approved PARPi cost-effective as maintenance treatment of platinum-sensitive recurrent ovarian cancer? *SGO Conference* (2018).
90. Dottino, J. A., Moss, H. A., Lu, K. H., Secord, A. A. & Havrilesky, L. J. U.S. Food and Drug Administration–Approved Poly (ADP-Ribose) Polymerase Inhibitor

Maintenance Therapy for Recurrent Ovarian Cancer: A Cost-Effectiveness Analysis. *Obstetrics & Gynecology* **133**, 795 (2019).

91. Dottino J.A., Moss H.A., Lu K.H., Secord A.A. & Havrilesky L.J. U.S. Food and Drug Administration-Approved Poly (ADP-Ribose) Polymerase Inhibitor Maintenance Therapy for Recurrent Ovarian Cancer: A Cost-Effectiveness Analysis. *Obstet Gynecol* **133**, 795–802 (2019).
92. Fernandez-Santos, J. & Garcia San Andres, B. RELAPSED OVARIAN CANCER TREATMENT COSTS COMPARISON IN SPAIN. *ISPOR | International Society For Pharmacoeconomics and Outcomes Research* https://www.ispor.org/heor-resources/presentations-database/presentation/ispor-22nd-annual-international-meeting/relapsed-ovarian-cancer-treatment-costs-comparison-in-spain (2017).
93. Fernandez-Santos, J. & Garcia San Andres, B. Relapsed ovarian cancer treatment costs comparison in Spain. *Value in Health* (2017).
94. Mark Fisher, Holly Guy & Lydia Walder. Cost-effectiveness of niraparib versus routine surveillance, olaparib, and rucaparib for the maintenance treatment of adult patients with ovarian cancer in the United States. *American Society of Clinical Oncology* (2018).
95. Fisher M., Guy H. & Walder L. Cost-effectiveness of niraparib versus routine surveillance and olaparib for the maintenance treatment of adult patients with ovarian cancer in the United States. *Value Health* **21**, S32 (2018).
96. Fisher, M., Guy, H. & Walder, L. COST-EFFECTIVENESS OF NIRAPARIB VERSUS ROUTINE SURVEILLANCE AND OLAPARIB FOR THE MAINTENANCE TREATMENT OF ADULT PATIENTS WITH OVARIAN

CANCER IN THE UNITED STATES. *ISPOR | International Society For Pharmacoeconomics and Outcomes Research* https://www.ispor.org/heor-resources/presentations-database/presentation/ispor-2018/cost-effectiveness-of-niraparib-versus-routine-surveillance-and-olaparib-for-the-maintenance-treatment-of-adult-patients-with-ovarian-cancer-in-the-united-states (2018).

97. Guy H., Walder L. & Fisher M. Cost-Effectiveness of Niraparib Versus Routine Surveillance, Olaparib and Rucaparib for the Maintenance Treatment of Patients with Ovarian Cancer in the United States. *Pharmacoeconomics* (2018) doi:10.1007/s40273-018-0745-z.
98. Liu A.Y., Cohen J.G., Walsh C.S., Holschneider C.H. & Sinno A.K. A cost-effectiveness analysis of three PARP inhibitors for maintenance therapy in platinum-sensitive recurrent ovarian cancer. *Gynecol. Oncol.* **147**, 196 (2017).
99. Mylonas C., Aravantinos G., Bamias A., Kourlaba G. & Maniadakis N. Economic evaluation of olaparib in patients with BRCA-mutated PSROC in GREECE. *Value Health* **19**, A732 (2016).
100. Overview | Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer | Guidance | NICE. https://www.nice.org.uk/guidance/ta528/.
101. NICE. Olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer | Guidance | NICE. https://www.nice.org.uk/guidance/ta620 (2020).
102. NICE. Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer | Guidance | NICE. https://www.nice.org.uk/guidance/ta611 (2019).

103. niraparib tosylate monohydrate (Zejula). *Scottish Medicine Consortium* https://www.scottishmedicines.org.uk/medicines-advice/niraparib-tosylate-monohydrate-zejula-fullsubmission-134118/.
104. Smith H.J., Walters Haygood C.L., Arend R.C., Leath C.A. & Straughn J.M. PARP inhibitor maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer: A cost-effectiveness analysis. *Gynecol. Oncol.* **139**, 59–62 (2015).
105. Smith H.J., Walters Haygood C.L., Arend R.C., Leath III C.A. & Straughn Jr. J.M. PARP inhibitors as maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer: Can we afford it? *Gynecol. Oncol.* **137**, 9 (2015).
106. Wolford J.E. *et al.* Evaluating the cost-effectiveness of current FDA-approved PARP inhibitors for the treatment of recurrent ovarian cancer. *J. Clin. Oncol.* **35**, (2017).
107. Juliet Elizabeth Wolford, Jiaru Bai, Lindsey E. Minion, Robin Keller, Ramez Nassef Eskander, John K. Chan, Bradley J. Monk, Krishnansu Sujata Tewari. Cost-effectiveness of maintenance therapy in advanced ovarian cancer: Paclitaxel, bevacizumab, niraparib, rucaparib, olaparib, and pembrolizumab. *Journal of Clinical Oncology* (2018).
108. Wolford J.E. *et al.* An economic analysis: Examining the cost-effectiveness of bevacizumab and olaparib as upfront maintenance treatment of advanced ovarian cancer. *Gynecol. Oncol.* **154**, 25 (2019).
109. Wolford J.E. *et al.* SOLO1 versus SOLO2: Cost-effectiveness of olaparib as maintenance therapy for newly diagnosed and platinum-sensitive recurrent

ovarian carcinoma among women with germline BRCA mutations (gBRCAmut). *J. Clin. Oncol.* **37**, (2019).

110. Zhong L., Tran A.T., Tomasino T., Smith J.A. & Nugent E.K. Cost-effectiveness of niraparib and olaparib as maintenance therapy for patients with platinum sensitive< recurrent ovarian cancer. *Value Health* **21**, S29 (2018).
111. Zhong L., Tran A.T., Tomasino T., Nugent E. & Smith J.A. Cost-effectiveness of niraparib and olaparib as maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer. *J. Manag. Care Spec. Pharm.* **24**, 1219–1228 (2018).
112. Zhong, L., Tran, A., Tomasino, T., Smith, J. & Nugent, E. COST-EFFECTIVENESS OF NIRAPARIB AND OLAPARIB AS MAINTENANCE THERAPY FOR PATIENTS WITH PLATINUM SENSITIVE- RECURRENT OVARIAN CANCER. *ISPOR | International Society For Pharmacoeconomics and Outcomes Research* https://www.ispor.org/heor-resources/presentations-database/presentation/ispor-2018/cost-effectiveness-of-niraparib-and-olaparib-as-maintenance-therapy-for-patients-with-platinum-sensitive-recurrent-ovarian-cancer (2018).
113. NICE. Guide to the methods of technology appraisal. (2013).
114. González-Martín, A. *et al.* Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *New England Journal of Medicine* **381**, 2391–2402 (2019).
115. A Study of Niraparib Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02655016.

116. GSK. Edinburgh Dataset. Data on file. (2020).
117. Grimm, C., Cropet, C. & Ray-Coquard, I. Maintenance olaparib plus bevacizumab (bev) after platinum-based chemotherapy plus bev in patients (pts) with newly diagnosed advanced high-grade ovarian cancer (HGOC): Efficacy by timing of surgery and residual tumor status in the Phase III PAOLA-1 trial. in (SGO, 2020).
118. Moore, K. *et al.* Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N. Engl. J. Med.* **379**, 2495–2505 (2018).
119. Mathews, C. A. *et al.* Maintenance olaparib after platinum-based chemotherapy in patients (pts) with newly diagnosed advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): Efficacy by surgical and tumor status in the Phase III SOLO1 trial. *JCO* **37**, 5541–5541 (2019).
120. Latimer, N. Survival analysis TSD – NICE Decision Support Unit.
121. Kaltenthaler, E., Tappenden, P., Paisley, S. & Squires, H. NICE DSU Technical Support Document 13: Identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models. 72 (2011).
122. NICE. Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy (TA381). Committee papers. Available at: • https://www.nice.org.uk/guidance/ta381/documents/ovarian-fallopian-tube-and-peritoneal-cancer-brca-1-or-2-mutated-relapsed-platinumsensitive-olaparib-maintenance-id735-committee-papers12 [accessed April 2018].

123. Woods, B., Sideris, E., Palmer, S., Latimer, N. & Soares, M. NICE DSU TECHNICAL SUPPORT DOCUMENT 19: Partitioned Survival Analysis for decision modelling in health care: a critical review. 72 (2017).
124. Anushka, I., Rye, T. & Churchman, M. Patterns of clinicopathological features and outcome in epithelial ovarian cancer patients: 35 years of prospectively collected data. *International Journal of Obstretics and Gynaecology* (2020).
125. NICE. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (TA598). (2018).
126. NICE. Position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product. (2019).
127. Han, S. N., Monk, B. J. & Gonzalez-Martin, A. Time to first subsequent therapy (TFST) and progression-free survival 2 (PFS2) from the phase 3 randomized, double-blind PRIMA/ENGOT-OV26/GOG-3012 study in patients with newly diagnosed ovarian cancer. in (SGO, 2020).
128. van Hout, B. *et al.* Interim Scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L Value Sets. *Value in Health* **15**, 708–715 (2012).
129. 1 Recommendations | Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy | Guidance | NICE. https://www.nice.org.uk/guidance/ta598/chapter/1-Recommendations.
130. Latimer, N. R. Survival Analysis for Economic Evaluations Alongside Clinical Trials—Extrapolation with Patient-Level Data: Inconsistencies, Limitations, and a Practical Guide. *Med Decis Making* **33**, 743–754 (2013).

131. Jackson, C. H., Thompson, S. G. & Sharples, L. D. Accounting for uncertainty in health economic decision models by using model averaging. *J R Stat Soc Ser A Stat Soc* **172**, 383–404 (2009).
132. NICE. Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy. https://www.nice.org.uk/guidance/ta598 (2019).
133. National life tables: UK - Office for National Statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables.
134. Friedlander, M. *et al.* Quality of life in patients with advanced epithelial ovarian cancer (EOC) randomized to maintenance pazopanib or placebo after first-line chemotherapy in the AGO-OVAR 16 trial. Measuring what matters-patient-centered end points in trials of maintenance therapy. *Ann. Oncol.* **29**, 737–743 (2018).
135. Havrilesky L.J. *et al.* Determination of quality of life-related utilities for health states relevant to ovarian cancer diagnosis and treatment. *Gynecol. Oncol.* **113**, 216–220 (2009).
136. Naik H. *et al.* Stage specific health utility index scores of Canadian cancer patients. *J. Clin. Oncol.* **33**, (2015).
137. NICE. Single Technology Appraisal. Olaparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer. [ID1296]. Committee Papers. (2018).
138. NICE. NICE. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer. (2018).

139. Overview | Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy | Guidance | NICE. https://www.nice.org.uk/guidance/ta598.
140. BNF. Medical forms - Niraparib. https://bnf.nice.org.uk/medicinal-forms/niraparib.html (2020).
141. NHS Improvement. NHS Reference Costs 2018/19. https://improvement.nhs.uk/resources/national-cost-collection/ (2020).
142. NICE. Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer [ID1485]. https://www.nice.org.uk/guidance/indevelopment/gid-ta10383/documents (2019).
143. NICE. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer [TA528].). (2017).
144. niraparib tosylate monohydrate (Zejula). *Scottish Medicine Consortium* https://www.scottishmedicines.org.uk/medicines-advice/niraparib-tosylate-monohydrate-zejula-fullsubmission-134118/.
145. A Phase 3 Trial of Bevacizumab in Ovarian Cancer | NEJM. https://www.nejm.org/doi/full/10.1056/NEJMoa1103799.
146. NHS England. CDF drug list. (2017).
147. GSK. Data on file. Niraparib CDF report. (2020).
148. Mirza, M. *et al.* Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *New England journal of medicine* **375**, 2154-2164 (2016).

149. Coleman, R. *et al.* Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* **(no pagination)**, (2017).
150. Anonymous. Tecentriq. *European Medicines Agency* https://www.ema.europa.eu/en/medicines/human/EPAR/tecentriq (2018).
151. Keytruda | European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda.
152. Guest J.F., Ruiz F.J., Greener M.J. & Trotman I.F. Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. *Eur. J. Cancer Care* **15**, 65–73 (2006).
153. Unit Costs of Health and Social Care 2019 | PSSRU. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/.
154. Gao, W. *et al.* Changing patterns in place of cancer death in England: a population-based study. *PLoS Med.* **10**, e1001410 (2013).
155. Latimer, N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. Available at http://www.nicedsu.org.uk [last accessed April 2017].

B.5 Appendices

Appendix C Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Please see Appendix C document.

Appendix D Clinical systematic literature review

Please see Appendix D document.

Appendix E: Subgroup analysis

Please see Appendix E document.

Appendix F: Adverse events

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Appendix I: Published cost and resource use studies

Please see Appendix I document.

Appendix J: Clinical outcomes and disaggregated results

Please see Appendix J document.

Appendix K: Checklist of confidential information

Please see Appendix K document.

Appendix L: University of Edinburgh Ovarian Cancer Database study protocol

Please see Appendix L document.

Appendix M: Targeted literature review for overall survival outcomes in patients with advanced ovarian cancer

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Appendix N: Questionnaire used for clinical interviews

Please see Appendix N document.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy ID1680

Clarification questions

July 2020

File name	Version	Contains confidential information	Date
ID1680 Niraparib maintenance ERG clarification questions_to company	0.1	Yes	17/06/20
ID1680 Niraparib maintenance ERG clarification questions_to company	0.2	Yes	01/07/20

Abbreviations

2L	Second-line
3L	Third-line
AE	Adverse event
AIC	Akaike information criterion
BIC	Bayesian information criterion
BICR	Blinded independent central review
BRCA	Breast cancer susceptibility gene
CI	Confidence interval
CM	Centimetre
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
DSU	Decision Support Unit
EQ-5D-3L	EuroQoL five dimensions three levels
EQ-5D-5L	EuroQoL five dimensions five levels
ERG	Evidence Review Group
FAS	Full analysis set
FSD	Fixed starting dose
HRD	Homologous recombinant deficient
IA	Investigator assessed
ICER	Incremental cost-effectiveness ratio
ISD	Individualised starting dose
ITT	Intention-to-treat
KM	Kaplan-Meier
KOL	Key opinion leader
MA	Marketing authorisation
mg	Milligram
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NVRD	No visible residual disease
OC	Ovarian cancer
OS	Overall survival
OWSA	One-way sensitivity analyses
PARPi	Poly (ADP-ribose) polymerase inhibitor
PD	Progressed disease
PET	Positron emission tomography
PFD	Progression-free disease
PFS	Progression-free survival
PFS2	Progression-free survival on subsequent therapy
PSSRU	Personal Social Services Research Unit
PS	Platinum-sensitive
PR	Platinum-resistant
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analyses

RS	Routine surveillance
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TEAE	Treatment emergent adverse events
TFST	Time to first subsequent treatment
UK	United Kingdom
US	United States
VRD	Visible residual disease
vs.	Versus
WTP	Willingness to pay

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Section A: Clarification on effectiveness data

A1. Priority question: For patients in PRIMA, please provide data (n [%]) on the following baseline characteristics:

a) **HRD+, HRD-, and HRD status unknown**

b) **BRCA+ and BRCA-**

c) **prior bevacizumab therapy and no prior bevacizumab (as 1st line therapy).**

Response:

Please find the requested information in Table 1.

Table 1: Proportion of patients by HRD status, BRCA status and prior bevacizumab treatment within the PRIMA trial

Parameter	Niraparib (N=487) n (%)	Placebo (N=246) n (%)
BRCA status		
BRCAmut	152 (31.2)	71 (28.9)
BRCA1	105 (21.6)	43 (17.5)
BRCA2	47 (9.7)	28 (11.4)
BRCAwt	310 (63.7)	163 (66.3)
BRCAnd	25 (5.1)	12 (4.9)
HRD status		
HRDpos	247 (50.7)	126 (51.2)
tBRCAmut	152 (31.2)	71 (28.9)
non-tBRCAmut	95 (19.5)	55 (22.4)
HRDneg	169 (34.7)	80 (32.5)
HRDnd	71 (14.6)	40 (16.3)
Prior bevacizumab	6 (1.2)	1 (0.4)

Abbreviations: BRCA, breast cancer susceptibility gene; HRD, homologous recombinant deficiency; pos, positive; mut, mutation; nd, not determined; neg, negative; wt, wild type
Source: PRIMA CSR.

A2. Priority question: The submission describes determination of both radiological and clinical progression. Please confirm which definition of progression was used for blinded, independent, central review (BICR) and investigator assessed (IA) progression free survival (PFS). If both definitions were used, please provide a sensitivity analysis of PFS based on the two definitions separately for IA and BICR.

Response:

The primary endpoint of PRIMA was progression-free survival (PFS) by blinded independent central review (BICR), defined either by radiological assessment as per RECIST v1.1 or by clinical criteria. Clinical criteria were defined as follows:

- CA-125 progression according to Gynecologic Cancer Intergroup (GCIG)-criteria AND additional diagnostic tests (e.g. histology/cytology, ultrasound techniques, endoscopy, positron emission tomography [PET]) which may identify new lesions or determine existing lesions qualify for unequivocal progressed disease (PD);

- CA-125 progression according to GCIG criteria (below) AND definitive clinical signs and symptoms of PD unrelated to non-malignant or iatrogenic causes, such as: [1] intractable cancer-related pain; [2] malignant bowel obstruction/worsening dysfunction or [3] unequivocal symptomatic worsening of ascites or pleural effusion.

Eight patients met PD via clinical criteria. The BICR charter allowed a blinded medical oncologist to adjudicate when the RECIST PD was not determined to ensure the clinical criteria was met. A sensitivity analysis was conducted for BICR using radiological review (excluding clinical progression) which showed alignment to the primary results; median PFS: 13.8 months (95% CI 11.8, 15.2) vs. 8.2 months (95% CI 7.3, 8.5); hazard ratio (HR) 0.61.

As investigator assessed (IA) PFS was itself a sensitivity analysis, this used both RECIST and clinical criteria; there is no further analysis of this assessment.

A3. Priority question: Please provide Kaplan-Meier plots for PFS, time to first subsequent therapy (TFST), progression free survival on next line of therapy (PFS2) and overall survival (OS) for the intention to treat (ITT) population in PRIMA with 95% confidence intervals (CI) and with number of patients at risk as detailed in Figure 2a and 2e of Morris TP, et al. BMJ Open 2019[11]

Response:

The requested Kaplan-Meier (KM) plots with number of patients at risk and 95% confidence intervals (CI) for PFS, time to first subsequent therapy (TFST) and progression-free survival on subsequent therapy (PFS2) and overall survival (OS) for the intention-to-treat (ITT) population in PRIMA are presented in Figure 1 to Figure 4, respectively.

Figure 1: Progression-free survival for the PRIMA ITT population

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival

Figure 2: TFST for the PRIMA ITT population

Abbreviations: CI, confidence interval; ITT, intention-to-treat; TFST, time to first subsequent treatment

Figure 3: PFS2 for the PRIMA ITT population

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PFS2, progression-free survival on subsequent therapy

Figure 4: OS for the PRIMA ITT population

Abbreviations: CI, confidence interval; ITT, intention-to-treat; OS, overall survival

A4. Priority question: Please provide subgroup analysis by dose for:

a) **Patients starting on fixed and individualised dosing. Please provide:**

   i. **Baseline characteristics (including HRD status, BRCA status and prior bevacizumab therapy)**

   ii. **Results for PFS and OS (event rates, medians and hazard ratios [HR] with 95% CI)**

b) **Patients starting on 300 mg and patients starting on 200 mg. Please provide:**

   i. **Baseline characteristics (including HRD status, BRCA status and prior bevacizumab therapy)**

ii. **Results for PFS and OS (event rates, medians and HR with 95% CI)**

c) **Patients stratified by 100 mg, 200 mg, 100 mg + 200 mg combined, and 300 mg dose at 6 months. Please provide:**

i. **Baseline characteristics (including HRD status, BRCA status and prior bevacizumab therapy)**

ii. **Results for PFS (event rates, medians and HR with 95% CI)**

Response:

Please find the requested information on baseline characteristics and outcomes per fixed and individualised starting dose in Table 2 and Table 3. Please note that OS data by starting dose (fixed versus individualised) is not currently available due to data immaturity. Please note that the analysis requested in b) and c) is not available. The trial was designed to look at the individualised and fixed dosing regimen specifically and not per individual *starting* dose, therefore the latter cannot be applied as a stratification factor.

Table 2: Patient Demographics and Baseline Characteristics – Individualised and Fixed Dose Subgroups (ITT Population)

Characteristic	Overall			
	Niraparib N (%)		Placebo N (%)	
	Fixed N=317	Individualised N=170	Fixed N=158	Individualised N=88
Age at time of screening				
Median	61.0	63.0	62.0	60.5
Min, Max	32, 83	39, 85	34, 88	33, 82
ECOG PS				
0	223 (70.3)	114 (67.1)	114 (72.2)	60 (68.2)
1	94 (29.7)	56 (32.9)	44 (27.8)	28 (31.8)
Cancer stage (FIGO) at time of diagnosis				
III, not otherwise specified	5 (1.6)	5 (2.9)	4 (2.5)	0
IIIA	3 (0.9)	4 (2.4)	4 (2.5)	0
IIIB	10 (3.2)	6 (3.5)	7 (4.4)	5 (5.7)
IIIC	186 (58.7)	99 (58.2)	88 (55.7)	50 (56.8)
IV	113 (35.6)	56 (32.9)	55 (34.8)	33 (37.5)
Primary tumor site				
Ovarian	249 (78.5)	139 (81.8)	130 (82.3)	71 (80.7)
Primary peritoneal	20 (6.3)	14 (8.2)	7 (4.4)	6 (6.8)
Fallopian tube	48 (15.1)	17 (10.0)	21 (13.3)	11 (12.5)
NACT				
Y	208 (65.6)	114 (67.1)	114 (72.2)	53 (60.2)
N	109 (34.4)	56 (32.9)	44 (27.8)	35 (39.8)
Best Response to first-line platinum-based chemotherapy				
CR	233 (73.5)	104 (61.2)	117 (74.1)	55 (62.5)
PR	84 (26.5)	66 (38.8)	41 (25.9)	33 (37.5)
HRD status				
HRDpos	160 (50.5)	87 (51.2)	83 (52.5)	43 (48.9)
tBRCAmut	99 (31.2)	53 (31.2)	45 (28.5)	26 (29.5)
non-tBRCAmut	61 (19.2)	34 (20.0)	38 (24.1)	17 (19.3)
HRDneg	108 (34.1)	61 (35.9)	54 (34.2)	26 (29.5)

Characteristic	Overall			
	Niraparib N (%)		Placebo N (%)	
	Fixed N=317	Individualised N=170	Fixed N=158	Individualised N=88
HRDnd	49 (15.5)	22 (12.9)	21 (13.3)	19 (21.6)
BRCA status				
BRCAmut	99 (31.2)	53 (31.2)	45 (28.5)	26 (29.5)
BRCAwt	199 (62.8)	111 (65.3)	106 (67.1)	57 (64.8)
BRCAnd	19 (6.0)	6 (3.5)	7 (4.4)	5 (5.7)
Prior therapy				
Bevacizumab	0 (0)	6 (3.5)	0 (0)	1 (1.1)

Abbreviations: BRCA, breast cancer susceptibility gene; CA-125, cancer antigen 125; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRDpos, homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors; ITT, intention-to-treat; Max, maximum; Min, minimum; mut, mutation; ND, not determined; PS, performance score; PR, partial response; ULN, upper limit of normal; US, United States; wt, wild type

In the overall study population, PFS as determined by BICR based on RECIST v1.1 was significantly improved (Table 3). The HR for the fixed starting dose (FSD) subgroup in the overall population was 0.59 (95% CI 0.457, 0.757; p<0.0001) and the HR in the individualised starting dose (ISD) subgroup in the overall population was 0.69 (95% CI 0.481, 0.982; p=0.0389). The CI is wide due to shorter duration of follow up in the ISD subgroup, therefore a smaller number of PFS events. The test of treatment interaction between starting dose subgroups was not statistically significant at the pre-specified 0.10-level (p=0.2957); hence there was no evidence of treatment difference between fixed and individualised dosing regimens.

Table 3: Progression-Free Survival Based on BICR Assessment by Starting Dose Group (ITT Population)

Population Parameter Statistic	Fixed		Individualised	
	Niraparib	Placebo	Niraparib	Placebo
Overall				
N	317	158	170	88
PFS (months)[a,b]				
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Censored observations, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Event rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
p-value[c]	[redacted]		[redacted]	
HR (95% CI)[d]	0.59 (0.457, 0.757)		0.69 (0.481, 0.982)	

Abbreviations: BICR, blinded independent central review; CI, confidence interval; CR, complete response; ITT, intention-to-treat; NE, not estimated; PFS, progression-free survival; PR, partial response.
a. Progression-free survival is defined as the time in months from the date of randomization to progression or death.
b. Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
c. Based on stratified log-rank test using randomization stratification factors: administration of neoadjuvant chemotherapy (yes/no), best response to platinum therapy (CR or PR), and homologous recombination deficiency test status (for overall ITT population only).
d. Based on stratified Cox proportional hazards model using randomization stratification factors as above.

A5. Priority question: Please assess if the proportional hazards assumption hold for the "no visible residual disease (NVRD) effect" hazard ratio between the two placebo curves in

a) PAOLA-1 (NVRD vs VRD);

b) SOLO-1 (ITT vs NVRD).

Please provide KM-plots, log cumulative hazards plots and Schoenfeld residual plots for both trials.

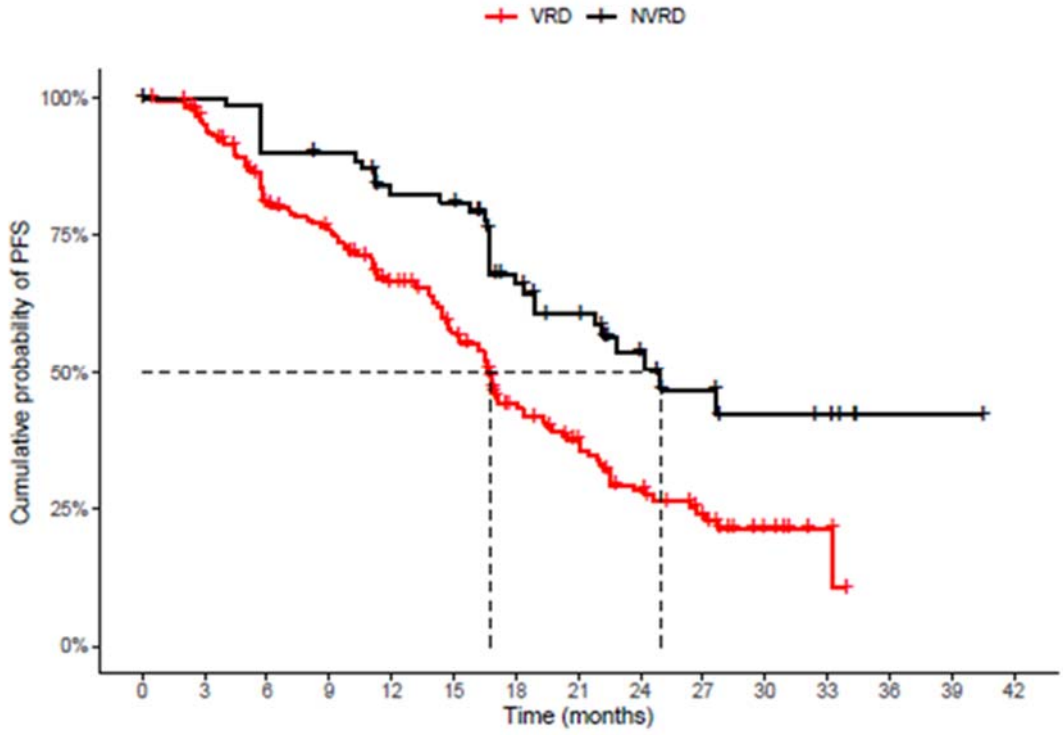
Response:

PAOLA-1 placebo + bevacizumab treatment arm

Figure 5, Figure 6 and Figure 7 present the PFS KM curves, the log-cumulative hazard plot and the Schoenfeld residuals plot for no visible residual disease (NVRD) versus visible residual disease (VRD) for the placebo plus bevacizumab treatment arms (control) of the PAOLA-1 trial. The proportional hazards assumption between the NVRD and VRD control arms of the PAOLA-1 trial cannot be rejected due to the following reasons:

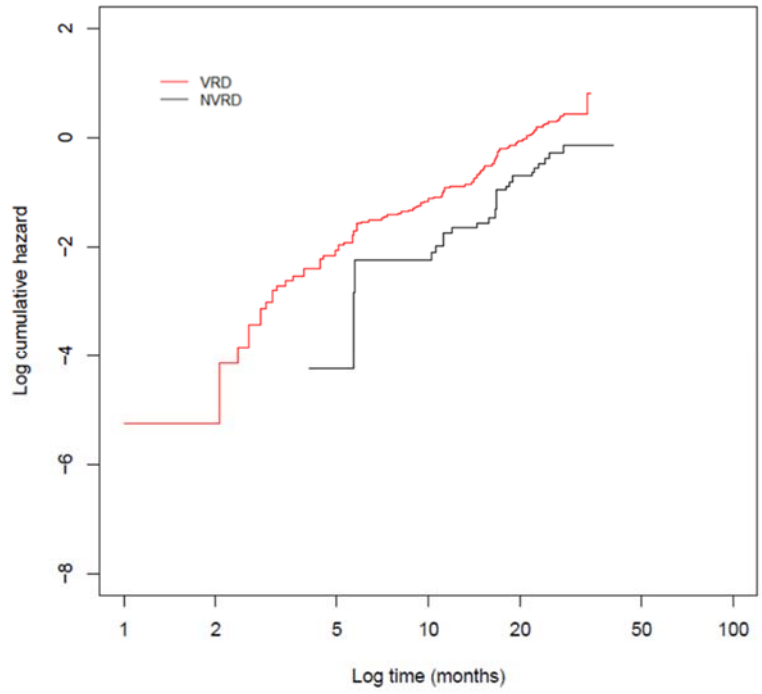
- The log-cumulative hazards for NVRD and VRD do not cross and tend to become parallel.
- The Schoenfeld residuals plot shows an approximate zero slope and the p-value is >0.05 (0.378) thus not rejecting the hypothesis of time independent residuals.

Figure 5: PFS KM for NVRD vs. VRD for placebo + bevacizumab treatment arms of the PAOLA-1 trial



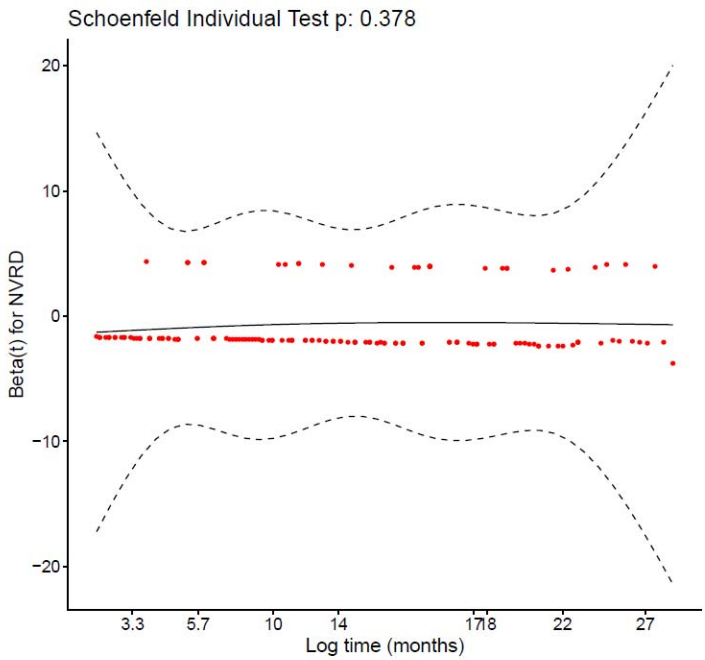
Abbreviations: KM, Kaplan-Meier; NVRD, no visible residual disease; PFS, progression-free survival; VRD, visible residual disease

Figure 6: PFS log-cumulative hazard plot for NVRD vs. VRD for placebo + bevacizumab treatment arms of the PAOLA-1 trial



Abbreviations: NVRD, no visible residual disease; PFS, progression-free survival; VRD, visible residual disease

Figure 7: PFS Schoenfeld residuals plot for NVRD vs. VRD for placebo + bevacizumab treatment arms of the PAOLA-1 trial



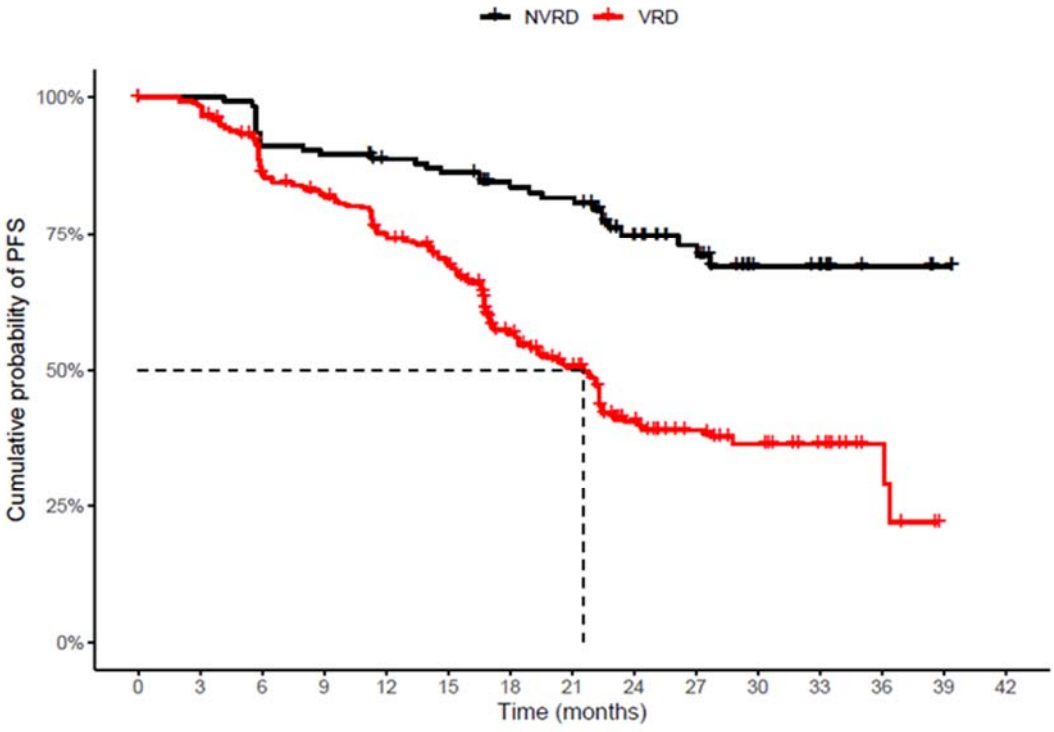
Abbreviations: NVRD, no visible residual disease; PFS, progression-free survival; VRD, visible residual disease

PAOLA-1 olaparib + bevacizumab treatment arm

Figure 8, Figure 9 and Figure 10 present the PFS KM curves, the log-cumulative hazard plot and the Schoenfeld residuals plot for NVRD versus VRD for the olaparib plus bevacizumab treatment arms (intervention) of the PAOLA-1 trial. The proportional hazards assumption between the NVRD and VRD intervention arms of the PAOLA-1 trial cannot be rejected as a result of this test for two reasons:

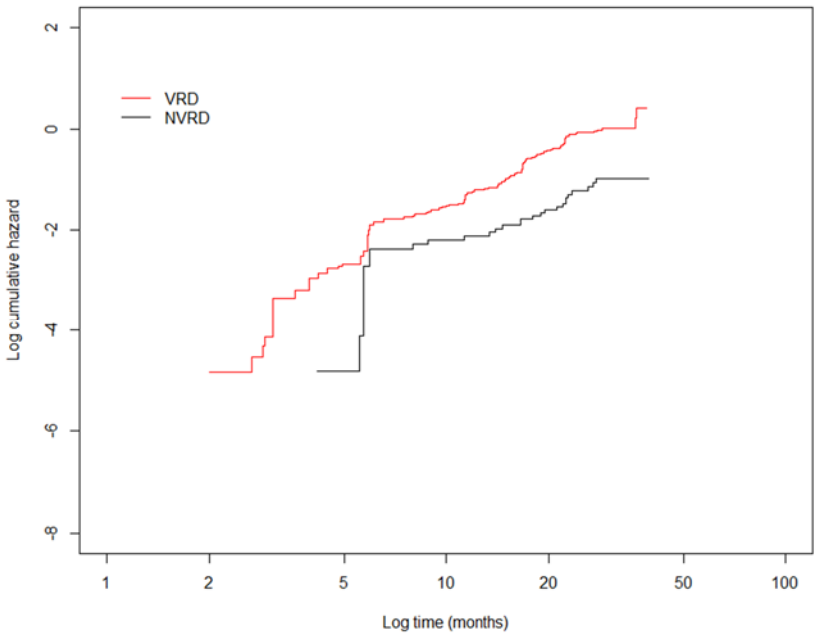
- The log-cumulative hazard plot shows converging curves up to Month 6, but thereafter the curves do not cross and become nearly parallel.
- The Schoenfeld residuals plot shows an approximate zero slope and the p-value is >0.05 (0.5869).

Figure 8: PFS KM for NVRD vs. VRD for olaparib + bevacizumab treatment arms of the PAOLA-1 trial



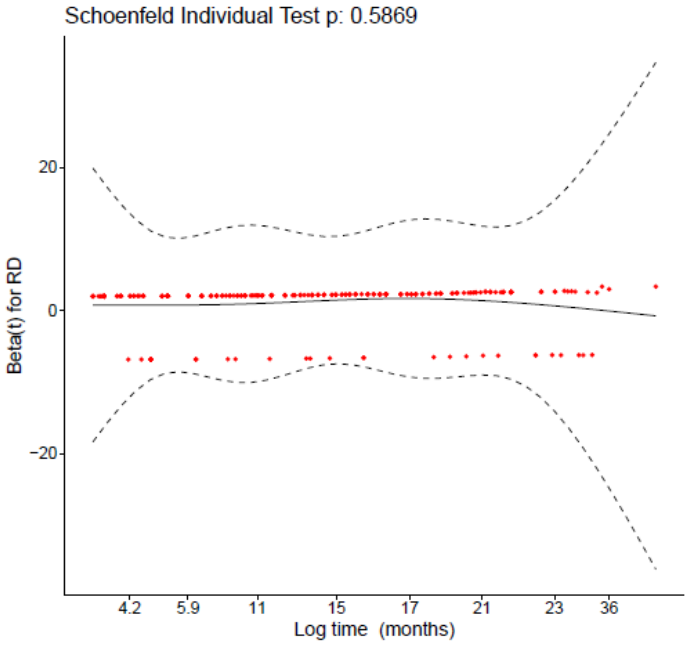
Abbreviations: KM, Kaplan-Meier; NVRD, no visible residual disease; PFS, progression-free survival; VRD, visible residual disease

Figure 9: PFS cumulative log hazard plot for NVRD vs. VRD for olaparib + bevacizumab treatment arms of the PAOLA-1 trial



Abbreviations: NVRD, no visible residual disease; PFS, progression-free survival; VRD, visible residual disease

Figure 10: PFS Schoenfeld residuals plot for NVRD vs. VRD for olaparib + bevacizumab treatment arms of the PAOLA-1 trial



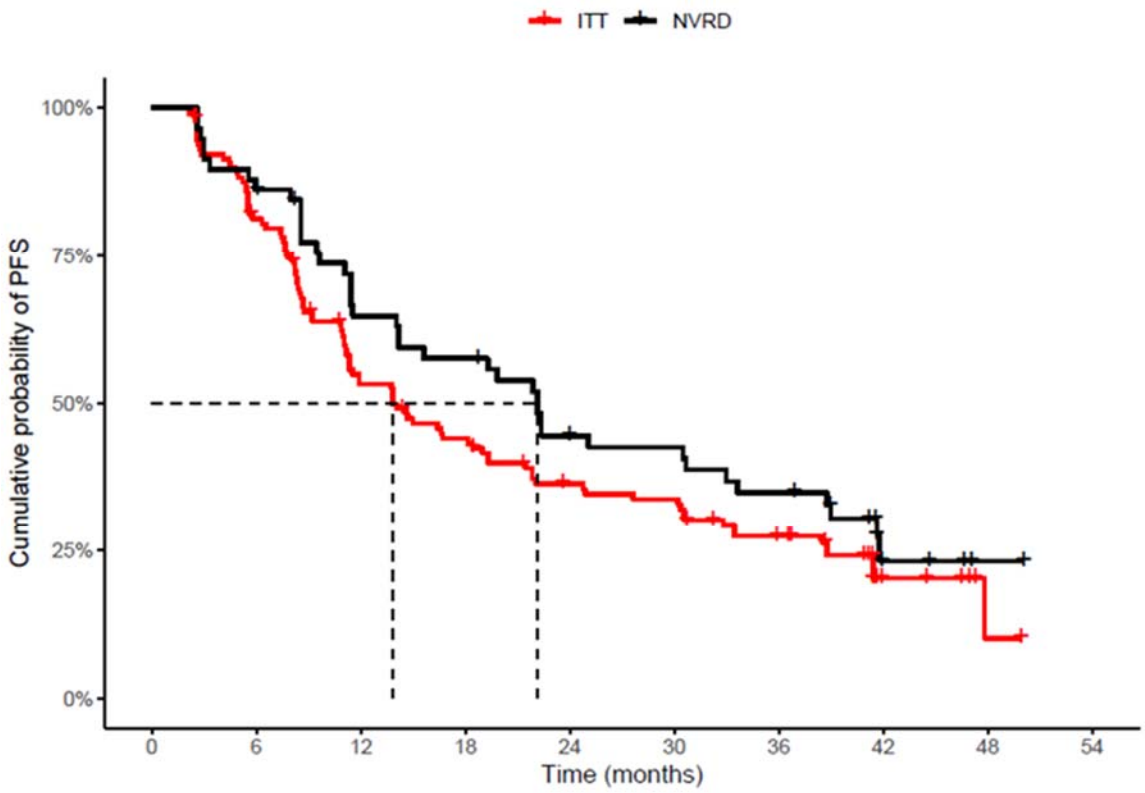
Abbreviations: NVRD, no visible residual disease; PFS, progression-free survival; VRD, visible residual disease

SOLO-1 placebo treatment arm

Figure 11, Figure 12 and Figure 13 present the PFS KM curves, the log-cumulative hazard plot and the Schoenfeld residuals plot for ITT versus NVRD for the placebo treatment arm (control) of the SOLO-1 trial. It should be noted that the ITT cohort of SOLO-1 includes patients with VRD and NVRD. The proportional hazards assumption between the ITT and NVRD control arms of the SOLO-1 trial cannot be rejected as a result of this test for two reasons:

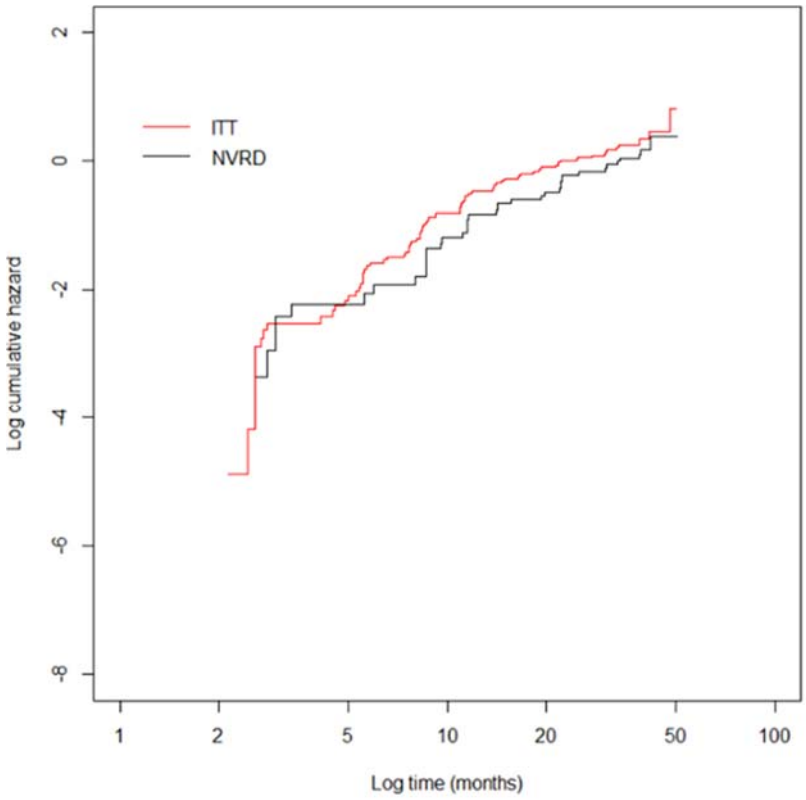
- The log-cumulative hazards do not cross outside of very early time points (before Month 6).
- The Schoenfeld residuals plot shows an approximate zero slope and the p-value is >0.05 (0.3282).

Figure 11: PFS KM for NVRD vs ITT for placebo treatment arms of the SOLO-1 trial



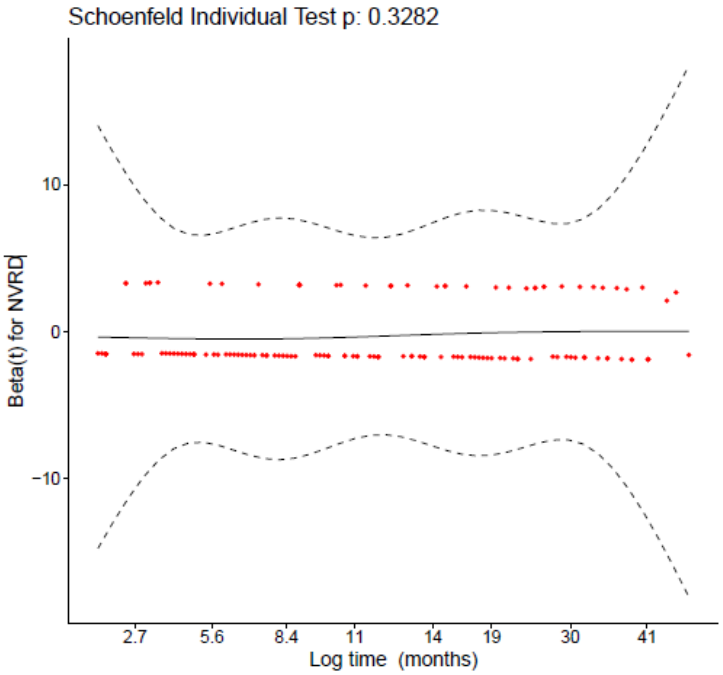
Abbreviations: KM, Kaplan-Meier; ITT, intention-to-treat; NVRD, no visible residual disease; PFS, progression-free survival

Figure 12: PFS log-cumulative hazard plot for NVRD vs. ITT for placebo treatment arms of the SOLO-1 trial



Abbreviations: ITT, intention-to-treat; NVRD, no visible residual disease; PFS, progression-free survival

Figure 13: PFS Schoenfeld residuals plot ITT vs. NVRD for placebo treatment arms of the SOLO-1 trial



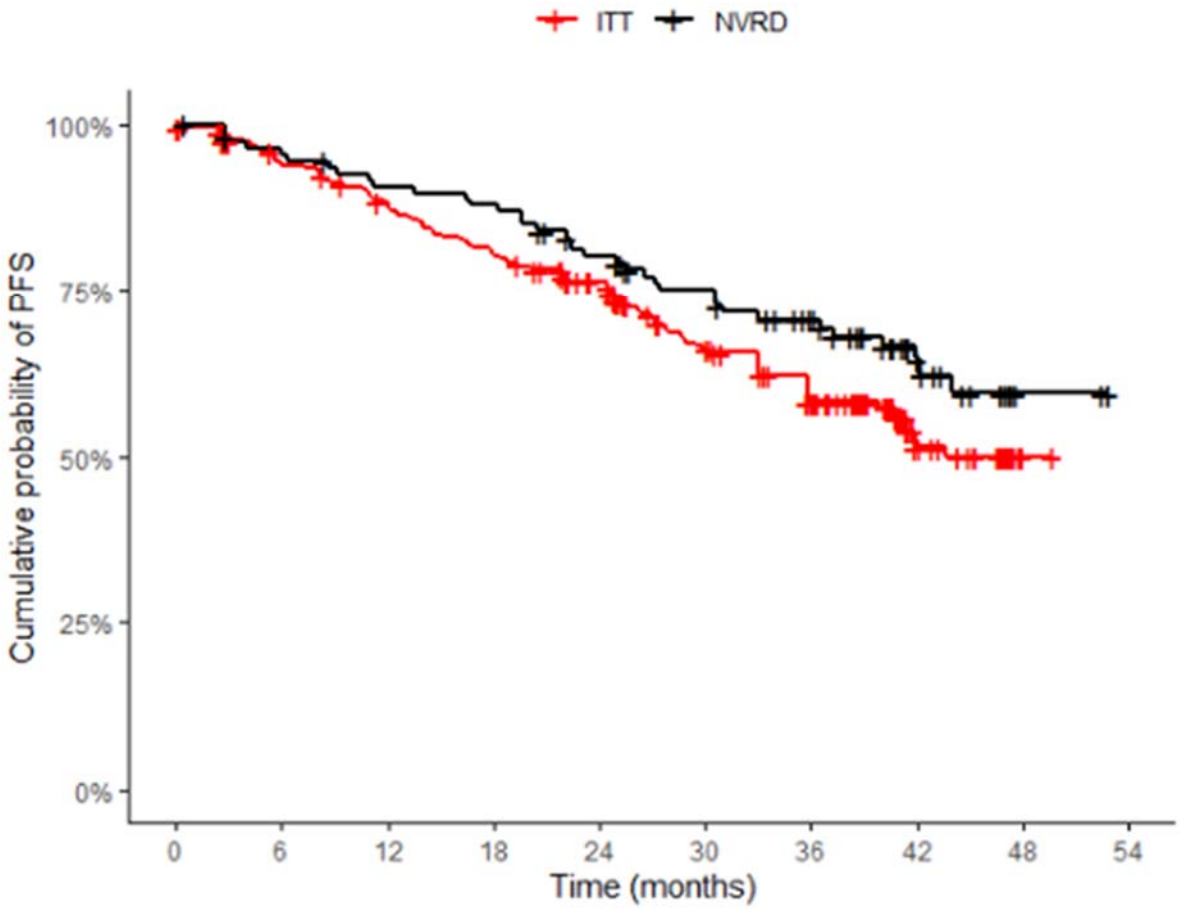
Abbreviations: ITT, intention-to-treat; NVRD, no visible residual disease; PFS, progression-free survival

SOLO-1 olaparib treatment arm

Figure 14, Figure 15 and Figure 16 present the PFS KM curves, the log-cumulative hazard plot and the Schoenfeld residuals plot for ITT versus NVRD for the olaparib treatment arm (intervention) of the SOLO-1 trial. The proportional hazards assumption between the ITT and NVRD intervention arms of the SOLO-1 trial cannot be rejected as a result of this test for two reasons:

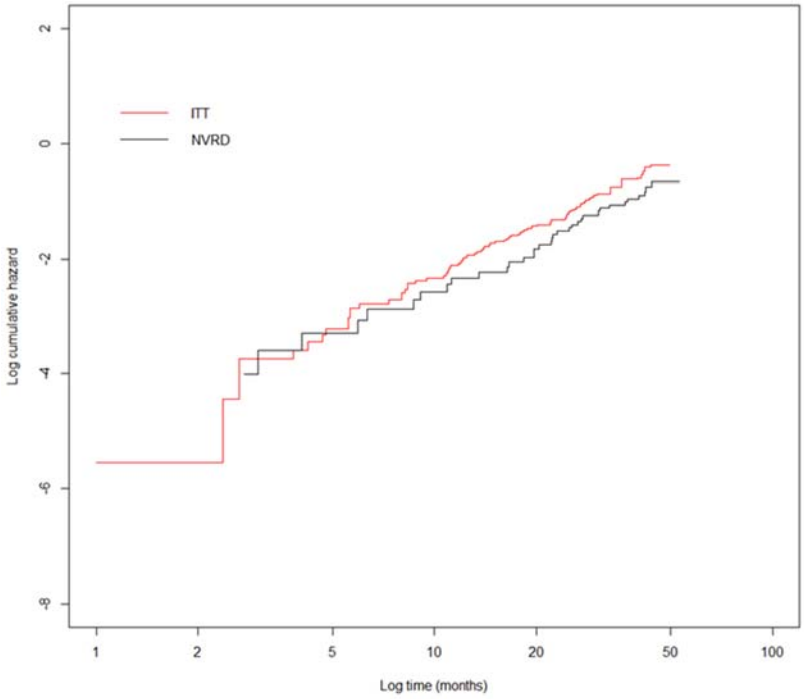
- The log-cumulative hazards do not cross outside of very early time points (before Month 6).
- The Schoenfeld residuals plot shows an approximate zero slope and the p-value is >0.05 (0.8626).

Figure 14: PFS KM for NVRD vs. ITT for olaparib treatment arms of the SOLO-1 trial



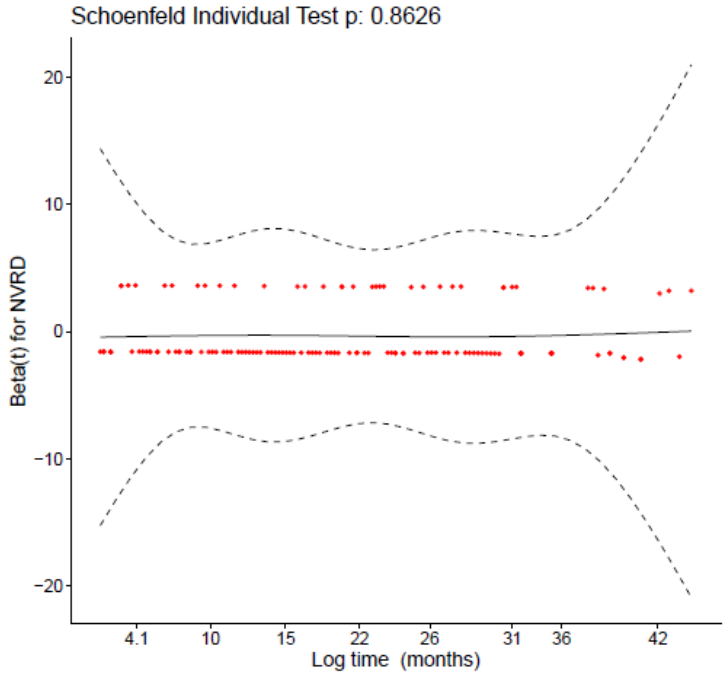
Abbreviations: KM, Kaplan-Meier; ITT, intention-to-treat; NVRD, no visible residual disease; PFS, progression-free survival

Figure 15: PFS log-cumulative hazard plot for NVRD vs ITT for olaparib treatment arms of the SOLO-1 trial



Abbreviations: ITT, intention-to-treat; NVRD, no visible residual disease; PFS, progression-free survival

Figure 16: PFS Schoenfeld residuals plot ITT vs. NVRD for olaparib treatment arms of the SOLO-1 trial



Abbreviations: ITT, intention-to-treat; NVRD, no visible residual disease; PFS, progression-free survival

A6. Priority question: Please provide a discussion around the possible impact on the estimated "NVRD effect" in PAOLA-1 of patients receiving concomitant bevacizumab therapy. Please take into account that all patients in PAOLA-1 received bevacizumab maintenance therapy, which has been shown to be more effective in patients at higher risk of progression (including but not limited to VRD) than in the overall population (including NVRD)[2]

Response:

The use of data obtained from the PAOLA-1 trial to inform the marketing authorisation (MA) extrapolation within the economic model is discussed in detail in the Company submission (CS) (Section B.3.3, page 140-145). Whilst the limitations of PAOLA-1 are acknowledged by the Company, feedback from United Kingdom (UK) clinical experts indicated that the PAOLA-1 trial was the best source of data available to estimate the "NVRD effect" as it is not restricted to a BRCAm based population.

In addition, the analysis applied in the economic model takes into account a relative effect of NVRD compared to VRD in the PAOLA-1 trial through the estimation of hazard ratios as opposed to an absolute effect.

As highlighted by the Evidence Review Group (ERG), evidence from existing bevacizumab trials (ICON-7[2,3]) within ovarian cancer (OC) shows that bevacizumab is more efficacious in patients who are at high risk of progression. The impact of the "NVRD effect" observed in PAOLA-1 may be underestimated as a result of this. If bevacizumab is more effective in patients who are at risk high (e.g. patients with VRD) it would be expected that the relative improvement of patients treated with bevacizumab would be greater in patients with VRD than in patients with NVRD. As such the difference in efficacy observed in PAOLA-1 bevacizumab monotherapy arms for patients with VRD and with NVRD may be reduced. As such the true "NVRD effect" could be expected to be larger than that estimated from the PAOLA-1 bevacizumab monotherapy arms.

Therefore, the use of the "NVRD effect" obtained from PAOLA-1 within the economic evaluation may underestimate PFS in both the niraparib and RS arms of the MA population.

A7. Priority question: Please provide a discussion about the likely impact on the estimated "NVRD effect" in SOLO-1 of all patients being BRCA+.

Response:

Data from the SOLO-1 trial were considered as a scenario analysis to inform the extrapolation to the anticipated MA population. As highlighted in Section B.3.3, page 144 of the CS, this data is limited by the fact that the SOLO-1 trial enrolled patients with a *BRCA* mutation only. Therefore, a decision was made to use data from the PAOLA-1 trial within the base case analysis. Both the presence of a *BRCA* mutation or the achievement of NVRD following primary cytoreductive surgery impact the prognosis of the patients with OC:

- The presence of a *BRCA* mutation significantly increases the lifetime risk of developing OC, but patients without a *BRCA* mutation are associated with worse survival than those who carry the mutation.[4–6] This improvement is evident from the PRIMA and PAOLA-1 trial, where the risk of progression was observed to be lower in patients with a *BRCA* mutation compared to those without.[7,8]

- Patients with Stage III NVRD following primary cytoreductive surgery have a better prognosis than patients with Stage III/IV VRD, irrespective of treatment received (Section B.2.14 of the CS patients).

Despite the evidence on how these factors individually affect patients' prognosis, the Company is unaware of evidence on how these two factors interact. The analysis conducted by the Company considered the relative difference between the SOLO-1 ITT and NVRD patient populations, and not the absolute difference. As such the *BRCA* mutation factor is included in both arms of the analysis and is not expected to have a large impact on the magnitude of the "NVRD" effect. However, the Company acknowledge the limitations of the SOLO-1 data and still consider the PAOLA-1 data to be the most appropriate source to inform the MA extrapolation within the analysis.

A8. Priority question: Please provide a discussion around the potential clinical rationale for the observed difference in niraparib treatment effect between patients in PRIMA with Stage III OC than those in the ITT population.

Response:

Stage of disease is a prognostic factor for PFS in advanced OC patients. Patients with Stage III disease have a better prognosis than those diagnosed at Stage IV.[9,10] In the PRIMA trial, Stage IV accounted for approximately one third of the ITT population.

Furthermore, the trial demonstrates that the benefit of niraparib compared to placebo is more pronounced when disease burden is minimal, reflected by the forest plot showing differential benefit by Stage.

These results reflect those seen with other PARP inhibitors, in the SOLO-1 and PAOLA-1 trials, where the impact of olaparib was more pronounced in patients with no to limited disease remaining after surgery and chemotherapy.[11,12, 7,13]

A9. Please provide the rationale for limiting inclusion in PRIMA to patients with VRD?

Response:

The aim of the PRIMA trial was to fulfil an unmet need of extending disease free survival in the most at-risk patients, and to do so in timely way. As such, the trial recruited a population at the highest risk of early relapse, with the greatest unmet need in the knowledge that if niraparib demonstrated a benefit in this group of patients, it would also be effective in a lower risk patient group, which is evident from other PARP inhibitor trials.[11,12, 7,13]

A10. For the real-world evidence obtained from the Edinburgh Ovarian Cancer Database, please provide:

a) The definition used for capturing NVRD and VRD and if the definition has changed at any time between 2000 and 2015? If the definition did change, when did this occur and what proportions of people in the marketing authorisation (MA) cohort and simulated-PRIMA cohort were enrolled prior and post this change?

b) Baseline characteristics for the PRIMA-simulated cohort on prior bevacizumab treatment (first-line bevacizumab) and the proportion of patients in the MA cohort and simulated-PRIMA cohort enrolled prior to bevacizumab becoming available through routine commissioning in Scotland?

Response:

Since the definition of NVRD and VRD has changed in the last decade, the analysis assessed the actual outcomes of the surgeries per remaining centimetre (cm) rather than the classifications. Outcomes were assessed per the available surgery descriptions, and all cases classified as <2 cm were grouped into 0 cm (complete macroscopic debulk) versus macroscopic residual disease using the database. Therefore, it was possible to observe the true ‘macroscopic residual present value absent’ data.

Patients treated with bevacizumab, either as a first-line combination treatment option or as maintenance therapy were excluded from the analysis. Bevacizumab was recommended for use by the Scottish Medicines Consortium in 2015. Since the database analysis included patients diagnosed between 2000-2015, there were only a few patients who were not included in the database analysis due to the above restriction. This is also in line with the patient population included within PRIMA; only a very small number of patients had received prior bevacizumab during their chemotherapy treatment course (please see response to question A1).

A11. Is the European marketing authorisation for niraparib expected to specify a maximum length of treatment and is it expected to be 3 years as in PRIMA?

a) Please provide the clinical rationale for the maximum 3-year treatment with niraparib in PRIMA.

Response:

The Summary of Product Characteristics (SmPC) will not specify a treatment duration of 3 years, however this treatment length was defined within the PRIMA protocol according to the following: “Patients can continue treatment until disease progression, unacceptable toxicity or for up to 3 years. Patients with evidence of disease at 3 years, who in the opinion of the treating physician can derive further benefit from continuous treatment, can be treated beyond 3 years”. It is expected that the use of niraparib in this indication will reflect the practice described in the protocol.

As the PRIMA trial enrolled high-risk Stage III patients; with disease remaining after primary surgery or those who had required neoadjuvant chemotherapy with interval debulking surgery, or Stage IV patients, maintenance treatment for approximately 3 years was felt to be optimum to maximise the chance of long-term remission. However, the protocol allows treatment of patients for more than 3 years if there is evidence of clinical benefit. There remains a need to balance treatment with not over-treating patients who have achieved a long-term remission.

A12. Please provide the incidence of any grade treatment-emergent adverse events (TEAEs) reported in ≥10% of patients in the niraparib group according to dose at onset of the event.

Response:

The requested information per starting dose is unfortunately not available, however it is available according to the stratification factors fixed and individualised dosing. Please find that information detailed in Table 4 and Table 5. The most frequently reported treatment emergent adverse events (TEAEs) were consistent with the known safety profile of niraparib seen in previous clinical studies.[14] Most of the common TEAEs were reported at a higher incidence in the niraparib arm compared

to the placebo arm, with the exception of disease related- symptoms, including abdominal pain and distension, and other pain-related symptoms, including arthralgia. All common TEAEs were reported at a lower incidence in patients who received an individualized starting dose compared to patients who received a fixed starting dose (Table 5).

Table 4: Summary of Treatment-Emergent Adverse Events (Safety Population)

TEAE Category	Niraparib			Placebo
	All n (%) N=484	Individualised n (%) N=169	Fixed n (%) N=315	All n (%) N=244
Any TEAE	478 (98.8)	[redacted]	[redacted]	224 (91.8)
Any related TEAE[a]	466 (96.3)	[redacted]	[redacted]	168 (68.9)
Any serious TEAE	156 (32.2)	[redacted]	[redacted]	32 (13.1)
Any related serious TEAE	118 (24.4)	[redacted]	[redacted]	6 (2.5)
Any TEAE with CTCAE Grade ≥3[b]	341 (70.5)	[redacted]	[redacted]	46 (18.9)
Any related TEAE with CTCAE Grade ≥3	316 (65.3)	[redacted]	[redacted]	16 (6.6)
Any TEAE leading to death	2 (0.4)	[redacted]	[redacted]	1 (0.4)
Any TEAE leading to dose interruption	385 (79.5)	121 (71.6)	264 (83.8)	44 (18.0)
Any TEAE leading to dose reduction	343 (70.9)	104 (61.5)	239 (75.9)	20 (8.2)
Any TEAE leading to study drug withdrawal	58 (12.0)	23 (13.6)	35 (11.1)	6 (2.5)

Abbreviations: CSR, clinical study report; CTCAE, common terminology criteria for adverse events; TEAE, treatment-emergent adverse event.
a. Related TEAEs are defined as possibly related, likely related, or related to study drug; TEAEs where the relationship to study drug was missing were considered as related to study drug treatment
b. Patients with more than 1 event of the same preferred term were counted only once for the event with the highest CTCAE grade.

Table 5: Most Common (≥10% Incidence Rate in Either Treatment Subgroup) Treatment-emergent Adverse Events by MedDRA Preferred Term (Safety Population)

Preferred Term	Niraparib			Placebo
	All n (%) N=484	Individualised n (%) N=169	Fixed n (%) N=315	All n (%) N=244
Any TEAE with ≥10% incidence rate	472 (97.5)	[redacted]	[redacted]	208 (85.2)
Nausea	278 (57.4)	[redacted]	[redacted]	67 (27.5)
Anaemia	307 (63.4)	[redacted]	[redacted]	43 (17.6)
Thrombocytopenia	222 (45.9)	[redacted]	[redacted]	9 (3.7)
Constipation	189 (39.0)	[redacted]	[redacted]	46 (18.9)
Fatigue	168 (34.7)	[redacted]	[redacted]	72 (29.5)
Vomiting	108 (22.3)	[redacted]	[redacted]	29 (11.9)
Headache	126 (26.0)	[redacted]	[redacted]	36 (14.8)
Insomnia	119 (24.6)	[redacted]	[redacted]	35 (14.3)
Platelet count decreased	133 (27.5)	[redacted]	[redacted]	3 (1.2)
Abdominal pain	106 (21.9)	[redacted]	[redacted]	75 (30.7)
Decreased appetite	92 (19.0)	[redacted]	[redacted]	20 (8.2)
Neutropenia	128 (26.4)	[redacted]	[redacted]	16 (6.6)
Diarrhoea	91 (18.8)	[redacted]	[redacted]	55 (22.5)
Hypertension	82 (16.9)	[redacted]	[redacted]	17 (7.0)
Dyspnoea	88 (18.2)	[redacted]	[redacted]	30 (12.3)
Cough	74 (15.3)	[redacted]	[redacted]	35 (14.3)
Dizziness	71 (14.7)	[redacted]	[redacted]	26 (10.7)
Asthenia	78 (16.1)	[redacted]	[redacted]	31 (12.7)
Neutrophil count decreased	82 (16.9)	[redacted]	[redacted]	5 (2.0)
Arthralgia	85 (17.6)	[redacted]	[redacted]	47 (19.3)
Back pain	64 (13.2)	[redacted]	[redacted]	24 (9.8)
Viral upper respiratory tract infection	49 (10.1)	[redacted]	[redacted]	25 (10.2)
Abdominal pain upper	41 (8.5)	[redacted]	[redacted]	22 (9.0)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
Note: If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.

A13. Please provide grade ≥3 Haematologic TEAEs according to dose at onset of the event.

Response:

The requested information per starting dose is unfortunately not available, however it is available according to the stratification factors fixed and individualised dosing. Table 6.

In the PRIMA study, 341 (71%) of 484 patients who received niraparib and 46 (19%) of 244 patients who received placebo experienced a Grade 3 or 4 TEAE. The most frequently reported Grade ≥3 TEAEs were related to myelosuppression and were more commonly reported by patients who received niraparib, including anaemia (31%), thrombocytopenia (29%), platelet count decreased (13%), neutropenia (13%), and neutrophil count decreased (8%). Other frequently reported Grade ≥3 TEAEs in the niraparib arm included hypertension (6%). The corresponding incidence of these Grade ≥3 TEAEs in placebo patients was ≤2%. Three Grade 5 TEAEs were reported in the PRIMA study including single events of an intestinal perforation and pleural effusion in the niraparib arm and an intentional overdose in the placebo arm; none of the Grade 5 TEAEs were assessed as related to study drug.

Clinically significant ≥ Grade 3 adverse events (AEs), were significantly reduced in patients who received the individualised starting dose (200 or 300 mg) as compared to those who received the fixed starting dose (300 mg): thrombocytopenia (14.8% ISD vs 36.2% FSD), anaemia (22.5% ISD vs 35.6% FSD), and neutropenia (9.5% ISD vs 14.6% FSD).

Table 6: Grade ≥3 Treatment-emergent Adverse Events Reported in ≥5% of Patients in Either Treatment Subgroup by MedDRA System Organ Class and Preferred Term (Safety Population)

MedDRA SOC Preferred Term	Niraparib			Placebo
	All n (%) N=484	Individualised n (%) N=169	Fixed n (%) N=315	All n (%) N=244
Any Grade ≥3 TEAE	341 (70.5)	[redacted]	[redacted]	46 (18.9)
Blood and lymphatic system disorders	255 (52.7)	[redacted]	[redacted]	6 (2.5)
Thrombocytopenia	139 (28.7)	[redacted]	[redacted]	1 (0.4)
Anaemia	150 (31.0)	[redacted]	[redacted]	4 (1.6)
Neutropenia	62 (12.8)	[redacted]	[redacted]	3 (1.2)
Investigations	99 (20.5)	[redacted]	[redacted]	8 (3.3)
Platelet count decreased	63 (13.0)	[redacted]	[redacted]	0
Neutrophil count decreased	37 (7.6)	[redacted]	[redacted]	0
Vascular disorders	32 (6.6)	[redacted]	[redacted]	4 (1.6)
Hypertension	29 (6.0)	[redacted]	[redacted]	3 (1.2)
General disorders and administration site conditions	21 (4.3)	[redacted]	[redacted]	4 (1.6)
Fatigue	9 (1.9)	[redacted]	[redacted]	1 (0.4)

Abbreviations: CSR, clinical study report; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class; TEAE, treatment-emergent adverse event.
Note: If a patient experienced more than 1 event in a given SOC, that patient was counted once for the SOC. If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.

Section B: Clarification on cost-effectiveness data

If as a result of the responses to the cost-effectiveness clarification questions the company base case analyses are revised, please indicate what assumptions are considered for the revised base case and provide updated results, probabilistic sensitivity analyses and deterministic sensitivity analyses in the response document.

Please provide all ERG-requested scenario analyses as drop-down menu options in the economic model to be run in combination with different scenarios.

A revised base-case as a result of the ERG questions is presented in Appendix 1. Table 24 details the changes made in the model to produce this revised base case.

B1. Priority question: In the ITT population, the modelled OS curve for the niraparib arm (and to a lesser extent the RS curve), considerably diverge from the KM data from approximately 2 years. Please clarify if more flexible modelling approaches were considered to estimate OS in the niraparib arm (for example, splines or piecewise models).

Response:

The modelled OS curve for niraparib closely aligns to the KM data up to Month 30 (Figure 26 of the CS).This coincides with the period for which there are sufficient number of patients remaining at risk (Table 7). At the tail of the KM curve, Month 32, [redacted]. This is mostly due to censoring as the number of events is low ([redacted]). This highlights the high level of immaturity in the niraparib OS KM data ([redacted]% of events). Therefore, a decision was made not to directly extrapolate the niraparib OS data collected in PRIMA and to find an alternative approach for use within the economic model. Full details and rationale are available in Section B.3.3 of the CS.

Table 7: Niraparib OS KM versus modelled OS curve

Months	No. at risk	KM	Modelled curve
0	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]

Abbreviations: ITT, intention-to-treat; OS, overall survival

Figure 25 of the CS shows that the modelled routine surveillance (RS) curve (log-logistic) has a relatively good visual fit to the observed KM data. The RS OS modelled curve and KM data closely align for approximately two years, which is the observed period with sufficient number of patients remaining at risk (Table 8).

Table 8: RS OS KM versus modelled OS curve

Months	No. at risk	KM	Modelled curve
0	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]

Abbreviations: ITT, intention-to-treat; OS, overall survival; RS, routine surveillance

Flexible modelling approaches (e.g. spline or piecewise models) were not considered, as standard models were deemed to provide a good fit to the observed data for RS, and flexible models would not have helped resolve the issue of immature data. Spline modelling approaches would require the estimation of more survival coefficients compared to standard parametric modelling, and hence increase the risk of bias given the data available. Piecewise models split the KM curve and base the extrapolation only on an (arbitrary) subset of the KM data, resulting in curves based on very low number of patients at risk. In addition, there is no clinical rationale that would suggest the cut to be made at a certain timepoint over the time horizon of the available KM curve. As neither the spline, nor the piecewise modelling approaches alleviate data immaturity issues and the log-logistic model provided a good fit to the observed RS data, these options were not considered for use in the economic model.

B2. Priority question: Please provide OS curves fitted to the OS KM data in PRIMA for niraparib following the Decision Support Unit (DSU) recommendation in Technical Support Document 14. Please incorporate the fitted curves in the model as options to estimate OS for niraparib (and please

consider the appropriateness of using more flexible models as per question B1).

Response:

As highlighted in Section B.3.3 of the CS the use of standard parametric modelling methods to estimate the OS curve for niraparib for use in the economic model was deemed inappropriate due to the high level of data immaturity ([redacted]%) and lack of long-term OS data to validate the extrapolation.

More flexible modelling approaches (e.g. spline or piecewise) would not compensate for data immaturity (please refer to response to B1). Therefore, these analyses have not been conducted.

The decision not to extrapolate immature OS data was also adopted in existing National Institute for Health and Care Excellence (NICE) technology appraisals for OC within both the first-line maintenance (TA598[15]) and second-line (2L) maintenance settings (TA528[16]).

B3. Priority question. Please discuss the validity of the methodological approach taken to estimate the relationship between PFS and OS in light of the methods proposed and discussed in the DSU report.[17]

Response:

The Decision Support Unit (DSU) review published by Davis *et al.* 2012 highlighted that there are a number of methods which may be suitable when analysing the relationship between PFS and OS, and that results may differ by chosen methodology, data used (aggregate or patient level) and by tumour type.[17] In addition, the review stated that even with evidence to support a correlation between treatment effects, it is unclear how such a relationship would be quantified within a cost-effectiveness model. The authors recommend that an analysis which utilises a PFS to OS relationship should:

1. Be supported with a transparent explanation of how the relationship is quantified

2. Be accompanied by sensitivity analyses exploring the uncertainty of the relationship

3. Be accompanied by a systematic review of papers examining the relationship in the relevant setting

The PFS:OS relationship adopted within this analysis is accompanied by points 1 and 2 recommended above. A full explanation of the relationship is provided in Section B.3.3 of the CS, and scenario analyses were conducted to explore the impact of different PFS:OS relationships and the impact of alternative PFS distributions (Table 56 of the CS). Across all scenario analyses on the PFS:OS relationship, the incremental cost-effectiveness ratio (ICER) remained below £26,000 per quality-adjusted life-year (QALY).

Whilst a full systematic review into the relationship between PFS and OS within OC was not conducted, the Company considered the long-term evidence within the maintenance setting, available from Study 19 only. Study 19 currently provides the most mature survival data for patients treated with PARP maintenance therapy and as such provides the best evidence to inform a PFS:OS relationship within this settings. The use of Study 19 as the best available evidence to inform OS in the absence of mature date for niraparib was accepted by the Committee during appraisal TA528.[16]

In order to provide additional evidence for the use of data from Study 19, a Spearman's rank correlation test was performed to assess the association between PFS and OS observed in Study 19. The proportion of patients progression-free and alive up to 12 months (time points where data for both PFS and OS were available) from both the olaparib and placebo arms of the Study 19 trial were used in the analysis (**Error! Reference source not found.**). The resulting Spearman's rank c orrelation coefficient indicated a strong positive correlation (R=0.95). This indicates that an increase in PFS is associated with an increase in OS.

B4. Priority question. In respect to the goal seek analysis used in the model to determine the HR applied to the routine surveillance (RS) OS arm to estimate the niraparib OS arm (and therefore apply different ΔPFS:ΔOS ratios), please include a scenario analysis where the mean PFS difference in the equation:

Niraparib mean OS = (RS mean OS + [Mean PFS difference x 2]) is estimated as the mean difference in the KM PFS curves in PRIMA. Please ensure that this scenario can be run in combination with varying the ΔPFS:ΔOS ratios option in the model.

Response:

The restricted mean PFS from the PRIMA KM curves were [redacted] and [redacted] months for niraparib and RS, respectively. The restricted mean PFS difference between the two treatments at the data cut-off point of PRIMA is therefore [redacted] months. An option has been added in the 'Clinical Inputs' sheet of the model to switch between the extrapolated PFS difference and the restricted KM PFS difference. Please refer to Appendix 1 for scenario analyses results.

The Company would like to highlight that whilst the ERG request has been completed, they do not deem this scenario as clinically appropriate. Truncating the PFS gain to that only observed in PRIMA [median follow-up of 13.9 months (CI 13.8, 16.0) and 13.8 months (CI 13.6, 14.1) for the niraparib and placebo groups, respectively] implies that patients treated with niraparib stop benefitting from treatment prior to treatment discontinuation. As highlighted in the CS (Section B.3.3), clinical expert opinion and evidence from the SOLO-1 trial indicate that the treatment effect of a PARP inhibitor is likely to be maintained during treatment and once a patient discontinues treatment.[11] As such it is not appropriate to truncate the benefit of niraparib at the end of the follow-up period.

B5. Priority question. Please provide further information regarding the approach to estimating OS in the model:

a) **Please provide a detailed description (with its rationale where appropriate) for the modelling approach chosen for the OS curves (where a proportion of cured and non-cured patients are included in the curves);**

b) **Please discuss the clinical plausibility (and the validation undertaken) of the cure rates used in the model (please note that the cure rates used in**

the base case suggest a higher probability of being cured in the RS arm - 54%; than in the niraparib arm - 29%);

c) **Please justify the choice of source used to determine the proportion of cured patients for the NVRD population, and discuss if other sources were considered;**

d) **If the company has robust evidence to justify the existence of a different survival trajectory for ovarian cancer patients who survive up to a certain point in time and therefore can substantiate the existence of a "cure" model, please replace the current modelling approach with a mixture cure model (MCM) where the proportion of cured patients is endogenously estimated in the model and the survival trajectory for short-term survivors can be appropriately estimated.[18,19]**

Response Part a:

Due to the immaturity of the OS data in the niraparib group of PRIMA, a relationship between the PFS benefit between RS and niraparib was used it estimate OS. This method of OS elicitation has been adopted in past submissions (TA528[16] and TA611[20]) and was used as evidence in a recent first-line OC appraisal (TA598[15]). Using this method, the niraparib OS curve was estimated based on the RS OS from PRIMA. Although the RS OS was also immature, real-world data was used to validate the most appropriate extrapolation.

A step by step description of how the niraparib and RS OS curves for the MA population were estimated (including the long-term remission assumption) is presented below.

1. RS OS curve extrapolated based on PRIMA RS patient level data (PLD) using DSU recommended standard parametric survival analysis techniques.

2. Log-logistic distribution selected as base-case curve based on clinical plausibility, statistical and visual fit (see Section B.3.3 [page 133] of CS).

3. Niraparib OS curve estimated through a mean ΔPFS: ΔOS relationship of 1:2 (see Section B.3.3 [page 134-135] of CS).

4. Application of long-term remission assumption at 7 years, such that patients remaining progression-free (PF) by this time were deemed to have achieved long-term remission and at risk of death by all-cause mortality only (see Section B.3.3 [page 139] of CS).

    i. Proportion of patients PF in ITT curve at 7 years estimated using the functions INDEX and MATCH

        - Niraparib – 'DataStore!M48'
        - RS – 'DataStore!M60'

    ii. Proportion of patients PF in NVRD curve at 7 years estimated

        - Niraparib – 'DataStore!O48': sourced from Du Bois *et al.* 2009[9] in absence of long-term PFS data available from PRIMA for patients with NVRD
        - RS – 'DataStore!O60': sourced from Du Bois *et al.* 2009[9] in absence of long-term PFS data available from PRIMA for patients with NVRD

    iii. Proportion of patients alive in ITT curve at 7 years estimated using the functions INDEX and MATCH

        - Niraparib - 'DataStore!M49'
        - RS – 'DataStore!M61'

    iv. Proportion of patients alive in NVRD curve at 7 years estimated:

        - Niraparib – 'DataStore!O49': sourced from Du Bois *et al.* 2009[9] in absence of long-term OS data available from PRIMA for patients with NVRD

- RS – ‘DataStore!O61’: sourced from Du Bois *et al.* 2009 in absence of long-term OS data available from PRIMA for patients with NVRD

v. Niraparib and RS OS curves for the ITT population split by PF and progressed disease (PD) (columns CE:CF and columns CZ:DB of Extrapolations). Long-term remission assumption applied to patients who are in the PF section of the OS curve (column CE [niraparib] and column CZ [RS]). Column CE/CZ and CF/DA weighted by the proportion of patients PF and PD (calculated in part IV) to produce an overall curve for the ITT population (column CG [niraparib] and column DB [RS]).

vi. Niraparib and RS OS curves for the NVRD population split by PF and PD (columns CH:CJ and columns DC:DE of Extrapolations). Long-term remission assumption applied to patients who are in the PF section of the OS curve (column CE [niraparib] and column CZ [RS]). Column CH/DC and CI/DD weighted by the proportion of patients PF and PD (calculated in part IV) to produce an overall curve for the ITT population (column CJ [niraparib] and column DE [RS]).

vii. Overall niraparib (column CK - Extrapolations) and RS (column DF – Extrapolations) OS curves for the full MA population produced by weighting ITT and NVRD OS curves by the proportion of patients in the MA population who have NVRD ([redacted]% - based on data available from the University of Edinburgh database). Final OS curves pulled into model calculations.

Response Part b:

The [redacted]% and [redacted]% figures represent the proportion of patients PF given the proportion of patients alive. At the long-term remission base case of 7 years, PFS and OS are higher in the niraparib arm compared to the RS arm. However, as less people are alive within the RS treatment arm, the ratio of PF:PD is higher for RS ([redacted] for RS

compared to [redacted] for niraparib). The chance of achieving long-term remission at 7 years is, as expected, higher in the niraparib arm ([redacted]%) than the RS ([redacted]%) arm.

The preliminary model outputs from the base case assumptions related to PFS and OS were validated through an advisory board (held April 2020) by a UK clinical and health economic experts in oncology.

Response Part c:

A targeted literature review was conducted to identify PFS and OS by residual disease status among OC patients (see Section B.2.14 of the CS for further details). Du Bois *et al* 2009.[9] was identified in this review and was selected for use within the long-term remission assumption in the model for the following reasons:

- Large sample size; n=3,129 OC patients from three prospective trials in Europe
- Assessment of a range of surgical outcomes
- Long follow-up period (144 months) allowing for PFS and OS data to be extracted at 5, 7 and 10 years

Other alternatives have not been explored to date; however, the model is not largely sensitive to the inputs extracted from Du Bois *et al.* when varied within the one-way sensitivity analyses (OWSA) and the probabilistic sensitivity analyses (PSA) (see Appendix 1). Data from Du Bois *et al.* is only applied in the MA population to differentiate between the ITT OS and the NVRD OS curves. The same assumptions are applied across the niraparib and RS treatment arms.

Response Part d:

There are three main evidence sources for the long-term remission assumption included within the economic model:

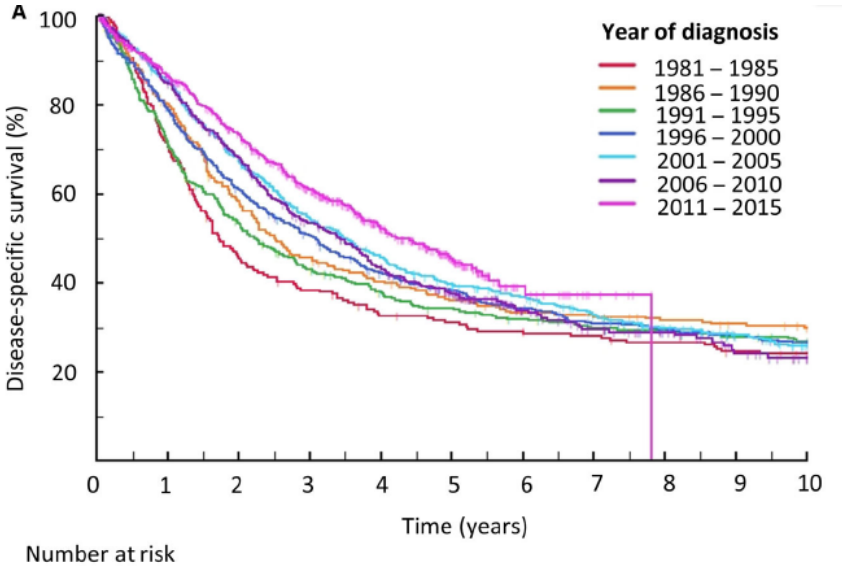
- Real world evidence (University of Edinburgh Ovarian Cancer database)
- UK expert opinion

- TA598 (SOLO-1 NICE appraisal)[15]

Real world evidence

Long-term real-world evidence from patients with OC highlights the potential for patients to achieve long-term remission, as described in Section B.2.14 of the CS The same academic group has recently published similar findings to those described in the submission. Figure 17 and Figure 18, obtained from this recent publication from the Edinburgh Cancer Centre indicates that after a relatively sharp drop at early time points, disease-specific survival (DSS) and PFS tend to plateau from approximately 6 years after diagnosis.[21] This evidence highlights that if patients remain progression-free for an extended time, their risk of relapse decreases substantially.

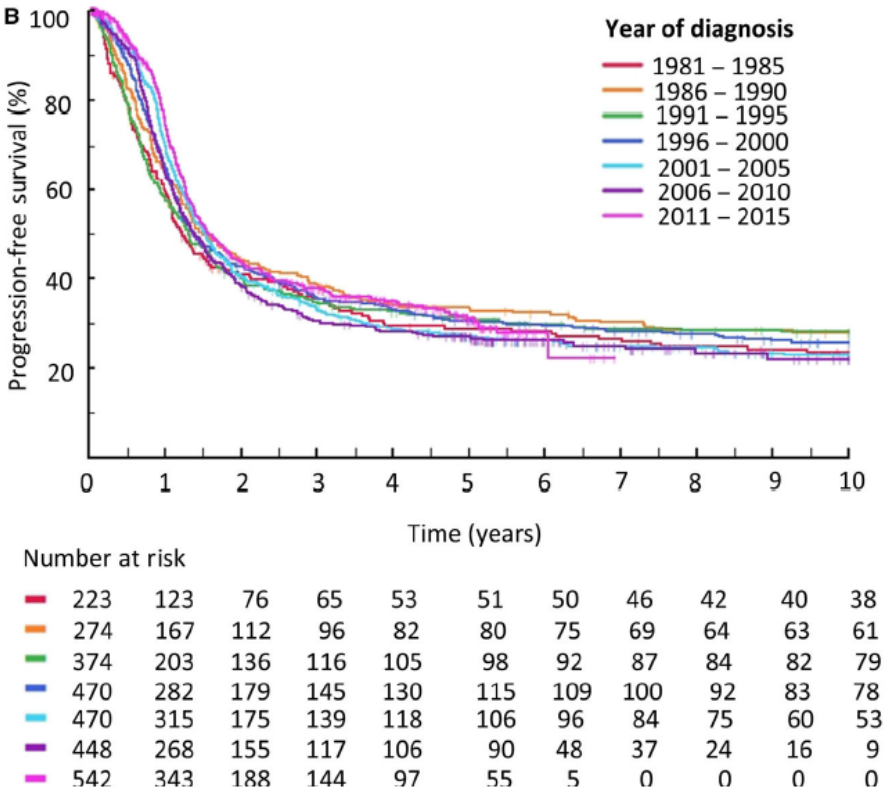
Figure 17: Disease-specific survival rate by year of diagnosis[21]



Number at risk

223	155	97	81	67	63	59	56	52	47	44
275	215	154	120	104	92	84	81	76	72	68
374	261	193	152	131	117	107	99	96	89	84
470	363	273	224	181	158	140	122	111	102	91
470	393	306	240	195	164	143	120	99	82	67
448	365	282	210	167	128	75	57	44	27	17
541	424	337	243	154	90	22	6	0	0	0

Figure 18: Progression-free survival rate by year of diagnosis[21]



UK expert opinion

Feedback obtained from UK key opinion leaders (KOLs) at an advisory board (April 2020) and through a series of interviews (January – February 2020) indicated that long-term remission could potentially be achieved by all patients regardless of mutation status or the level of residual disease following primary cytoreductive surgery. The consensus obtained from clinicians was that a 7-year time point for long-term remission was a clinically reasonable assumption.

TA598

A long-term remission assumption was modelled in TA598 (olaparib first-line NICE submission). The Company presented evidence which supported a 7-year long-term remission assumption, stating[15]:

- "Expert advice that patients free of progression 5 years after completing 2 years of olaparib therapy are expected to be 'exceptional' responders and considered for discharge to primary care"

- "Relapse of 5 years of disease-free survival is rare in ovarian cancer[22]"
- "Data from the Edinburgh Ovarian Cancer Database suggest that the rate of relapse following diagnosis of ovarian cancer reduces to zero at approximately 7-8 years"

Mixture cure model

The Company acknowledge that a mixture cure model (MCM) may provide a robust modelling approach when considering a subset of patients that are deemed 'cured'. However, due to the lack of long-term patient-level data available from PRIMA or access to patient level data from real world sources (for example from the University of Edinburgh Ovarian Cancer Database) to inform an endogenously estimated trajectory of patients 'cured' within an MCM model, this modelling approach is currently not feasible.

Considering the evidence presented above to support a long-term remission assumption, the current modelling approach adopted by the Company makes best use of the available evidence and is appropriate to the decision problem.

B6. Priority question. Please provide an option in the model to remove the weighting of the OS curve by cured and non-cured patients (i.e. to have a standard parametric OS curve) for both treatment arms. Please make this option flexible so that it can be combined with the request in question B2 and B4.

Response:

A scenario to turn off the long-term remission assumption (i.e. remove the weighting of the OS curve by cured and non-cured patients) is already included within the economic model. Please see cell "='Clinical Inputs'!cure_switch". To model the OS curves for both niraparib and routine with no long-term remission assumption this switch should be set to "No". This switch is usable for all scenarios programmed into the model, including that requested in B4. Please refer to the response to question B2 for the rationale as to why extrapolating the niraparib OS KM data from PRIMA was deemed not appropriate.

B7. Priority question. Please provide an option in the economic model for the MA population, where only the NVRD HR is applied to generate NVRD curves, but a HR of 1 is assumed for the treatment effect (i.e. please assume no treatment effect for niraparib across NVRD and RD patients).

Response:

An option has been provided in the model 'Clinical Inputs' sheet to use the 'NVRD effect' only, with a HR of 0.49. This HR was calculated from the PAOLA-1 study and estimates the difference in PFS between the Stage III NVRD group and the Stage III/IV patients with VRD in the placebo plus bevacizumab treatment arm. This HR excludes the additional improvement in PFS that treatment with a PARP inhibitor has on patients with NVRD, as demonstrated by a lower HR of 0.34 when comparing the treatment arms. As such, assuming no treatment effect for niraparib potentially underestimates the treatment effect in patients with NVRD. Please refer to Appendix 1 for scenario analyses results.

B8. Priority question. Please provide a tabular comparison of point survival estimates (using landmarks of 1; 2; 3; 5; 10; 20; 30 years) for:

a) **The modelled ITT RS PFS curves (i.e. the generalised gamma with the cure approach used in the model) compared with**

   i. **PFS KM data from PRIMA;**

   ii. **Eight-year follow up PFS data from the CHORUS trial[23] for the group randomised to primary surgery followed by six cycles of chemotherapy;**

   iii. **The modelled MA RS PFS curves (i.e. the generalised gamma with the cure approach used in the model).**

b) **The modelled ITT niraparib PFS curves (i.e. the generalised gamma with the cure approach used in the model) compared with**

   i. **PFS KM data from PRIMA;**

ii. **PFS data reported in other available niraparib studies even if not in the right treatment line (for example the NOVA study);**

iii. **PFS data reported in SOLO-1 (assuming a class effect across niraparib and olaparib) and with the caveat that SOLO-1 was conducted in BRCA+ patients;**

iv. **The modelled MA niraparib PFS curves (i.e. the generalised gamma with the cure approach used in the model).**

c) **The modelled ITT RS OS curve (i.e. estimated with the log-logistic model and with the cure approach used to estimate the curves described in question B5) compared with**

i. **The OS RS curve requested in question B6;**

ii. **OS KM data from PRIMA;**

iii. **Eight-year follow up OS data from the CHORUS trial for the group randomised to primary surgery followed by six cycles of chemotherapy;**

iv. **The modelled MA RS OS curve (i.e. estimated with the log-logistic model and with the cure approach).**

i. **The OS niraparib curve requested in question B6 (combined with the company's base);**

d) **The modelled ITT niraparib OS curve (i.e. estimated with the ∆PFS:∆OS ratio and the log-logistic model, with the cure approach used to estimate the curves described in question B5) compared with**

ii. **The OS niraparib curve requested in question B6 (combined with B2);**

iii. **OS KM data from PRIMA;**

iv. **OS data reported in other available niraparib studies even if not in the right treatment line (for example the NOVA study);**

v. **OS data reported in SOLO-1 (assuming a class effect across niraparib and olaparib) and with the caveat that SOLO-1 was conducted in BRCA+ patients;**

vi. **The modelled MA niraparib OS curve (i.e. estimated with the ∆PFS:∆OS ratio and the log-logistic model and with the cure approach).**

Response Part a:

The requested RS PFS data are presented in Table 9. It is noted that PFS observed in the primary surgery cohort of the CHORUS trial are lower than the observed PRIMA KM data or modelled PFS estimates presented. The Company would like to draw the ERG's attention to the authors of the CHORUS trial acknowledgement that patients in the CHORUS study had less than expected OS. The authors propose the lower survival in comparison to other trials be attributed to the higher age, high proportion of patients with poorly differentiated tumours and lower performance status scores of patients in the CHORUS trial. The authors acknowledge that the trial assessed "a group of patients with more adverse prognostic features than in other clinical trials".[23] The CHORUS trial has also been criticised due to the low number of patients in whom surgery achieved complete cytoreduction at immediate primary surgery; debulking to less than 1cm of residual disease was achieved in 41.6% of the patients in CHORUS. Therefore, the RS PFS observed in PRIMA and estimated in the model should not be compared closely with the PFS observed in CHORUS.

Table 9: Routine surveillance progression-free survival at landmark points

Data set	Proportion progression-free at year:						
	1	2	3	5	10	20	30
Modelled RS ITT population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RS KM from PRIMA ITT	34.8%	22.5%	-	-	-	-	-
Modelled RS MA population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHORUS (primary surgery) – digitised from published KM[23]	43.9%	15.3%	13.3%	8.2%	N/A	N/A	N/A

Abbreviation: ITT, intention-to-treat; KM, Kaplan Meier; MA, marketing authorisation; RS: routine surveillance

Response Part b:

The requested niraparib PFS data are presented in Table 10. Data are unavailable for the NOVA trial overall or 'ITT' population as the trial population was randomised into two separate groups (germline mutation breast cancer susceptibility gene [g*BRCA*mut] and non-g*BRCA*mut), therefore PFS data from other niraparib studies are not presented. Presenting data from SOLO-1 was not deemed appropriate as the study enrolled patients with a *BRCA* mutation only (outside the scope of this appraisal), whereas the PRIMA trial enrolled patients regardless of their *BRCA* mutation status. Therefore, the efficacy data of PRIMA and SOLO-1 are not comparable.

Table 10: Niraparib progression-free survival at landmark points

Data set	Proportion progression-free at year:						
	1	2	3	5	10	20	30
Modelled niraparib ITT population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Niraparib KM from PRIMA ITT population	53.2%	31.9%	-	-	-	-	-
Modelled niraparib MA population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ITT, intention-to-treat; KM, Kaplan Meier; MA, marketing authorisation

Response Part c:

The requested ITT RS OS data are presented in Table 11, including survival data from the CHORUS trial. The Company would like to draw the ERG's attention to the authors' comments acknowledging the lower OS observed in the trial when compared with other trials and proposing that poorer outcomes are due to a group of patients with more adverse prognostic features than in other clinical trials, such as higher age and lower performance status scores. Therefore, due to the differences in the patient populations, a comparison should not be made between the outcomes observed in the CHORUS study and those observed in PRIMA or modelled as part of this submission.[16]

Table 11: Routine surveillance overall survival data at landmark points

Data set	Proportion alive at year:						
	1	2	3	5	10	20	30
Modelled RS OS in the ITT population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RS OS curve with no long-term remission assumption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RS OS KM from PRIMA ITT population	[redacted]	[redacted]	-	-	-	-	-
Modelled RS OS in the MA population with long-term remission assumption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHORUS OS (primary surgery cohort) – digitised from published KM[23]	69.4%	47.3%	31.9%	15.8%	-	-	-

Abbreviations: ITT, intention-to-treat; KM, Kaplan Meier; MA, marketing authorisation; OS, overall survival; RS, routine surveillance

Response Part d:

The requested niraparib OS data are presented in Table 12. The OS data observed in the PRIMA trial is highly immature (~11%) and as such, it cannot be used to extrapolate long-term survival within the model [please see response to B1 and B2]. Therefore, the data requested in parts i) and ii) have not been presented. Mature OS KM data from the NOVA trial are not available yet, therefore it is not possible to present the requested data. Furthermore, a like-for-like for comparison between the PRIMA and NOVA trials would not be possible because the NOVA trial randomised patients into two separate groups (g*BRCA*mut and non-g*BRCA*mut) as opposed to an overall ITT population. OS data from SOLO-1 would be inappropriate to compare to PRIMA, as there are prognostic differences between the *BRCA*mut and ITT populations, and the subgroup data in SOLO-1 is outside the scope of this appraisal.

Table 12: Niraparib overall survival data at landmark points

Data set	Proportion alive at year:						
	1	2	3	5	10	20	30
Modelled niraparib OS in the ITT population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Niraparib OS KM from PRIMA ITT population	[redacted]	[redacted]	-	-	-	-	-
Modelled niraparib OS in the MA population (base case curve with mean ΔPFS:ΔOS relationship)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ITT, intention-to-treat; KM, Kaplan Meier; MA, marketing authorisation; OS, overall survival; PFS, progression-free survival; N/A, not available

B9. Priority question. With regards to PFS2 data in PRIMA, please

a) **Provide a clinical rationale for the results obtained in the PFS2 analysis (Figure 14.2.3.1 in the clinical study report [CSR]) showing [redacted]. Please discuss the possible relationship between PFS2 outcomes; subsequent treatments received in the trial; and time to first subsequent treatment received;**

b) **Provide the KM data shown in Figure 14.2.3.1 in the economic model, together with the number of patients at risk;**

c) **Please consider including PFS2 data in the model as to fully capture the effect of second progression events on patients' quality of life. The ERG notes that if the company has a strong clinical rationale to justify the [redacted], more flexible modelling options (such as piecewise models) could be applied to fit PFS2 curves. If this approach is not followed, please discuss the implications of not explicitly modelling PFS2 (with a focus on capturing patients' QoL).**

Response:

a) As of the data cut-off of 17 May 2019 for reporting, in the overall population, [redacted]% of niraparib treated subjects and [redacted]% of placebo treated subjects were censored; as such, the data maturity is only 20%[24], and all conclusions from PFS2 are preliminary. The survival distribution KM curve for niraparib for PFS2 was consistently above that of placebo until Month 24 when they crossed over, which is a reflection of the immaturity of the data. At 24 months, only [redacted] and [redacted] patients were at risk in the niraparib and placebo treatment arms, respectively.

   In addition, the median follow-up time on the study was 13.8 months, after which the tails of the curves become unstable and therefore PFS2 based on the current data cut should not be considered a true reflection of long-term outcomes.

b) PFS2 data from PRIMA is highly immature (20%)[24] and any conclusions based on these data would be unreliable. As such, PFS2 KM data has not been incorporated into the economic model, however the figures requested during the follow-up discussions with the ERG are included below. Please find the KM curves for the outcomes of PFS, PFS2 and OS separately for the niraparib and the placebo arms (Figure 19 and Figure 20) showing that PFS2 is supportive of the OS assumptions.

Figure 19: Niraparib Kaplan-Meier curves for OS, PFS and PFS2 for the ITT population

Abbreviations: ITT, intention-to-treat; KM, Kaplan Meier; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on subsequent therapy

Figure 20: RS Kaplan-Meier curves for OS, PFS and PFS2

Abbreviations: ITT, intention-to-treat; KM, Kaplan Meier; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on subsequent therapy; RS, routine surveillance

c) Whilst developing the economic model, the Company did consider the use of PFS2 to allow explicitly tracking patients on and off second-line treatment in the PD health state. However, as highlighted in Section B.3.2 of the CS the PD health was not split by on and off treatment for the following reasons:

- Subsequent treatments (second-line and third-line) are expected to be relatively similar between the two treatment arms with the exception of the proportion of patients receiving chemotherapy treatment options based on their platinum sensitive status, which is captured in the one-off sum approach.

- The NICE position statement explicitly states that the economic base case should not consider treatment options that are not available through routine commission.[25] The base case considers the use of subsequent PARP inhibitors available through routine commissioning (i.e. olaparib third-line for platinum-sensitive *BRCA*mut patients for patients who have not previously received a PARP therapy). PARPs licensed in second-line

setting are available through the Cancer Drugs Fund (CDF) only and are therefore not included in the base case. As such, only a small proportion of RS patients (<8%) are eligible to receive a PARP within the economic analysis; olaparib third-line maintenance for platinum-sensitive patients with a *BRCA* mutation. This means that between niraparib and RS only a minor difference would be observed in third-line subsequent treatment costs. The introduction of a fourth health state would not help to capture the effect of the third-line treatments, only of those received in second-line.

- Time to event data from PRIMA to explicitly track subsequent treatments is immature. PFS2 data would be used to define second and further subsequent lines of therapy. PFS2 from PRIMA is only 20% mature[24], which is 11% less mature than that observed in SOLO-1 (31% maturity). Therefore, splitting the PD health state by on or off second-line subsequent treatment would have required making further assumptions about the timing and proportion of patients who receive them. Furthermore, the addition of PFS2 would not alleviate any uncertainty that arise around long-term OS assumptions.

- The evidence elicited from ENGOT-OV16/NOVA and Study 19 suggests that the overall use of platinum and non-platinum chemotherapy in third and subsequent lines of therapy is likely to be similar and therefore have a limited impact on the incremental results.[42,43]

Whilst acknowledging the ERG's suggestions of more flexible modelling approaches for PFS2, the Company would like to highlight that these suggestions do not alleviate the issue of immature PFS2 (a key reason as to why the PD health state could not be split by on and off second-line subsequent treatment). Please see response to question B1 for further details.

With respect to a patient's quality of life upon progression, data from the PRIMA trial indicates that patients EuroQoL five dimensions five levels (EQ-5D-5L) utility scores remain relatively stable within the PD health state (~0.8 – please see Table 23). Furthermore, published literature indicates that utilities over subsequent lines of treatment do not decrease considerably (please see CS Table 32 and 33). This

could be credited to patients experiencing a higher quality of life whilst on active treatments, regardless of their therapy line. Splitting the PD health state into on and off second-line subsequent treatment would most likely result in slightly lower utility values being applied as the patient progresses through different subsequent treatment lines. It is anticipated the proportional change in total QALYs in the PD health state would be similar across treatment arms if lower PD utility values were applied (please see illustrative example in Table 13). Therefore, splitting the PD health state and applying different utilities values is not expected to have a large impact on the overall incremental QALYs between niraparib and RS.

Table 13. Impact of lowering the PD utility – illustrative example only

Treatment	Total undiscounted QALYs in the PD health state		Proportional decrease due to lower PD utility
	PD = 0.736	PD = 0.650	
Niraparib	[redacted]	[redacted]	11.3%
RS	[redacted]	[redacted]	11.7%

Abbreviations: PD, progressed disease; QALY, quality adjusted life-year; RS, routine surveillance

B10. Please include the total undiscounted life years underpinning the final ICERs in the model and update the results tables in the company submission (e.g. Table 50 and Table 51) with the undiscounted life year values.

Response:

Please find the undiscounted life years underpinning the final ICERs presented in Table 50 and 51 of the CS presented in Table 14 and Table 15, respectively. Please refer to Appendix 1 for the revised base case results.

Table 14: Base-case results for niraparib versus RS for the anticipated MA population

Technologies	Total costs (£)	Total LYs	Total LYs (undiscounted)	Total QALYs	Total QALYs (undiscounted)	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER versus baseline (£/QALY)
RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,870

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; MA, marketing authorisation; QALYs, quality-adjusted life years; RS, routine surveillance.

Table 15: Base-case results for niraparib versus RS for the ITT population

Technologies	Total costs (£)	Total LYs	Total LYs (undiscounted)	Total QALYs	Total QALYs (undiscounted)	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER versus baseline (£/QALY)
RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,856

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention to treat; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance.

B11. Please confirm if the AIC and BIC statistics reported in tab “Survival Analytics Coefficients”, AW26:BG44 are the correct statistics for the OS curves fitted to the RS arm of PRIMA (reported in Figure 24 of the CS).

Response:

The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics included in the model are the correct statistics for the OS curves fitted to the RS arm of PRIMA. The below AIC and BIC statistics are those resulting from the survival analysis and match the values presented in the model.

Table 16: AIC and BIC statistics for routine surveillance OS

Distribution	Routine surveillance	
	AIC	BIC
Exponential	359.81	363.31
Weibull	344.02	351.03
Gompertz	349.17	356.18
Log-logistic	343.55	350.56
Log-normal	342.27	349.28
Generalised Gamma	344.12	354.64

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival

Health-related quality of life

B12. Priority question. Please include age-related utility decrements using the algorithm published by Ara and Brazier 2010[26]

Response:

The model has been updated to include an age-related utility decrement as requested by the ERG as part of a sensitivity analysis. Using Ara and Brazier’s formula model 1[26], utility decrements due to age were incorporated with a baseline age of 61.

Section 5.3.7 of the NICE methods guide states that in some circumstances adjustments to utility values, for example for age or comorbidities, may be needed.[27] Whilst it is accepted that for some conditions (e.g. long-term chronic conditions), this type of adjustment is justifiable, for OC it is not deemed to be appropriate. The utilities derived from the trial are the most valid source for use in the model as they are derived from patients of different ages with the condition, and so already capture

how quality of life changes during the period observed. The quality of life for people who are long-term responders, where the question of whether or not age-adjustment is appropriate may arise, is characterised by:

- Longer duration of life expectancy
- Achieving long-term remission

There is no reason to cap quality of life for these people: 50% of the population are above the population norm, and for someone in long-term remission there is no evidence to suggest that they should be restricted in terms of their quality of life to the mean. Furthermore, in terms of the EQ-5D domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), patients who achieve long-term remission would not be expected to be limited by any of these domain aspects. This adds further justification as to not restricting the achievable quality of life.

There is also a concern about equality for age and gender should this approach be used. The population within the submission is older and predominately female and so there may be an equalities issue for these two protected characteristics. When age-adjusted utilities are carried out during NICE submissions they tend to increase the ICER, thus increasing the hurdle to the product being reimbursed in the UK. The decline in utilities with age observed in general population studies is not linear; because of the non-linear relationship of utility, this may disproportionately affect appraisals with an older mean age, making this hurdle even larger. Further, not all submissions apply age-adjustment and so to apply one in this older female population could be of detriment to this population.

Therefore, it was deemed appropriate to not implement age adjusted utilities within the base case. However, this adjustment has been considered in a scenario analysis.

B13. Priority question. For the base-case time point of 7 years, patients still progression-free are assumed to stay progression-free subject to all-cause mortality for the remainder of the time horizon. As a scenario analysis, please

apply general population utilities to these "cured" patients, using the algorithm published by Ara and Brazier 2010.

a) **Please allow this scenario to be run in combination with the alternative cure thresholds already included in the model (e.g. 10 years).**

Response:

Model traces have been adapted to incorporate the age-adjusted utility decrements from Ara and Brazier 2010[26]; this scenario can be run with varying long-term remission assumptions. Please refer to Appendix 1 for scenario analyses results.

B14. Priority question. In the company submission, it states that a "simple descriptive analysis was conducted on the data to estimate the mean utilities for PFD and PD". Please provide more detail on this analysis.

Response:

Patient level EQ-5D-5L data based on the overall ITT population from the PRIMA trial were converted into a weighted health state index by applying a mapping algorithm by van Hout *et al.* 2012[28] which predicted 3L utility values from 5L responses on a UK value set (Dolan *et al.* 1997[29]). The patient and visit mapped utility values were then analysed by health state to estimate summary statistics (e.g. the mean utility value for patients who were progression-free disease (PFD) and PD at time of assessment). These descriptive statistics are presented in Table 31 of the CS. Further statistics are presented in response to question B15.

B15. Priority question. Please provide descriptive statistics for the mapped EQ-5D-3L data captured in PRIMA, including the following at each time point of data collection: mean, median, standard deviation, 95% confidence interval, number of responders, mean age of responders and compliance rate.

Response:

Table 17 below presents descriptive EuroQoL five dimensions three levels (EQ-5D-3L) statistics by time point of data collection as requested by the ERG.

Table 17: Descriptive mapped EQ-5D-3L statistics by time point of data collection

Study visit	Mean	Median	Standard deviation	Mean age of responders	Number of responders	Compliance rate	Lower 95% CI	Upper 95% CI
SCREENING	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 3 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 5 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 7 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 9 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 11 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 13 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 15 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 18 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 21 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 24 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 27 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 30 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
END OF TREATMENT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
POST-TREATMENT PRO ASSESSMENT-WEEK 1 - 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
POST-TREATMENT PRO ASSESSMENT-WEEK 5 - 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
POST-TREATMENT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study visit	Mean	Median	Standard deviation	Mean age of responders	Number of responders	Compliance rate	Lower 95% CI	Upper 95% CI
PRO ASSESSMENT-WEEK 9 - 12								
POST-TREATMENT PRO ASSESSMENT-WEEK 13 - 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
POST-TREATMENT PRO ASSESSMENT-WEEK 25 - 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
POST-TREATMENT PRO ASSESSMENT-WEEK 37 - 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
POST-TREATMENT PRO ASSESSMENT-WEEK 49 - 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
POST-TREATMENT PRO ASSESSMENT-WEEK 61 - 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: CI, confidence interval; PRO, patient reported outcome

B16. Please explain why the impact of adverse events on patients' quality of life is assumed to be one cycle (one month) for all adverse events.

Response:

AEs were incorporated into the model as a one-off decrement on cost and quality of life and applied in the first cycle of the model (applied in columns AE and AV of the niraparib and RS model traces for the first cycle only). As described in Document B (Section B.3.4) this approach was taken under the assumption that AEs are likely to occur very soon after treatment initiation and will only require acute care. It is expected that AEs are managed quickly with either dose reductions or dose interruptions which are captured within the observed dose received in PRIMA (Figure 38 of the CS). Furthermore, this approach is aligned with previous technology appraisals in the maintenance therapy of OC (NICE TA528 and NICE TA598[30,31]). Based on the trial data, niraparib's AE profile has only a small impact on patients' quality of life and overall cost, as such the decision to apply the impact of AEs in the first cycle of treatment was deemed appropriate to the decision problem.

Intervention costs

B17. Priority question. If such data exist, please provide longer follow-up data than the 12-month data provided for the niraparib dose received in PRIMA. If these data are available, please use these in the economic model instead of the assumption of carrying the 12th month observation into the remaining timeframe of the model.

Response:

The niraparib dose received in PRIMA is available until 18 months (Figure 21). The model has been updated to use the additional data. Please refer to Appendix 1 for revised base case results.

Figure 21: Dose level by month of the first 18 months on treatment

Abbreviations: mg, milligram

B18. Priority question. Please provide the clinical rationale for assuming that [redacted] of patients are assumed to continue treatment beyond 3 years.

Response:

Since the current data cut of the PRIMA trial does not provide information on the proportion of patients who would likely still benefit treatment at 3 years, which is the criteria for treatment continuation in the trial protocol, an assumption was made that this number is approximately [redacted]% based on data available from the SOLO-1 trial and feedback from UK clinical experts. This value was tested in scenario analyses to reduce uncertainty around this input.

Disease management

B19. Priority question. The draft SmPC for niraparib recommends weekly heart rate and blood pressure monitoring for the first month, followed by monthly

monitoring for the first year of treatment. Please provide a scenario analysis including the costs associated with these tests.

Response:

As highlighted in the CS (Section B.3.5.) feedback from UK KOLs as well as the preliminary wording of the label indicates that heart rate and blood pressure monitoring would be performed in the home setting, with the recommendation for patients to contact their health care provided in the case of a rise in blood pressure. However, the model has been updated to include the scenario requested by the ERG. Please refer to Appendix 1 for scenario analyses results.

B20. Priority question. Please amend the model so that resource use for the PFS state is incurred in both treatment arms until patients are considered "cured".

a) **Please allow this scenario to be run in combination with the alternative cure thresholds already included in the model (e.g. 10 years).**

Response:

The model has been updated to remove resource use in the PFD health state when patients are deemed cured for both niraparib and RS treatment arms; this option can be run with varying long-term remission assumptions. Please refer to Appendix 1 for revised base case results.

B21. Priority question. Please include a scenario in the model where the resource use for the PFS state of the RS arm consists of: a CT scan every 6 months; outpatients visits every 3 months for the first year of treatment and once every 6 months after that and the same for blood counts. Please apply these costs until patients are considered "cured" in the company's base case and in the alternative cure thresholds already included in the model (e.g. 10 years).

Response:

The model has been updated to include the scenario requested by the ERG; this scenario can be run with varying long-term remission assumptions. Please refer to Appendix 1 for scenario analyses results.

B22. Priority question. Please amend the model (or provide a scenario analysis) so that there is no differentiation between PFS on and off treatment for RS. Please ensure the scenario analysis in Table 44 is amended to reflect this.

Response:

The current base case model settings assume the same resource use for RS for both on and off treatment (Table 18, adapted from Table 43 of the CS). Therefore, a change to the model is not required. Table 44 of the CS is based on UK expert opinion and is considered as a scenario analysis.

Table 18: Base case disease management resource use and unit costs for the RS treatment arm

Intervention	Health state	Outpatient visit Oncology – consultant led (503; Gynaecological Oncology)	CT scan (RD20A)	Complete blood count (DAPS05)	Outpatient visit Oncology – non consultant led (503; Gynaecological Oncology)	Total cost per cycle (£)
Unit cost (£)		£126.91	£83.23	£2.79	£131.01	--
RS	**PFD on treatment**	**0.3**	**0.3**	**0.3**	**0.0**	**£64**
	PFD off treatment	**0.3**	**0.3**	**0.3**	**0.0**	**£64**
	PD	1.0	0.3	0.3	0.0	£153

Abbreviations: CT, computerised tomography; PD, progressed disease; PFD, progression-free disease; RS, routine surveillance

Subsequent treatment

B23. Priority question. Please clarify if 3L+ treatments in PRIMA consisted of chemotherapy agents only (as reported in Table 14.2.6.1a of the CSR).

Response:

Third-line treatments recorded within PRIMA included all follow-up anti-cancer therapies (e.g. PARP and PD-L1 inhibitors), with the exception of hormonal therapy.

B24. Priority question. Please clarify if the treatments reported in Table 14.2.6.2a of the CSR were all given at 2L of therapy. If that is not the case, please provide the summary of treatments given per respective treatment line.

a) **Please clarify which of the treatments reported in Table 14.2.6.2a of the CSR were given as combination therapies and the proportion of patients who received these as combination or single therapies. Also, please clarify which of the treatments in the table were given as maintenance therapy.**

b) **If the treatments reported in Table 14.2.6.2a of the CSR are not all 2L treatments, please model these according to their respective line of treatment in scenario 3 reported in the company submission (i.e. the scenario reflecting subsequent treatments in PRIMA).**

Response:

Data on next anti-cancer therapy by specific treatment reported in Table 14.2.6.2a of the Clinical Study Report (CSR) were not recorded from the sites by line of therapy or by whether they were given as combination or single therapies. As such no further details can be provided. Therefore, it was not possible to update the economic model as requested in part b. In order to alleviate the uncertainty surrounding subsequent treatment a number of scenarios were considered in the analysis (please refer to section B.3.5 of the CS for further details).

B25. Priority question. Based on the CSR Table 14.2.6.1b, please indicate if the proportion of patients in PRIMA who receive 2L chemotherapy are similar or different to what is expected in clinical practice and why.

Response:

Hall *et al.* 2020 reported that in the UK 57% (192/332) of the patients treated with first-line treatment received some form of second-line treatment, with 93% of these patients receiving second-line chemotherapy treatment in some form.[32] Furthermore, the OSCAR study found that the proportion of patients receiving second-line chemotherapy after first-line bevacizumab was 52% at the data cut-off point.[33]

The figures observed in the OSCAR study are considerably higher than what has been observed in the PRIMA trial, but the expectation is that as the data becomes more mature, the results would get closer to what has been observed in the real world setting.

B26. Priority question. When subsequent treatments are informed by PRIMA data, please replace the average of the three PARPis with the proportion who receive each PARPi in PRIMA (see page 2,999 of the CSR and DataStore! R372:S372).

Response:

The model has been updated in line with the change requested by the ERG. Please refer to Appendix 1 for revised base case results.

B27. Priority question. Please update the proportion of patients eligible to receive olaparib as a 3L treatment (7.81%) using the proportion of BRCA+ patients and proportion of platinum-sensitive patients recorded in PRIMA.

Response:

The proportion of platinum-sensitive patients after third-line chemotherapy (i.e. eligible for olaparib maintenance) was not recorded in PRIMA as the data on next anticancer treatment was not explicitly reported by line of therapy (see response to B24). As such it was not possible to update the model as requested, however given the immaturity of the trial data, it would not be a reliable source for such an estimate.

The proportion of platinum-sensitive patients after third-line chemotherapy (31.25%) was based on feedback obtained through UK KOL interviews conducted by GSK in January-February 2020. This proportion was then multiplied by the proportion of patients with a *BRCA* mutation to give the proportion of patients eligible for olaparib third-line maintenance therapy (25% x 31.25% = 7.81%).

B28. Priority question. Please estimate the number of new progression events in both arms of the model in order to calculate the proportion of patients who receive subsequent treatments in every model cycle (and respective costs).

Response:

A switch has been built into the model to allow the proportion of patients who receive subsequent treatments in every model cycle to be estimated based on:

- The number of new progression events OR
- The number of patients entering the PD health state

Please see Appendix 1 for revised base case results.

B29. Priority question. Please explain (and provide a clinical rationale if this is not an error) for why 2L treatments for the niraparib and RS arms, and 3L treatments on the niraparib arm sum to 100%, while these exceed 100% in the 3L RS arm (see Table 38 of the company submission)?

Response:

The Company acknowledge the discrepancy highlighted by the ERG, however, would like to clarify that this is not an error. The percentage of third-line treatments in the RS arm exceeds 100% as these treatments represent both the third-line chemotherapy and third-line maintenance therapy treatments. The third-line chemotherapy treatments (all listed with the exception of poly (ADP-ribose) polymerase inhibitors [PARPi]) sum to 100% and represent the proportion of patients receiving each type of chemotherapy class. PARP maintenance therapy would be given after the completion of third-line chemotherapy; hence patients would receive both chemotherapy and PARP maintenance therapy. As such the total proportions in the RS third-line arm exceed 100%.

The second-line subsequent treatments do not exceed 100% as the base-case analysis includes subsequent PARP treatments available through routine commissioning (i.e. third-line olaparib). As such the second-line subsequent treatment regimens for niraparib and RS consist of chemotherapy treatments only which total 100%.

B30. Priority question. Instead of applying a discount for all second-line PARPis equivalent to the niraparib discount applied in the second-line setting, please use the list prices to inform the cost of olaparib and rucaparib.

a) **Please include a scenario analysis which uses the list price of the cheapest PARPi (olaparib) to inform the cost of olaparib and rucaparib.**

Response:

The model has been updated in line with the change requested by the ERG with the addition for the scenario requested in B30 part a. Please refer to Appendix 1 for revised results.

B31. For olaparib, the cost of a 100 mg tablet pack is the same as a 150 mg tablet pack. Please update the value in Data Store! G372 from 100 to 150.

Response:

The model has been updated in line with the change requested by the ERG. Please refer to Appendix 1 for revised base case results.

B32. Please clarify why the subsequent treatment costs associated with platinum-sensitive patients (DataStore!R345) are used to inform the subsequent treatment costs for all chemotherapy regimens in PRIMA (DataStore!J194).

Response:

The base case assumption applies respective treatment costs to platinum-sensitive and platinum-resistant regimens for the second (DataStore!AQ197:266; DataStore!BB197:266) and third (DataStore!R273:342; DataStore!BB273:342) subsequent treatments. Platinum-sensitive treatment costs (DataStore!R347:377) are an average of all subsequent treatment costs included in the model (DataStore!Q347:377). Platinum-resistant treatment costs (DataStore!S347:377) are

based on an average of treatments used for platinum-resistant patients, based on clinical expert opinion (source GSK KOL interviews January-February 2020).

In relation to the ERG's question, platinum sensitive treatment costs are applied to PRIMA (second-line) and NOVA (third-line) regimens for the purpose of scenario analyses only. This is due to the treatments in PRIMA and NOVA regimens aligning with the treatments considered for platinum-sensitive patients. The base case applies respective costs to the appropriate platinum-sensitive and resistant regimens.

Section C: Textual clarification and additional points

C1. On page 62 of the submission it is stated that "the median time on treatment was [redacted] months and [redacted] months, respectively". Please confirm if this is time on study rather than time on treatment?

a) Please clarify the difference between median time on study and median follow up.

Response:

The numbers highlighted by the ERG refer to the median time on study. Time on study is defined as the duration from first dose date to last contact date/death date (Table 19). Follow-up for PFS is estimated using KM method from randomisation date to last tumor assessment date prior to progression/censoring at the time of progression.

Table 19: Median time on study vs median follow-up

Endpoint	Definition	Niraparib (months)	Placebo (months)
Median follow-up for PFS	Duration from randomisation to last tumour assessment date prior to progression/censoring	13.9	13.7
Median time on study	Duration from first dose to last contract date/death	14.8	14.7

Abbreviations: vs. versus

C2. Please provide the definition of the full analysis set (FAS) population mentioned on page 123 of the submission. Please confirm if the clinical data used in the cost effectiveness analysis were based on the FAS or ITT population of PRIMA.

Response:

The full analysis set (FAS) was mentioned as a synonym for ITT population, it was not defined separately in the trial protocol from the ITT population.

C3. Please provide the KM data underpinning Figure 14.2.4.1 in the CSR.

Response:

Please see below the data requested in Table 20.

Table 20. Time to first subsequent therapy from PRIMA

Parameter	Statistic	Niraparib (N=487)	Placebo (N=246)
Time to First Subsequent Therapy (months) [1] [2]	75th Percentile (95% CI)	NE (NE,NE)	NE (20.3,NE)
	Median (95% CI)	18.6 (15.8,24.7)	12.0 (10.3,13.9)
	25th Percentile (95% CI)	9.1 (7.9,10.2)	6.7 (6.3,7.9)
Survival Distribution Function (SDF) [3]			
6-month		0.90 (0.86,0.92)	0.83 (0.78,0.88)
12-month		0.65 (0.60,0.69)	0.50 (0.43,0.56)
18-month		0.51 (0.45,0.56)	0.39 (0.32,0.46)
24-month		0.44 (0.38,0.51)	0.30 (0.21,0.40)
30-month		0.41 (0.33,0.50)	0.30 (0.21,0.40)
Censored Observations	n (%)	277 (56.9)	108 (43.9)
Event Rate, Overall	n (%)	210 (43.1)	138 (56.1)
p-value [4]		0.0001	
Hazard Ratio, Niraparib: Placebo [5]	HR (95% CI)	0.65 (0.521,0.802)	

[1] Time to first subsequent therapy is defined as the time from the date of randomization to the date of first dose of follow-up anti-cancer treatment or death, whichever occurs first. Patients alive and not starting a first follow-up anti-cancer treatment will be censored at the date last known alive.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on stratified log-rank test using randomization stratification factors: Administration of neoadjuvant chemotherapy (yes/no), best response to platinum therapy (CR or PR), and HRD status (HRDpos or HRDneg/HRDnd for Overall cohort only).
[5] Based on stratified Cox proportional hazards model using randomization stratification factors as above.
Abbreviations: CI, confidence interval; HR, hazard ratio; NE, Not Evaluable.

C4. The ERG found an “if statement” in the model (cure_switch='Data Store'!L15=Off), that can never be TRUE as the cure switch cell can only assume the values “no” or “long term …”. Please ensure that this does not impact the correct implementation of formulae in the model (please check that this has not been repeated outside tab extrapolations, column CK).

Response:

The Company acknowledge the error identified by the ERG and have amended the formula accordingly. This change has no impact on the correct implementation of the formula and hence the model results.

C5. In Table 31 of the company submission, please clarify why there are [redacted] PFD observations in the overall data set and not [redacted]

Response:

The Company acknowledge the discrepancy highlighted by the ERG and would like to confirm that a typographical error is present in Table 31 of the submission for the total number of placebo PFD observations. The total of number of observations is N=[redacted](niraparib [n=[redacted]] + placebo **[n=[redacted]]**)

C6. In Table 31 of the company submission, please clarify why there are [redacted] PD observations in the overall data set and not [redacted].

Response:

The Company acknowledge the discrepancy highlighted by the ERG and would like to confirm that a typographical error is present in Table 31 of the submission for the total number of niraparib PD observations. The total of number of observations is N=[redacted] (niraparib [redacted] + placebo [redacted]).

C7. Please include a worksheet in the model which enables results of the scenario analyses in Table 56 of the company submission to be generated.

Response:

The model has been updated to include a worksheet which enables scenario analyses to be generated.

C8. Please vary the proportion of patients across niraparib dose categories (i.e. Table 36 in the company submission) in PSA.

Response:

The model has been updated in line with the change requested by the ERG. Please refer to Appendix 1 for revised base case results.

C9. Please vary the HRs included in the analysis within their 95% confidence intervals.

Response:

The model has been updated in line with the change requested by the ERG. Please refer to Appendix 1 for revised base case results.

C10. The currency code used to inform the cost of IV chemotherapy administrations (SB15Z) is based on delivering subsequent elements of a chemotherapy cycle. A currency code related to the first infusion of a cycle (SB12Z) would be more appropriate. Please amend this to the appropriate currency code.

Response:

The model has been updated in line with the change requested by the ERG. Please refer to Appendix 1 for revised base case results.

C11. The ERG has identified discrepancies in the end of life cost in the company submission (£7,798 in Table 48 of the company submission and £7,576 on page 180 of the company submission). Please clarify the correct cost in 2018/19 prices and apply this cost in the model. The model infers that the end of life cost has been inflated to 2017/18 prices (see DataStore!F385).

Response:

The Company acknowledge the discrepancy highlighted by the ERG and can confirm that the cost reported in Table 48 of the CS is a typographical error. The end of life cost used in the model is that reported on page 180 (£7,576). This cost was sourced from Guest et al. 2006 and was inflated to a 2018/19 cost year Personal Social Services Research Unit (PSSRU) inflation indices.[34,35] Cell 'DataStore!F385' in the model has been updated to read "Multiplier to 2018/19".

C12. Please clarify the NHS Reference Cost year used to inform AE treatment costs as there are discrepancies in the model (see 'DataSore! B122', B127 and G123). Please ensure NHS Reference Costs for 2018/19 are used where possible.

Response:

The National Health Service (NHS) Reference cost year used to inform the AE treatment costs are presented in Table 21. Where possible the 2018/19 cost year were used, however codes XD25Z and XD26Z are not available in the 2018/19 data set so were soured from the 2017/18 data set and inflated to a 2018/19 cost year. AEs are not a main driver of the model results hence this method was deemed reasonable.

Table 21: Adverse event costs data sources

Code	Source
SA04G	NHS Reference costs 2018/19[36]
SA04H	
SA04J	
SA04K	
SA04L	
SA12G	
SA12H	
SA12J	
SA12K	
EB04Z	
XD25Z	NHS Reference costs 2017/18[37]
XD26Z	

Abbreviations: NHS, National Health Service

C13. Please provide reference [u] in the model.

Response:

The reference [u] stands for a 'user defined input' and does not refer to a specific reference. This is defined on the 'Introduction' sheet of the model in cells J:N31.

C14. Please provide the KOL responses to N.1.8 on Treatment Monitoring.

Response:

The KOL responses from N.1.8 of the GSK interview questions are included within the economic model datastore (cells W141:AP168).

C15. Please correct the denominator used to inform the proportion of patients on bevacizumab treatment in the RS arm from [redacted] to [redacted] (see 'DataStore!D111).

Response:

The Company acknowledge the error highlighted by the ERG and the denominator in 'DataStore!D211' has been updated to [redacted]. This change does not impact the base-case results.

C16. A systematic literature review was conducted to identify cost and resource use data. Please clarify how the results of this review were used to inform cost and resource use data in the model.

Response:

Full details of the cost and resource use systematic literature review (SLR) are provided in Appendix I of the CS. Table 22 details how the results of this SLR were used to inform the base case cost and resource use data in the model.

Table 22: Sources for base-case cost and resource use data in the model

Category	Source	Identified in SLR
Treatment acquisition costs (maintenance and subsequent chemotherapy)	British National Formulary 2020	N/A Appropriate data source for the decision problem
Subsequent treatment resource use	UK expert opinion	N/A UK expert opinion were deemed an appropriate choice for subsequent chemotherapy regimens
Disease management unit costs	NHS Reference Costs 2018/19	Yes – code selection for unit costs were based on TA598 which was identified in the SLR[30]
Disease management resource use	TA598	Yes
AE unit costs	NHS Reference costs 2017/18 and 2018/19	Yes – code selection for AE costs were based on methods adopted in TA528 and TA598 which was identified in the SLR[30,31]
Terminal care unit cost and resource	Guest et al. 2006[38] Gao et al. 2013[39]	Yes – Guest et al. and Gao et al. were referenced within TA598 and TA528 (Guest et al. only) which were both identified in the SLR.[30,31]

Abbreviations: AE, adverse events; NHS, National Health Service; N/A, not applicable; SLR, systematic literature review; TA, technology appraisal; UK, United Kingdom

C17. On page 59 of the company submission it states “the US value set was used”:

a) Please provide the reference for this value set

b) Please explain why a US value set was used instead of a UK value set

c) Please provide the adjusted mean EQ-5D values and associated standard errors by study visit in the ITT population (i.e. the equivalent of Figure 12) using the value set for England published by Devlin et al. 2010.[8]

Response:

The United States (US) value set available from EuroQoL (EQ-5D-5L Crosswalk value sets) was used for the EQ-5D-5L data analysis in the CSR, developed in the US.[40] Table 23 provides the adjusted means and associated standard error (SE) for

the EQ-5D-5L index values by study visit in the ITT population, based on the value set for England published by Devlin *et al*. 2018.[41]

For the purpose of the economic model, utilities were based on EQ-5D-5L values mapped to the EQ-5D-3L and valued using the weights published by Dolan *et al.* 1997 (appropriate for the decision problem).[29] Please refer to Table 31 of the CS.

Table 23: Mean EQ-5D-5L and standard error by study visit for the ITT population based on the value set for England (Devlin et al. 2018)[41]

Study visit	Niraparib		Placebo		Overall	
	Mean	SE	Mean	SE	Mean	SE
SCREENING	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 3 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 5 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 7 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 9 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 11 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 13 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 15 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 18 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 21 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 24 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 27 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 30 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ITT, intention-to-treat; SE, standard error

References

1. Morris TP, Jarvis CI, Cragg W, *et al.* Proposals on Kaplan-Meier plots in medical research and a survey of stakeholder views: KMunicate. *BMJ Open* 2019. 9: e030215.
2. Perren TJ, Swart AM, Pfisterer J, *et al.* A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med* 2011. 365: 2484–2496.
3. Oza A.M., Cook A.D., Pfisterer J., *et al.* Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): Overall survival results of a phase 3 randomised trial. *Lancet Oncol* 2015. 16: 928–936.
4. Janavičius R. Founder BRCA1/2 mutations in the Europe: implications for hereditary breast-ovarian cancer prevention and control. *EPMA J* 2010. 1: 397–412.
5. Chetrit A, Hirsh-Yechezkel G, Ben-David Y, *et al.* Effect of BRCA1/2 Mutations on Long-Term Survival of Patients With Invasive Ovarian Cancer: The National Israeli Study of Ovarian Cancer. *J Clin Oncol* 2008. 26: 20–25.
6. Moschetta M, George A, Kaye SB, *et al.* BRCA somatic mutations and epigenetic BRCA modifications in serous ovarian cancer. *Ann Oncol Off J Eur Soc Med Oncol* 2016. 27: 1449–1455.
7. Harter P, Mouret-Reynier M-A & Pignata S. Phase III PAOLA-1/ENGOT-ov25: maintenance olaparib with bevacizumab in patients with newly diagnosed, advanced ovarian cancer treated with platinum-based chemotherapy and bevacizumab as standard of care. 2019. at <https://oncologypro.esmo.org/meeting-resources/esmo-2019-congress/Phase-III-PAOLA-1-ENGOT-ov25-trial-Olaparib-plus-bevacizumab-bev-as-maintenance-therapy-in-patients-pts-with-newly-diagnosed-advanced-ovarian-cancer-OC-treated-with-platinum-based-chemotherapy-PCh-plus-bev>
8. González-Martín A, Pothuri B, Vergote I, *et al.* Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med* 2019. 0: null.
9. du Bois A, Reuss A, Pujade-Lauraine E, *et al.* Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). *Cancer* 2009. 115: 1234–1244.
10. Ovarian cancer survival statistics. *Cancer Research UK* 2015. at <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/survival>
11. Moore K., Colombo N., Scambia G., *et al.* Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2018. 379: 2495–2505.
12. Mathews CA, Moore KN, Colombo N, *et al.* Maintenance olaparib after platinum-based chemotherapy in patients (pts) with newly diagnosed advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): Efficacy by surgical and tumor status in the Phase III SOLO1 trial. Poster presented at the ASCO Annual Meeting, Chicago, USA on May 31–June 4, 2019. *J Clin Oncol* 2019. 37: 5541–5541.
13. Ray-Coquard IL, Pautier P, Pignata S, *et al.* PAOLA-1/ENGOT-ov25 trial: Phase III Olaparib plus bevacizumab (bev) as maintenance therapy in patients with newly diagnosed, advanced ovarian cancer (OC) treated with platinum-based chemotherapy (PCh) plus bev. *Ann Oncol* 2019. 30:
14. Mirza MR. A randomized, double-blind phase 3 trial of maintenance therapy with niraparib vs placebo in patients with platinum-sensitive reucurrent ovarian can... ESMO

2016 Congress | OncologyPRO. 2016. at <https://oncologypro.esmo.org/Meeting-Resources/ESMO-2016/A-randomized-double-blind-phase-3-trial-of-maintenance-therapy-with-niraparib-vs-placebo-in-patients-with-platinum-sensitive-recurrent-ovarian-cancer-ENGOT-OV16-NOVA-trial>
15. Overview | Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy | Guidance | NICE. at <https://www.nice.org.uk/guidance/ta598>
16. NICE. NICE. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer. 2018. at <https://www.nice.org.uk/guidance/ta528/documents/final-appraisal-determination-document>
17. Davis S, Tappenden P & Cantrell A. *A Review of Studies Examining the Relationship between Progression-Free Survival and Overall Survival in Advanced or Metastatic Cancer*. (National Institute for Health and Care Excellence (NICE), 2012). at <http://www.ncbi.nlm.nih.gov/books/NBK425826/>
18. Bullement A, Cranmer HL & Shields GE. A Review of Recent Decision-Analytic Models Used to Evaluate the Economic Value of Cancer Treatments. *Appl Health Econ Health Policy* 2019. 17: 771–780.
19. Othus M, Bansal A, Koepl L, *et al.* Accounting for Cured Patients in Cost-Effectiveness Analysis. *Value Health J Int Soc Pharmacoeconomics Outcomes Res* 2017. 20: 705–709.
20. NICE. Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer | Guidance | NICE. 2019. at <https://www.nice.org.uk/guidance/ta611>
21. Anushka I, Rye T & Churchman M. Patterns of clinicopathological features and outcome in epithelial ovarian cancer patients: 35 years of prospectively collected data. *Int J Obstretics Gynaecol* 2020. at <https://obgyn.onlinelibrary.wiley.com/doi/10.1111/1471-0528.16264>
22. Rubin SC, Randall TC, Armstrong KA, *et al.* Ten-year follow-up of ovarian cancer patients after second-look laparotomy with negative findings. *Obstet Gynecol* 1999. 93: 21–24.
23. Kehoe S, Hook J, Nankivell M, *et al.* Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *The Lancet* 2015. 386: 249–257.
24. Han SN, Monk BJ & Gonzalez-Martin A. Time to first subsequent therapy (TFST) and progression-free survival 2 (PFS2) from the phase 3 randomized, double-blind PRIMA/ENGOT-OV26/GOG-3012 study in patients with newly diagnosed ovarian cancer. in (SGO, 2020). at <https://www.sgo.org/wp-content/uploads/2020/03/SGO-2020-Annual-Meeting-Oral-Abstracts.pdf>
25. NICE. Position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product. 2019. at <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/cancer-drugs-fund/CDF-comparator-position-statement.pdf>
26. Ara R & Brazier J. Populating an economic model with health state utility values: moving towards better practice. *Value Health* 2010. 37.
27. NICE. Guide to the methods of technology appraisal. 2013. at <https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781>

28. van Hout B, Janssen MF, Feng Y-S, *et al.* Interim Scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L Value Sets. *Value Health* 2012. 15: 708–715.
29. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997. 35: 1095–1108.
30. Overview | Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy | Guidance | NICE. at <https://www.nice.org.uk/guidance/ta598>
31. NICE. NICE. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer. 2018. at <https://www.nice.org.uk/guidance/ta528/documents/final-appraisal-determination-document>
32. Hall JP, Chang J, Moon R, *et al.* Real-world treatment patterns in patients with advanced (stage III-IV) ovarian cancer in the USA and Europe. *Future Oncol Lond Engl* 2020. 16: 1013–1030.
33. Hall M, Bertelli G, Li L, *et al.* Role of front-line bevacizumab in advanced ovarian cancer: the OSCAR study. *Int J Gynecol Cancer Off J Int Gynecol Cancer Soc* 2020. 30: 213–220.
34. Unit Costs of Health and Social Care 2019 | PSSRU. at <https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/>
35. Guest JF, Ruiz FJ, Greener MJ, *et al.* Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. *Eur J Cancer Care (Engl)* 2006. 15: 65–73.
36. NHS Improvement. NHS Reference Costs 2018/19. 2020. at <https://improvement.nhs.uk/resources/national-cost-collection/>
37. NHS Improvement. NHS Reference Cost 2017/18. at <https://improvement.nhs.uk/resources/reference-costs/>
38. Guest J.F., Ruiz F.J., Greener M.J., *et al.* Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. *Eur J Cancer Care (Engl)* 2006. 15: 65–73.
39. Gao W, Ho YK, Verne J, *et al.* Changing patterns in place of cancer death in England: a population-based study. *PLoS Med* 2013. 10: e1001410.
40. Crosswalk Index Value Calculator – EQ-5D. at <https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/>
41. Devlin NJ, Shah KK, Feng Y, *et al.* Valuing health-related quality of life: An EQ-5D-5L value set for England. *Health Econ* 2018. 27: 7–22.

Appendix 1 – Revised base case results

The changes to the Company base case as a result of the ERG questions are presented in Table 24.

Table 24: Changes to Company base case following ERG questions

Category	Original base-case	Revised base-case	ERG question
Treatment costs	PRIMA observed dose up to Month 12	PRIMA observed dose up to Month 18	B17
Resource use	Monitoring continued after patients are deemed to be in long-term remission	Monitoring stopped once patients are deemed in long-term remission	B20
Subsequent treatment	Average of PARPi treatment costs	Weighted average by proportions in PRIMA trial by treatment costs	B26
Subsequent treatment	Number of patients receiving subsequent treatment based on proportion entering the PD health state	Number of patients receiving subsequent treatment based on proportion leaving the PF health state	B28
Subsequent treatment	CDF discount price on PARPi (olaparib and rucaparib)	List price on PARPi (olaparib and rucaparib)	B30
Subsequent treatment	100 mg tablets for olaparib	150 mg tablets for olaparib	B31
Subsequent treatment	Administration code SB15Z	Administration code SB12Z	C10
Subsequent treatment	Denominator n=346 in cell DataStore!D211	Denominator n=246 in cell DataStore!D211	C15

Abbreviations: CDF, Cancer Drugs Fund; ERG, Evidence Review Group; HRQoL, health-related quality of life; mg, milligram; PARPi, PARP inhibitor; PD, progressed disease; PF, progression-free

Base-case incremental cost-effectiveness analysis results

MA population

Total costs, life years (LYs), quality adjusted life-years (QALYs), and incremental cost per QALY gained for niraparib versus RS for the anticipated MA population for niraparib are presented in Table 25. In the base case analysis, niraparib generates [redacted] incremental QALYs and £[redacted] incremental costs over a lifetime horizon compared with RS, resulting in an ICER of £13,456 per QALY gained.

ITT population

The results from the ITT population is presented can be used to give increased confidence in the MA population results, as the ICER for the MA population was seen to be more cost effective than for the ITT population. The total costs, LYs, QALYs, and incremental cost per QALY gained for niraparib versus RS for the ITT are presented in Table 26. In the base case analysis, niraparib generates [redacted] incremental QALYs and £[redacted] incremental costs over a lifetime horizon compared with RS, resulting in an ICER of £18,689 per QALY gained.

Table 25: Base-case results for niraparib versus RS for the anticipated MA population

Technologies	Total costs (£)	Total LYs	Undiscounted total LYs	Total QALYs	Undiscounted total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER versus baseline (£/QALY)
RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,456

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance.

Table 26: Base-case results for niraparib versus RS for the ITT population

Technologies	Total costs (£)	Total LYs	Undiscounted total LYs	Total QALYs	Undiscounted total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER versus baseline (£/QALY)
RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,689

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention to treat; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance.

Base-case disaggregated results

MA population

A summary of the QALYs by health state for the MA population is presented in Table 27. It can be observed that the largest QALYs for both niraparib and RS were in the PFD health state. The incremental QALYs (niraparib versus [vs.] RS) were evenly distributed across health states, with a marginal higher proportion in the PFD health state.

Table 27: Summary of QALYs by health state for the anticipated MA population

Health state	Niraparib	RS	Increment	% increment
PFD	[redacted]	[redacted]	[redacted]	52
PD	[redacted]	[redacted]	[redacted]	48
Total	[redacted]	[redacted]	[redacted]	100

Abbreviations: MA, marketing authorisation; PFD, progression-free disease; PD, progressed disease; QALY, quality-adjusted life year.

A summary of the costs by health state for the MA population is presented in Table 28. As expected, the largest proportion of costs was accrued in the PFD health state for niraparib and in the PD health state for RS. Niraparib is also associated with incremental PD costs and reduced terminal care costs as patients are expected to live longer.

Table 28: Summary of costs by health state for the anticipated MA population

Health state	Niraparib (£)	RS (£)	Increment (£)	% increment
PFD	[redacted]	[redacted]	[redacted]	99
PD	[redacted]	[redacted]	[redacted]	2
Dead	[redacted]	[redacted]	[redacted]	-1
Total costs	[redacted]	[redacted]	[redacted]	100

Abbreviations: MA, marketing authorisation; PFD, progression-free disease; PD, progressed disease.

A summary of the costs by category for the MA population is presented in Table 29. Treatment costs account for largest incremental costs between niraparib and RS. These were followed by disease management costs.

Table 29: Summary of costs by category for the anticipated MA population

Cost category	Niraparib (£)	RS (£)	Increment (£)	% increment
Treatment costs	[redacted]	[redacted]	[redacted]	92
Disease management costs	[redacted]	[redacted]	[redacted]	15
Subsequent treatment costs	[redacted]	[redacted]	[redacted]	-6
Adverse event costs	[redacted]	[redacted]	[redacted]	1
Total costs	[redacted]	[redacted]	[redacted]	100

Difference in totals may be due to rounding.

ITT population

A summary of the QALYs by health state for the ITT population is presented in Table 30. It can be observed that the largest QALY gains for both niraparib and RS were in the PFD health state. The incremental QALYs (niraparib vs. RS) were evenly distributed across health states, with a marginal higher proportion in the PFD health state.

Table 30: Summary of QALYs by health state for the ITT population

Health state	Niraparib	RS	Increment	% increment
PFD	[redacted]	[redacted]	[redacted]	55
PD	[redacted]	[redacted]	[redacted]	45
Total	[redacted]	[redacted]	[redacted]	100

Abbreviations: MA, marketing authorisation; PFD, progression-free disease; PD, progressed disease; QALY, quality-adjusted life year.

A summary of the costs by health state for the ITT population is presented in Table 31. As expected, the largest proportion of costs was accrued in the PFD health state for niraparib and in the PD health state for RS. Niraparib is also associated with incremental PD costs and reduced terminal care costs as patients are expected to live longer.

Table 31: Summary of costs by health state for the ITT population

Health state	Niraparib (£)	RS (£)	Increment (£)	% increment
PFD	[redacted]	[redacted]	[redacted]	103
PD	[redacted]	[redacted]	[redacted]	-2
Dead	[redacted]	[redacted]	[redacted]	-1
Total costs	[redacted]	[redacted]	[redacted]	100

Abbreviations: MA, marketing authorization; PFD, progression-free disease; PD, progressed disease.

A summary of the costs by category for the ITT population is presented in Table 32. Treatment costs account for largest incremental costs between niraparib and RS. These were followed by disease management costs.

Table 32: Summary of costs by category for the ITT population

Cost category	Niraparib (£)	RS (£)	Increment (£)	% increment
Treatment costs	[redacted]	[redacted]	[redacted]	96
Disease management costs	[redacted]	[redacted]	[redacted]	12
Subsequent treatment costs	[redacted]	[redacted]	[redacted]	-8
Adverse event costs	[redacted]	[redacted]	[redacted]	1
Total costs	[redacted]	[redacted]	[redacted]	100

Difference in totals may be due to rounding.

Sensitivity analyses

Probabilistic sensitivity analysis

MA population

Total costs, LYs, QALYs, and incremental cost per QALY gained for niraparib versus RS for the anticipated MA population for niraparib generated through a PSA are presented in Table 33. In the PSA, niraparib generates [redacted] incremental QALYs and £[redacted] incremental costs over a lifetime horizon compared with RS, resulting in an ICER of £13,882 per QALY gained. The corresponding ICEP, CEAC and CEAF are presented in Figure 22 to Figure 24, respectively. At a willingness to pay (WTP) threshold of £30,000 niraparib had a 100% probability of being cost-effectiveness compared to RS in the MA population.

ITT population

Total costs, LYs, QALYs, and incremental cost per QALY gained for niraparib versus RS for the ITT generated through a PSA are presented in Table 34. In the PSA, niraparib generates [redacted] incremental QALYs and £[redacted] incremental costs over a lifetime horizon compared with RS, resulting in an ICER of £18,419 per QALY gained. The corresponding ICEP, CEAC and CEAF are presented in Figure 25 to Figure 27, respectively. At a WTP threshold of £30,000 niraparib had a 96.3% probability of being cost-effectiveness compared to RS in the ITT population.

Table 33: PSA results for niraparib versus RS for the anticipated MA population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£) (SD)	Incremental QALYs (SD)	ICER versus baseline (£/QALY)
RS	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	13,882

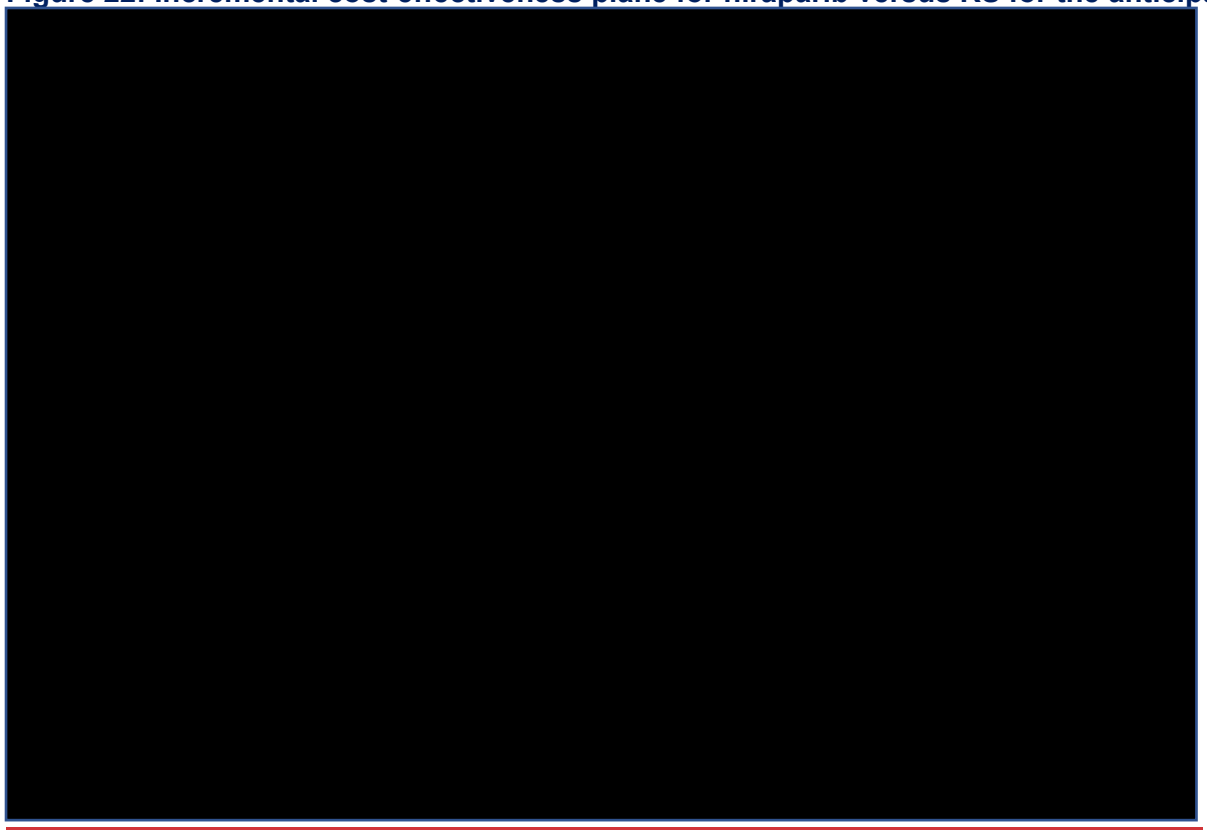
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analyses; QALYs, quality-adjusted life years; RS, routine surveillance.

Table 34: PSA results for niraparib versus RS for the ITT population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£) (SD)	Incremental QALYs (SD)	ICER versus baseline (£/QALY)
RS	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	18,419

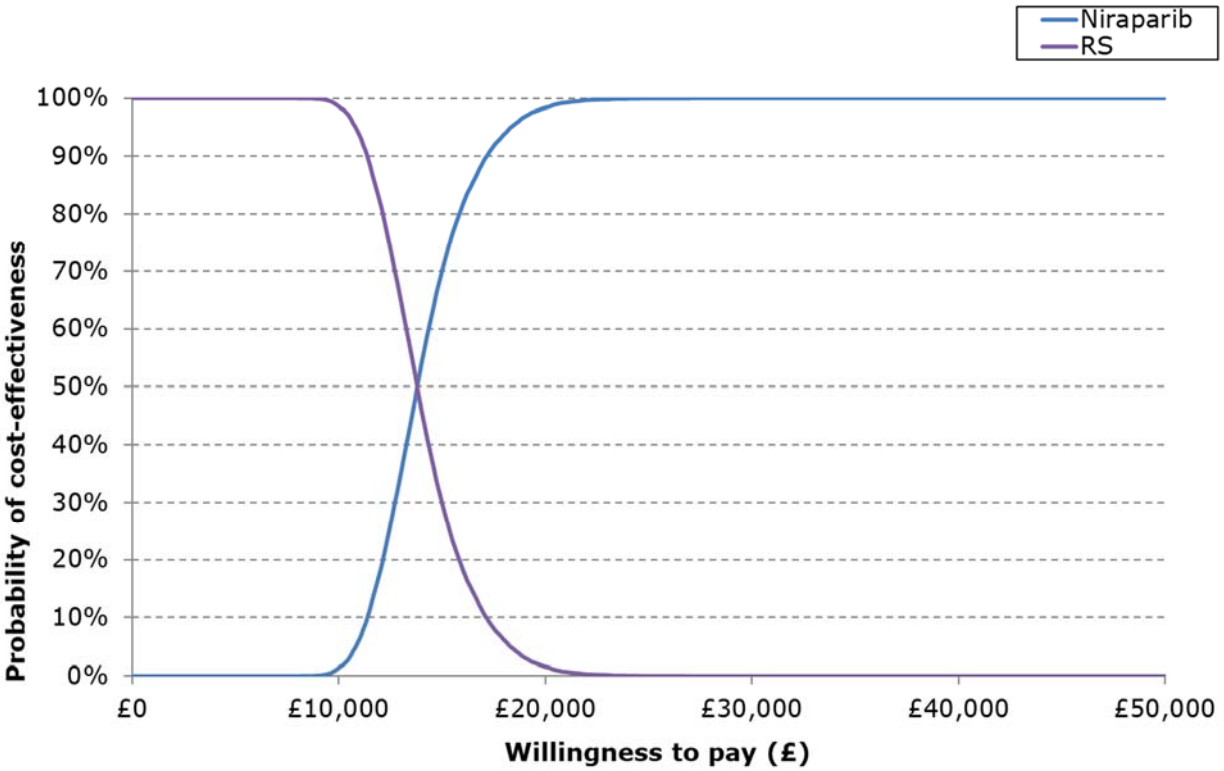
Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention to treat; LYG, life years gained; PSA, probabilistic sensitivity analyses; QALYs, quality-adjusted life years; RS, routine surveillance.

Figure 22: Incremental cost-effectiveness plane for niraparib versus RS for the anticipated MA population (10,000 iterations)



Abbreviations: QALYs, quality-adjusted life years; RS, routine surveillance

Figure 23:_Cost-effectiveness acceptability curve for niraparib versus RS for the anticipated MA population (10,000 iterations)*

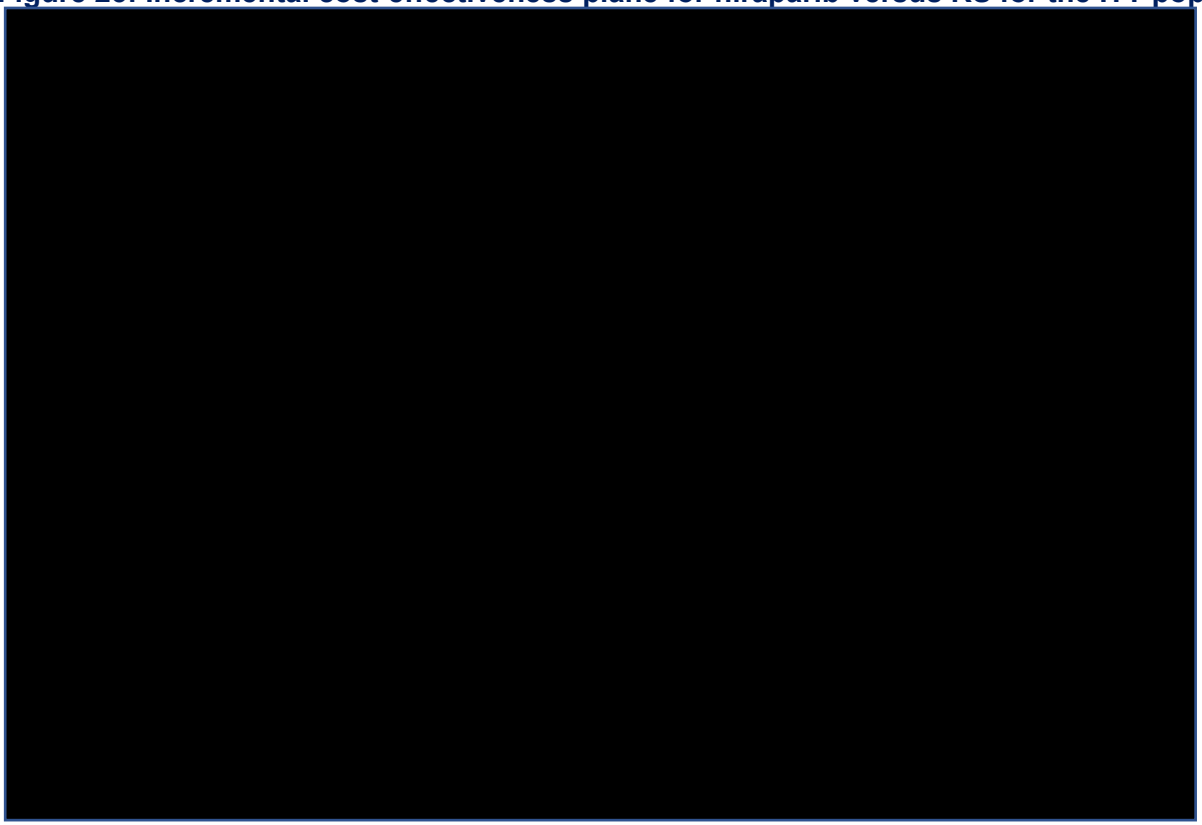


Abbreviations: RS, routine surveillance

Figure 24: Cost-effectiveness acceptability frontier for niraparib versus RS for the anticipated MA population (10,000 iterations)

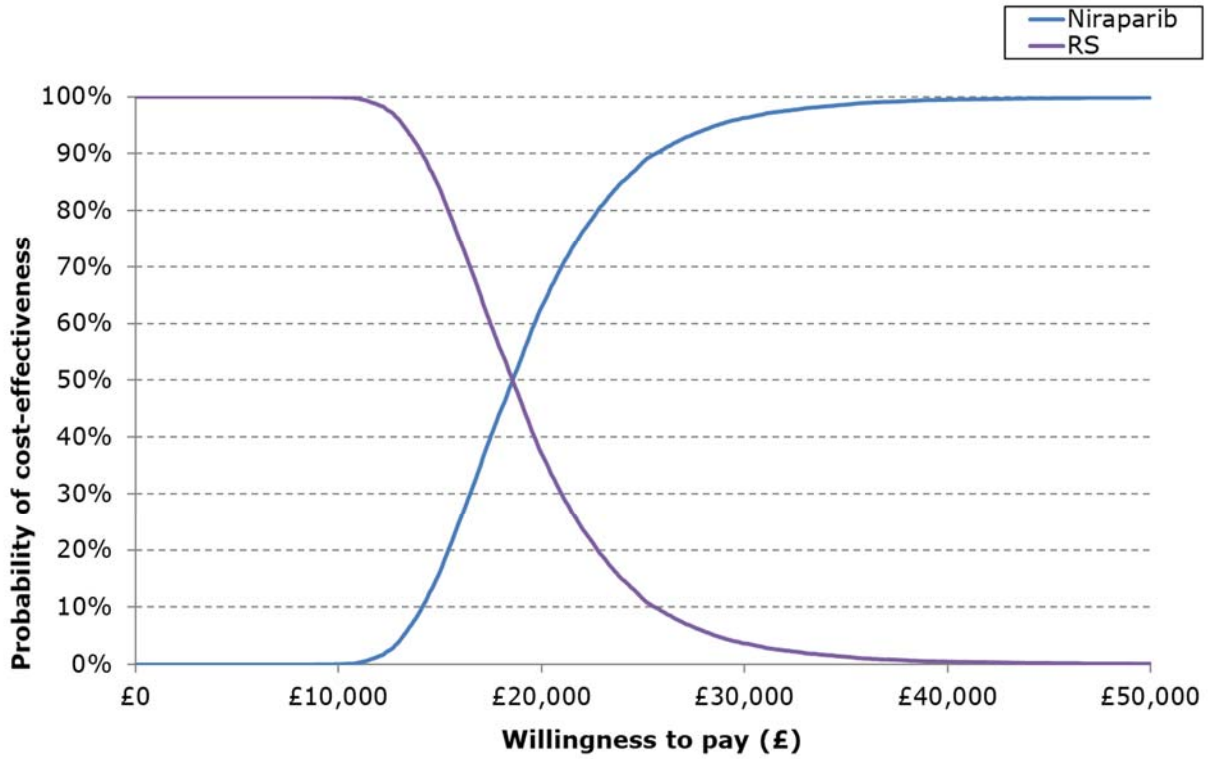
Abbreviations: RS, routine surveillance

Figure 25: Incremental cost-effectiveness plane for niraparib versus RS for the ITT population (10,000 iterations)



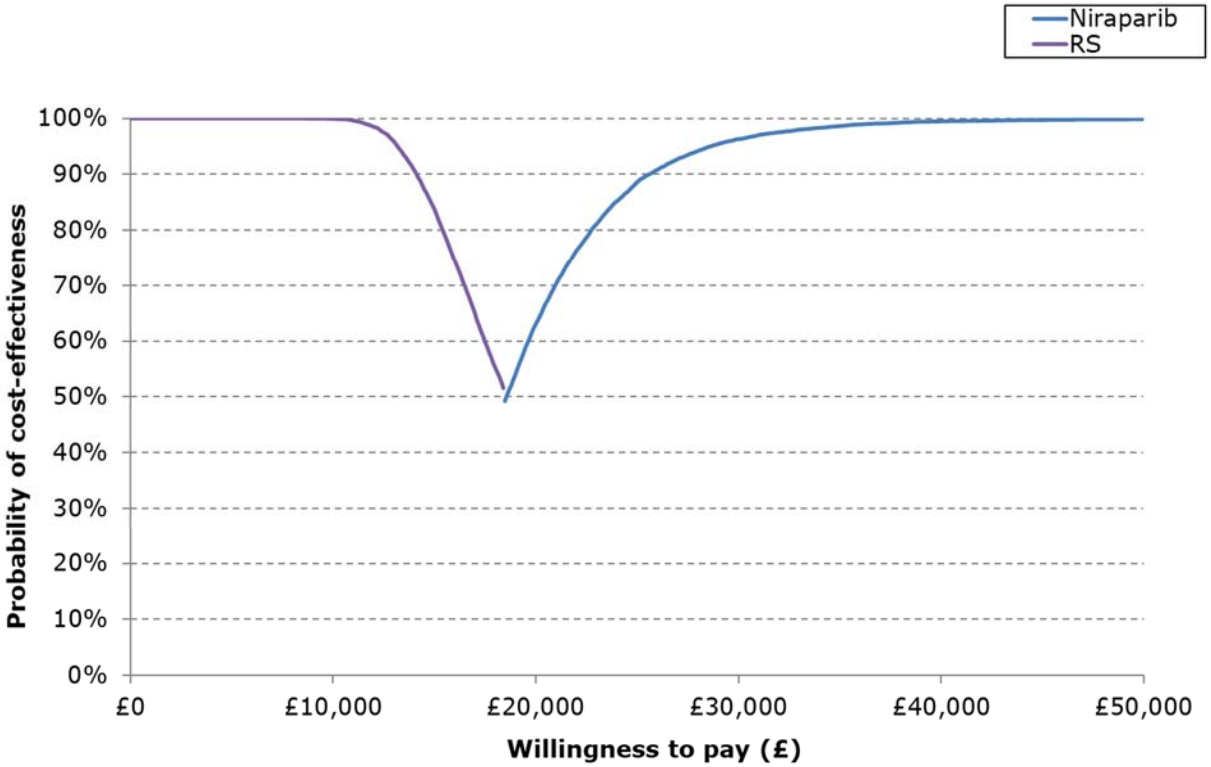
Abbreviations: QALYs, quality-adjusted life years; RS, routine surveillance

Figure 26: Cost-effectiveness acceptability curve for niraparib versus RS for the ITT population (10,000 iterations)



Abbreviations: RS, routine surveillance

Figure 27: Cost-effectiveness acceptability frontier for niraparib versus RS for the ITT population (10,000 iterations)



Abbreviations: RS, routine surveillance

Deterministic sensitivity analysis

MA population

A OWSA tornado diagram presenting the top 20 most sensitive parameters for the MA population is presented in Figure 28, with tabulated results presented in Table 35. Within the OWSA all ICERs remained below £17,191 per QALY gained. The model was most sensitive to the shape and scale of the niraparib and RS PFS distributions, the hazard ratio estimating Stage III NVRD patients from the ITT patients for niraparib and RS, and the percentage of patients with Stage III NVRD at baseline.

ITT population

A OWSA tornado diagram presenting the top 20 most sensitive parameters for the ITT population is presented in Figure 29, with tabulated results presented in Table 36. Within the OWSA all ICERs remained below £30,066 per QALY gained. The model was most sensitive to the shape and scale of the niraparib and RS PFS distributions, RS subsequent treatment total costs, the shape and scale of the niraparib TTD distribution and the niraparib arm resource use (PD) for outpatient visits.

Figure 28: OWSA tornado diagram for the MA population

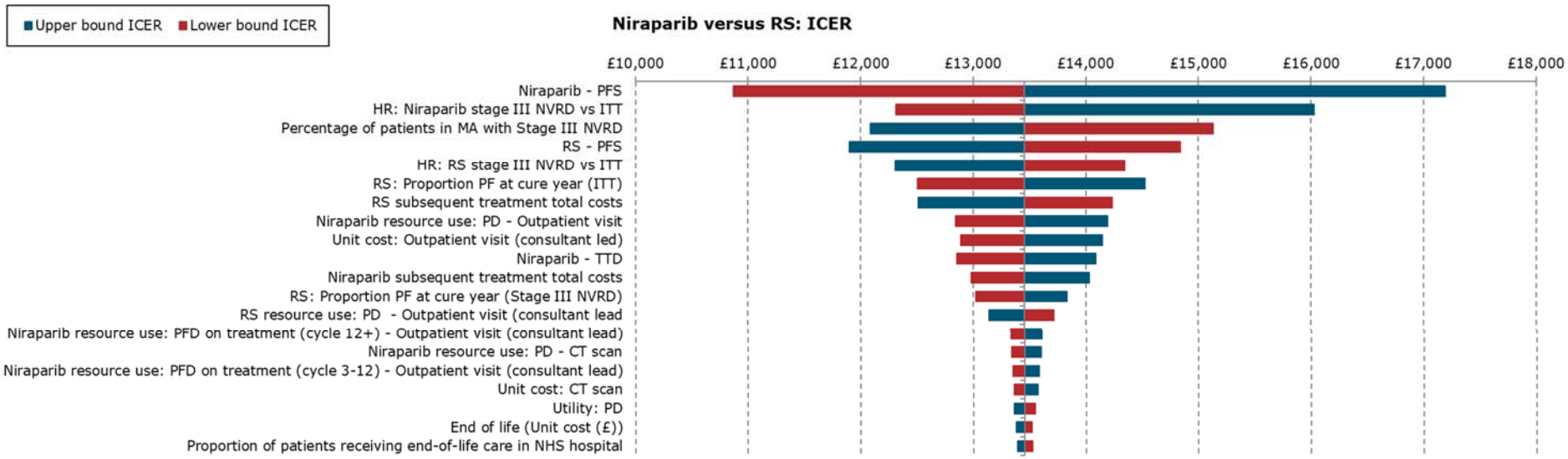


Table 35: Tabulated OWSA results for the MA population

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Niraparib - PFS	[redacted]	[redacted]	[redacted]	10,871	17,191	6,320
HR: Niraparib stage III NVRD vs ITT	0.34	0.23	0.50	12,311	16,026	3,715
Percentage of patients in MA with Stage III NVRD	0.25	0.16	0.35	15,134	12,086	3,048
RS - PFS	[redacted]	[redacted]	[redacted]	14,840	11,901	2,940
HR: RS stage III NVRD vs ITT	0.49	0.33	0.73	14,348	12,307	2,041
RS: Proportion PF at cure year (ITT)	[redacted]	[redacted]	[redacted]	12,506	14,523	2,017
RS subsequent treatment total costs	7,832	5,068	11,187	14,234	12,512	1,722
Niraparib resource use: PD - Outpatient visit	1.00	0.65	1.43	12,846	14,197	1,351
Unit cost: Outpatient visit (consultant led)	126.91	82.13	181.28	12,888	14,146	1,258
Niraparib - TTD	[redacted]	[redacted]	[redacted]	12,856	14,090	1,235
Niraparib subsequent	5,195	3,362	7,420	12,982	14,031	1,049

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
treatment total costs						
RS: Proportion PF at cure year (Stage III NVRD)	[redacted]	[redacted]	[redacted]	13,024	13,833	810
RS resource use: PD - Outpatient visit (consultant lead	1.00	0.65	1.43	13,717	13,139	578
Niraparib resource use: PFD on treatment (cycle 12+) - Outpatient visit (consultant lead)	1.00	0.65	1.43	13,331	13,608	277
Niraparib resource use: PD - CT scan	0.30	0.19	0.43	13,336	13,602	266
Niraparib resource use: PFD on treatment (cycle 3-12) - Outpatient visit (consultant lead)	1.00	0.65	1.43	13,352	13,582	230
Unit cost: CT scan	83.23	53.87	118.89	13,362	13,571	209
Utility: PD	0.74	0.73	0.75	13,551	13,364	187
End of life (Unit cost (£))	7,576	4,903	10,822	13,519	13,381	138
Proportion of patients receiving	0.51	0.31	0.71	13,525	13,388	137

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
end-of-life care in NHS hospital						

Figure 29: OWSA tornado diagram for the ITT population

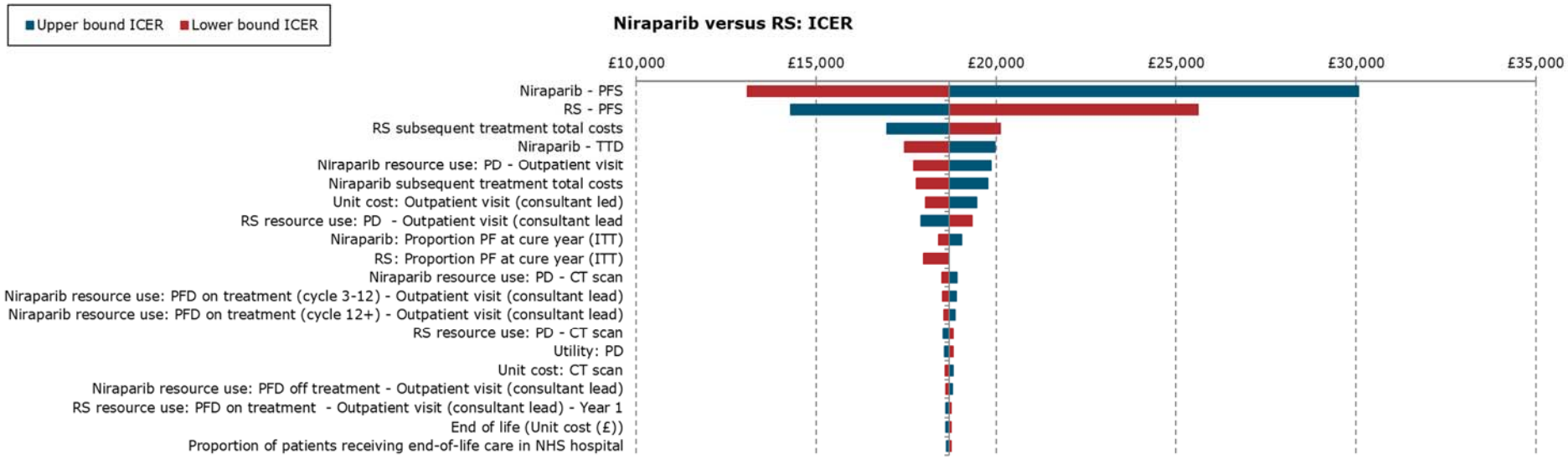


Table 36: Tabulated OWSA results for the ITT population

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Niraparib - PFS	[redacted]	[redacted]	[redacted]	13,089	30,066	16,977
RS - PFS	[redacted]	[redacted]	[redacted]	25,607	14,287	11,320
RS subsequent treatment total costs	7,832	5,068	11,187	20,108	16,966	3,142
Niraparib - TTD	[redacted]	[redacted]	[redacted]	17,453	19,968	2,516
Niraparib resource use: PD - Outpatient visit	1.00	0.65	1.43	17,722	19,863	2,140
Niraparib subsequent treatment total costs	5,195	3,362	7,4203	17,792	19,779	1,987
Unit cost: Outpatient visit (consultant led)	126.91	82.13	181.28	18,048	19,468	1,420
RS resource use: PD - Outpatient visit (consultant lead	1.00	0.65	1.43	19,325	17,917	1,407
Niraparib: Proportion PF at cure year (ITT)	[redacted]	[redacted]	[redacted]	18,410	19,048	639
RS: Proportion PF at cure year (ITT)	[redacted]	[redacted]	[redacted]	17,982	18,457	475

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Niraparib resource use: PD - CT scan	0.30	0.19	0.43	18,499	18,920	421
Niraparib resource use: PFD on treatment (cycle 3-12) - Outpatient visit (consultant lead)	1.00	0.65	1.43	18,515	18,901	386
Niraparib resource use: PFD on treatment (cycle 12+) - Outpatient visit (consultant lead)	1.00	0.65	1.43	18,549	18,859	311
RS resource use: PD - CT scan	0.30	0.19	0.43	18,814	18,537	277
Utility: PD	0.74	0.73	0.75	18,814	18,568	246
Unit cost: CT scan	83.23	53.87	118.89	18,587	18,813	225
Niraparib resource use: PFD off treatment - Outpatient visit (consultant lead)	0.30	0.19	0.43	18,606	18,790	183
RS resource use: PFD on treatment - Outpatient visit (consultant lead) - Year 1	0.30	0.19	0.43	18,751	18,614	138

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
End of life (Unit cost (£))	7,576	4,903	10,822	18,751	18,614	138
Proportion of patients receiving end-of-life care in NHS hospital	0.51	0.31	0.71	18,758	18,621	137

Scenario analysis

Table 37 details scenario analyses results versus RS for the MA and ITT population. Across both populations results were most sensitive to using the PRIMA KM PFS to determine the PFS:OS relationship, varying the mean ΔPFS:ΔOS relationship, varying the PFS distribution for niraparib and RS, and applying a 0% or 6% discount rate. Besides using the PRIMA KM PFS to determine the PFS:OS relationship, the ICER remained below £25,053 and £34,566 across all scenarios explored for the MA and ITT population, respectively.

Table 37: Scenario analyses for the anticipated MA and ITT population for niraparib versus and RS

Population →			Marketing authorisation population				ITT population			
Category	**Base case**	**Scenario**	**Inc. costs (£)**	**Inc. LYs**	**Inc. QALYs**	**ICER (£)**	**Inc. costs (£)**	**Inc. LYs**	**Inc. QALYs**	**ICER (£)**
Base case			[redacted]	[redacted]	[redacted]	13,456	[redacted]	[redacted]	[redacted]	18,689
Discount rate	3.5%	0.0%	[redacted]	[redacted]	[redacted]	9,495	[redacted]	[redacted]	[redacted]	13,191
		1.5%	[redacted]	[redacted]	[redacted]	11,097	[redacted]	[redacted]	[redacted]	15,432
		6.0%	[redacted]	[redacted]	[redacted]	16,715	[redacted]	[redacted]	[redacted]	23,127
Weight	PRIMA	UK data	[redacted]	[redacted]	[redacted]	13,456	[redacted]	[redacted]	[redacted]	18,689
Time horizon	39 years	35 years	[redacted]	[redacted]	[redacted]	13,511	[redacted]	[redacted]	[redacted]	18,745
		30 years	[redacted]	[redacted]	[redacted]	13,791	[redacted]	[redacted]	[redacted]	19,025
		25 years	[redacted]	[redacted]	[redacted]	14,592	[redacted]	[redacted]	[redacted]	19,809
PFS	G. gamma	Log-log for both niraparib and RS	[redacted]	[redacted]	[redacted]	18,957	[redacted]	[redacted]	[redacted]	28,143
		Weighted LLG/GG	[redacted]	[redacted]	[redacted]	15,820	[redacted]	[redacted]	[redacted]	22,403
Label population	PAOLA-1 approach	SOLO-1 approach	[redacted]	[redacted]	[redacted]	17,788	N/A	N/A	N/A	N/A
		PAOLA-1 approach with R0 effect only	[redacted]	[redacted]	[redacted]	15,896	N/A	N/A	N/A	N/A
		PRIMA	[redacted]	[redacted]	[redacted]	13,538	N/A	N/A	N/A	N/A
Long- term remission (LTR)	LTR at 7-years	No remission	[redacted]	[redacted]	[redacted]	11,228	[redacted]	[redacted]	[redacted]	18,087
		LTR at 10 years	[redacted]	[redacted]	[redacted]	13,466	[redacted]	[redacted]	[redacted]	20,755
		LTR at 5 years	[redacted]	[redacted]	[redacted]	13,069	[redacted]	[redacted]	[redacted]	16,415
NVRD (MA population)	[redacted]%	[redacted]%	[redacted]	[redacted]	[redacted]	12,739	N/A	N/A	N/A	N/A
		[redacted]%	[redacted]	[redacted]	[redacted]	11,613	N/A	N/A	N/A	N/A
	Modelled mean PFS	Restricted KM mean	[redacted]	[redacted]	[redacted]	136,151	[redacted]	[redacted]	[redacted]	116,787

Population →			Marketing authorisation population				ITT population			
Category	**Base case**	**Scenario**	**Inc. costs (£)**	**Inc. LYs**	**Inc. QALYs**	**ICER (£)**	**Inc. costs (£)**	**Inc. LYs**	**Inc. QALYs**	**ICER (£)**
Base case			[redacted]	[redacted]	[redacted]	13,456	[redacted]	[redacted]	[redacted]	18,689
Mean ΔPFS:ΔOS relationship		PFS observed in PRIMA								
	1:2	1:1	[redacted]	[redacted]	[redacted]	25,053	[redacted]	[redacted]	[redacted]	34,566
		1:1.25	[redacted]	[redacted]	[redacted]	19,461	[redacted]	[redacted]	[redacted]	28,106
		1:1.5	[redacted]	[redacted]	[redacted]	16,820	[redacted]	[redacted]	[redacted]	23,889
		1:1.75	[redacted]	[redacted]	[redacted]	14,908	[redacted]	[redacted]	[redacted]	20,911
		1:2.5	[redacted]	[redacted]	[redacted]	11,392	[redacted]	[redacted]	[redacted]	15,584
		1:3	[redacted]	[redacted]	[redacted]	9,990	[redacted]	[redacted]	[redacted]	13,506
OS	Log-logistic for RS	Log-normal for RS	[redacted]	[redacted]	[redacted]	15,573	[redacted]	[redacted]	[redacted]	19,102
TTD	Weibull for niraparib	Log-logistic for niraparib	[redacted]	[redacted]	[redacted]	14,858	[redacted]	[redacted]	[redacted]	20,064
Treatment costs	Monthly dosing from PRIMA	Fixed niraparib dose	[redacted]	[redacted]	[redacted]	15,055	[redacted]	[redacted]	[redacted]	20,655
		Dose intensity	[redacted]	[redacted]	[redacted]	15,055	[redacted]	[redacted]	[redacted]	20,655
	Dose per treatment cycle (up to 18 cycles)	Dose per treatment cycle (up to 12 cycles)	[redacted]	[redacted]	[redacted]	13,435	[redacted]	[redacted]	[redacted]	18,667
	Apply wastage	No wastage	[redacted]	[redacted]	[redacted]	13,461	[redacted]	[redacted]	[redacted]	18,694
	[redacted]% discontinue at 3 years	No stopping rule	[redacted]	[redacted]	[redacted]	14,533	[redacted]	[redacted]	[redacted]	19,500
	[redacted]% discontinue at 3 years	[redacted]% discontinue at 3 years	[redacted]	[redacted]	[redacted]	12,584	[redacted]	[redacted]	[redacted]	18,546

Population →			Marketing authorisation population				ITT population			
Category	**Base case**	**Scenario**	**Inc. costs (£)**	**Inc. LYs**	**Inc. QALYs**	**ICER (£)**	**Inc. costs (£)**	**Inc. LYs**	**Inc. QALYs**	**ICER (£)**
Base case			[redacted]	[redacted]	[redacted]	13,456	[redacted]	[redacted]	[redacted]	18,689
Resource use	Literature	KOL	[redacted]	[redacted]	[redacted]	13,377	[redacted]	[redacted]	[redacted]	18,399
		ERG scenario for RS	[redacted]	[redacted]	[redacted]	13,595	[redacted]	[redacted]	[redacted]	18,877
	Blood pressure and heart rate monitoring excluded	ERG: Blood pressure and heart rate monitoring based on draft SmPC	[redacted]	[redacted]	[redacted]	13,782	[redacted]	[redacted]	[redacted]	18,953
	Patients in long-term remission are not monitored	Patients in long-term remission are monitored	[redacted]	[redacted]	[redacted]	13,964	[redacted]	[redacted]	[redacted]	19,562
Subsequent treatment	KOL with second-line and third-line chemotherapy, and third-line PARPi	PRIMA in second-line; no third-line costs applied	[redacted]	[redacted]	[redacted]	13,456	[redacted]	[redacted]	[redacted]	18,689
		KOL with second-line PARPi; no third-line costs applied	[redacted]	[redacted]	[redacted]	10,322	[redacted]	[redacted]	[redacted]	12,924
		No subsequent treatment cost	[redacted]	[redacted]	[redacted]	14,317	[redacted]	[redacted]	[redacted]	20,168

Population →			Marketing authorisation population				ITT population			
Category	**Base case**	**Scenario**	**Inc. costs (£)**	**Inc. LYs**	**Inc. QALYs**	**ICER (£)**	**Inc. costs (£)**	**Inc. LYs**	**Inc. QALYs**	**ICER (£)**
Base case			[redacted]	[redacted]	[redacted]	13,456	[redacted]	[redacted]	[redacted]	18,689
	Apply cost to patients leaving PFD	Apply cost to patients entering PD	[redacted]	[redacted]	[redacted]	13,803	[redacted]	[redacted]	[redacted]	19,101
	List price per PARP treatment	CDF discount	[redacted]	[redacted]	[redacted]	13,456	[redacted]	[redacted]	[redacted]	18,689
		Cheapest PARP list price (olaparib) applied to all PARPs	[redacted]	[redacted]	[redacted]	13,456	[redacted]	[redacted]	[redacted]	18,689
	100 mg olaparib tablet	150 mg olaparib tablet	[redacted]	[redacted]	[redacted]	13,456	[redacted]	[redacted]	[redacted]	18,689
	PARP average cost based on PRIMA	PARP simple average cost	[redacted]	[redacted]	[redacted]	13,456	[redacted]	[redacted]	[redacted]	18,689
	Administration HRG: SB15Z	Administration HRG: SB12Z	[redacted]	[redacted]	[redacted]	13,421	[redacted]	[redacted]	[redacted]	18,652
Adverse event costs	Do not apply AE 'day case' cost	Apply AE 'day case' cost	[redacted]	[redacted]	[redacted]	13,381	[redacted]	[redacted]	[redacted]	18,554
Quality of life	PRIMA descriptive analysis Published disutilities	Apply utility age decrement	[redacted]	[redacted]	[redacted]	14,506	[redacted]	[redacted]	[redacted]	20,037
		General population utilities applied to	[redacted]	[redacted]	[redacted]	13,856	[redacted]	[redacted]	[redacted]	19,130

Population →			Marketing authorisation population				ITT population			
Category	**Base case**	**Scenario**	**Inc. costs (£)**	**Inc. LYs**	**Inc. QALYs**	**ICER (£)**	**Inc. costs (£)**	**Inc. LYs**	**Inc. QALYs**	**ICER (£)**
Base case			[redacted]	[redacted]	[redacted]	13,456	[redacted]	[redacted]	[redacted]	18,689
		patients in long-term remission								
		TA598 - PFD capped at general population, PD from OVA-301	[redacted]	[redacted]	[redacted]	14,353	[redacted]	[redacted]	[redacted]	19,879
		TA528 - EQ-5D-3L ENGOT-OV16/ NOVA	[redacted]	[redacted]	[redacted]	13,589	[redacted]	[redacted]	[redacted]	18,862

Abbreviations: AE, adverse event; HTS, health technology appraisal; HR-d, homologous recombinant deficient; ICER. Incremental cost-effectiveness ratio; Inc. incremental; ITT, intention to treat; KOL, key opinion leader; MA, marketing authorisation, N/A, not applicable; OS, overall survival; PD, progressed disease; PFD, progression-free disease; QALY, quality-adjusted life year; RS, routine surveillance; TA, technology appraisal; TTD, time to treatment discontinuation; UK, United Kingdom

Request:

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1680]

Dear xxxx,

The ERG have an urgent request for the company.

Can the company please provide baseline characteristics for each treatment arm in PRIMA on:

- the number of patients (%) who had primary debulking surgery and how many of these had NVRD and VRD respectively.
- the number of patients (and %) who had interval debulking surgery and how many of these had: a) NVRD and were stage III disease patients; b) NVRD and were stage IV disease patients; and c) had VRD after interval debulking surgery.

Could you provide a response as soon as you can?

Best wishes,

Jeremy

Response from GSK:
Dear Jeremy,

Please find attached the requested analysis.

It shows that only [redacted] FIGO stage III patient had no visible residual disease (R0) outcome after primary debulking surgery as it was and exclusion criteria in the PRIMA trial. However, 46% of patients who were stage III after interval debulking surgery or stage IV did achieve no visible residual disease outcome. Please note that in advanced epithelial ovarian cancer, the

aim is complete cytoreduction of all macroscopic visible disease, since this has been shown to be associated with a significantly increased OS and PFS (Ledermann, ESMO 2016). Over the past few years primary chemotherapy with interval surgery has become more widely accepted in the attempt to first shrink the tumour then enable improved surgical outcomes. However, interval debulking surgery remains the treatment modality primarily for patients with poor performance status at presentation, low albumin levels and in those with very extensive tumour dissemination (Ledermann, ESMO 2016). Therefore, due to selection bias, survival outcomes for patients receiving primary surgery are much more favourable compared to those receiving interval debulking surgery, even if complete resection to no visible residual disease is achieved. With FIGO staging remaining the most powerful indicator of prognosis (Ledermann, ESMO 2016) means that patients with the most favourable outcome are those diagnosed with stage III disease and achieving complete cytoreduction (NVRD) after primary surgery.

Best regards, xxx

Parameter	Statistic	Cancer stage (FIGO) III			Cancer stage (FIGO) IV		
		Niraparib (N=318)	Placebo (N=158)	Overall (N=476)	Niraparib (N=169)	Placebo (N=88)	Overall (N=257)
Primary Debulking Surgery (PDS)	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R0	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R1/R2	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing [1]	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interval Debulking Surgery (IDS)	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R0	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R1/R2	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing [1]	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Debulking Surgery (NDS)	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

References:

Ledermann et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Annals of Oncology 24 (Supplement 6): vi24–vi32, 2013

NICE National Institute for Health and Care Excellence

Patient organisation submission

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1680]

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Ovacome Ovarian Cancer Charity
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are charity formed in 1996 offering information and support to anyone affected by ovarian cancer. We raise awareness of the disease and work with medical schools through the survivors teaching students programme. We have 9 full-time members of staff and 1 part-time; there is also 1 part time temporary post. We are funded through charitable donations, trusts and foundations donations, community fundraising and donations. Our members currently number around 4000.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Between April 2019 and April 2020 we received the following funding: £397.28 from Clovis for a speaking engagement £5,000.00 of restricted trusts and foundations funds from Roche to support our 'Survivors Teaching Students' education programme.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	Knowledge and experience from 24 years providing support to those affected by ovarian cancer. Feedback through My Ovacome online forum.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Ovarian cancer has a significant impact on quality of life. The majority of women are diagnosed at Stage III when it has already spread outside of the pelvis. This means treatment is aimed at minimising the burden of the disease and maximising periods of wellness between treatments. As treatment lines are exhausted, women fear being told there is no more treatment available to manage their ovarian cancer. The surgery undertaken is most usually a total abdominal hysterectomy and bilateral salpingo-oophorectomy. This operation can have long term effects on abdominal organs and particularly the bowel with associated continence issues. Women may have to manage a stoma, either short or long term. Associated issues include fatigue and changes to body image and function affecting sexuality.

	Women live with the anxiety of possible recurrence. The time after treatment whereby women are under routine surveillance can be psychologically very hard to cope with. Having a choice of maintenance therapy to extend progression free survival and continued input from oncology teams offers significant psychological as well as health benefits. For both the women and their carers, ovarian cancer can be very isolating, due to its comparative rarity they may not meet anyone else with the same condition or facing the same issues of managing their cancer as a chronic condition rather than aiming for a cure.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	They are concerned that treatment options are limited and lines of treatment to control the disease will be exhausted leaving palliative care only. The development of biological therapies is offering hope when there had been no new chemotherapy options for many years.
8. Is there an unmet need for patients with this condition?	Currently no PARP inhibitors are routinely available first line for BRCA-negative patients (olaparib is only available first line for BRCA-positive patients and niraparib and rucaparib second line through CDF). Niraparib's efficacy as first-line therapy has been established through the PRIMA trial which found niraparib significantly improved progression-free survival in patients with platinum-sensitive ovarian cancer who had achieved a response to platinum-based chemotherapy. For women without the BRCA mutation niraparib has the potential to routinely offer a new patient group the option of a first-line PARP inhibitor which was previously unavailable to them. For women with the BRCA mutation it offers a choice of PARP inhibitor. Niraparib as an oral medication offers patients greater choice and flexibility regarding location of treatment as hospital attendance is not necessary for administration. There is a psychological benefit of having a PARP inhibitor available where none existed before: for women without the BRCA mutation to have PARP treatment earlier at first line and not feel they are waiting for a recurrence in order to access PARP treatment.

	They will also benefit from knowing that PARP-inhibitor treatment is no longer restricted for them but will be routinely available. Additionally, for patients on follow-up knowing their cancer is likely to recur, having a choice of maintenance therapy and continued input from oncology teams offers significant psychological as well as health benefits compared to routine surveillance.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	It is expanding availability of PARP inhibitors to patients previously excluded; also a choice of PARP inhibitors first line for women with the BRCA mutation. It is a treatment that offers longer progression free survival with manageable side effects, enabling a good quality of life. In April 2020, three of our members gave the following feedback: “An alternative option would be most welcome by clinicians and patients alike. I am currently taking Niraparib and feeling the best I have felt since diagnosis.” “I really do believe that if I had been given access to it after my first diagnosis … then I would have had a much better chance of [progression free survival]. But now I am on it, I feel I almost have my life back. It has given me a certain quality of life back, and would really champion that other women have the chance to try it too.” “Niraparib has played a key role in enabling me to keep focused on the things that matter and the time to explore personal interests. Despite the side effects, Niraparib has allowed me another window of wellness. It has given me sufficient quality of life to continue to enjoy my “new normal” as a cancer patient. I don’t expect its effectiveness to last indefinitely, but as my guiding principle in life is “quality” not necessarily “quantity” and “how” and not “how long”, Niraparib has importantly helped me live well. For platinum sensitive patients like myself, Niraparib is a blessing and opens new horizons.”

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	While they are aware of a drug's side effects they are often prepared to manage these for increased progression free survival.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Ovarian cancer is frequently managed as a chronic condition rather than curative and therefore expanding maintenance therapies for this group of patients is vital.
- The PRIMA trial has proven Niraparib's efficacy in extending progression free survival for women with and without BRCA mutations and that health-related quality-of-life scores were similar between the niraparib and control arms.
- For patients on follow-up knowing their cancer is likely to recur, having a choice of maintenance therapy and continued input from oncology teams offers significant psychological as well as health benefits compared to routine surveillance.
- Niraparib as an oral medication offers patients greater flexibility and convenience regarding location of treatment than chemotherapy or other IV treatments, minimising detrimental impact on quality of life.

Thank you for your time.

NICE National Institute for Health and Care Excellence

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1680]

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Ovarian Cancer Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Ovarian Cancer Action was founded in 2005 to raise awareness, to fund much needed research, and to give a voice to all those affected by the disease. We have been working ever since, driven by a clear vision – a world where no woman dies of ovarian cancer. We're committed to funding research to accelerate progress in three main areas: prevention, diagnosis and treatment. And while our scientists are busy in the lab, we're on the ground campaigning for change and raising awareness of the disease, so that every woman and healthcare professional knows the signs to look out for. Together, these priorities will help women survive ovarian cancer. Fundamentally we demand that every woman should have the best treatment available. The charity is funded through a range of sources that includes trust funding and donations; we do not receive government funding.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	September 2019: £25,000 sponsorship of Helene Harris Memorial Trust (HHMT) International Forum on Ovarian Cancer

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	This information was gathered through direct conversations with patients relating to these drugs and living with ovarian cancer, previous information given to us by patients about their experiences, and through consultation with medical experts currently treating patients and using these drugs in practice.
Living with the condition	
6. What is it like to live with the condition? What do carers	A diagnosis of ovarian cancer can be devastating, significantly affecting the quality of life of patients. Women not only suffer from the consequences of the disease but also have to live with the long-term impact of its treatment.

experience when caring for someone with the condition?	Most women diagnosed with ovarian cancer are diagnosed at stage 3 or 4 and this means that the majority of women diagnosed with ovarian cancer have a poor prognosis. This has a significant impact emotionally with patients experiencing high levels of fear and anxiety. Even after a seemingly successful course of treatment there is still fear and anxiety due to the possibility of a recurrence as recurrence rates for ovarian cancer are very high – approx. 70%. This creates a sense of uncertainty about the future and this uncertainty is difficult to live with. This fear and anxiety is not just experienced by patients but family and friends too. In addition to the emotional impact of ovarian cancer, patients experience a number of physical symptoms that result from the disease itself (ascites, bloating, abdominal pain) and its treatment. Surgery used in the treatment of ovarian cancer leads many women to go into premature menopause, with its resulting effects, and chemotherapy can cause a number of short and long term effects impacting quality of life. For an ovarian cancer patient, their condition affects every aspect of their life – their relationships, work, family life and social life. And, in many cases there can be additional challenges due to stigma, cultural insensitivity, a feeling of isolation and in some cases unaddressed psychosexual issues. Furthermore family members and carers are also impacted by all of these issues. Many of our patient group members have experienced a recurrence and this is a very difficult time for them. Some patients do experience severe side effects with chemotherapy with one carer stating that *“I was witness to the heavy side effects. The side effects were even worse the second time around*”. From one of our supporters: “*To live with OC is like learning to ride a bike through a bog of mud. It is a journey that you don’t want to have to make - or push upon those you love. But there is little choice in the matter and one way or another you find the path that works for you. For me personally after the initial diagnosis and first lot of treatment I thought there is just no way I can do that again. Chemotherapy is so tough. You have the*

	trauma of knowing it is most likely coming back and you access all the support you can. Whether friends, counselling, charities etc. Then you learn to live in a new way. For me I have looked at balancing my mental health through meditation, exercise and art. I eat well and have learnt acceptance. From that brings appreciation and thus gratitude. I am probably now the most happy and content that I have ever been, I am 10 years in, which was never expected initially. I love my life, and am simply grateful for it."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The main concern that patients and carers have about treatment is the worry is that the high recurrence rate means treatment is not effective, and they live with the anxiety that they will have to repeat chemotherapy again and again. Many experience severe side effects and their treatment schedule is quite intense requiring regular hospital visits and so the prospect of repeating this is a huge worry.
8. Is there an unmet need for patients with this condition?	There remains an unmet need for more effective maintenance therapies in the first line setting especially for the non-BRCA mutated population. From one of our supporters: *"Yes there is a huge unmet need.* *We need a screening tool. We need earlier diagnosis. We need treatments that stop it coming back.* *We need more alternatives to chemotherapy which is so gruelling."*

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The benefits that patients appreciate with Niraparib are: • It improves progression free survival providing more hope to patients • It improves overall survival and gives them more time with their family and friends • Side effects that do occur are still more manageable than having regular chemotherapy • Having a tablet taken orally makes is an easy and convenient drug to administer and puts the control into the patient's hands From some of our supporters: *"Niraparib means I can get on with doing things and feeling healthy while at the same time knowing something is suppressing the tumours which feels more proactive than just waiting. I'm able to do things I couldn't do on chemo- travel, improve my Italian, go to the opera again."* *"Unlike chemotherapy where you have to go to hospital and be rigged up to have it by IV, Niraparib is tablet form so the onus is very much on me to remember to take it."* *"The main advantage would be to delay the disease coming back. And that it is less gruelling than chemotherapy. Patients can live a much more 'normal' life."* *"As I've had two recurrences, progression free survival is of utmost importance to me."*

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Ovarian Cancer Action has received numerous anecdotal comments and concerns regarding side effects of treatments. We assert that adverse effects of treatment and health-related quality of life should certainly be considered as significant in any outcome assessments. Patients are concerned about any short and long term side effects of the treatments, as key for them is that the time they are living with this disease is of good quality and enjoyable. Evaluation of the technology should include discussion of dosage and method of delivery as this should factor into health-related quality of life assessment as it is a frequently mentioned concern by our supporters. Niraparib does cause some side effects including: anaemia, fatigue, nausea and decreased platelet count however we're told these side effects are easier to deal with than those of regular chemo. From some of our supporters: *"In my case the blood pressure has remained stable but the platelet count has dropped on a couple of occasions. And then you have to stop for a week, measure them again, and fortunately they've moved up in both cases back to normal levels so you start [treatment] again."* *"I have a little bit of nausea and fatigue at the mo, but it's nothing like when I was on chemo and I am told those symptoms will abate as my body learns to tolerate the treatment."*

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It is likely that the non-BRCA mutant population will benefit from the suggested technology, by allowing them the access to more treatment options.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	Ovarian Cancer Action see BRCA as an opportunity for cancer prevention. In any economic analysis, it is worthwhile pointing out that the genetic testing offered as part of ovarian cancer treatment pathways will, in future years, reduce the incidences of ovarian cancer. This will reduce overall spending in the NHS for generations. Based on the current statistics of 7500 diagnoses per year in the UK, approximately 1250 of those may be caused by a BRCA mutation, and these cases could be prevented through risk-reducing surgery provided the individuals know about this in time. Of these, as many as half have no family history to have prompted genetic testing and therefore had no opportunity to take risk-reducing action, so it is the first opportunity to test and inform the patient and their family. Currently not all high grade serous ovarian cancer patients are offered BRCA testing at diagnosis, despite guidelines issued in 2015. When PARP inhibitors were available only to BRCA+ patients, this gave a therapeutic incentive to offer testing. With greater access to drugs for those without a BRCA mutation, it is a concern is that women will no longer have this incentive. As such, whilst we support greater access to effective treatments for both BRCA+ and BRCA- patients, we strongly encourage BRCA testing for ovarian cancer be embedded in the treatment pathway for patients' personal and family health, and for the aforementioned economic reasons.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- The majority of ovarian cancer patients (70%) will relapse. This technology provides an additional option for women and their families. This additional extension of life is highly valued by patients.
- The feedback we have from supporters is that maintenance treatments allow greater quality of life, added hope, more time with family members (and of greater quality). Although not always measurable, these cannot be overstated in terms of the difference they make to entire families.

- When PARP inhibitors were available only to BRCA+ patients, this gave a therapeutic incentive to offer testing. With greater access to drugs for those without a BRCA mutation, it is a concern is that women will no longer have this incentive to even consider testing. As such, whilst we support greater access to effective treatments for both BRCA+ and BRCA- patients, we strongly encourage BRCA testing for ovarian cancer be embedded in the treatment pathway for patients' personal and family health, and for the aforementioned economic reasons.

- Ovarian Cancer Action supports new options being made available to women via the NHS that can give them more time, and good quality time, with their families and friends.

Thank you for your time.

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About you

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	Target Ovarian Cancer
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Target Ovarian Cancer is the UK's leading ovarian cancer charity. We work to: • Improve early diagnosis, • Fund life-saving research, • Provide much-needed support to women with ovarian cancer
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Yes GSK - a £10,000 grant. The grant was for the running of Target Ovarian Cancer's nurse-led Support Line as part of our response to the coronavirus pandemic

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	• Patient survey on their experience of cancer drugs in general and niraparib specifically • Calls to the Target Ovarian Cancer support line • Target Ovarian Cancer Pathfinder 2016
Living with the condition	
6. What is it like to live with the condition? What do carers	Around 6,900 women are diagnosed with ovarian cancer in England each year; many women face a delayed diagnosis and over a quarter are diagnosed following an emergency presentation. Survival rates for ovarian cancer trail those for many other cancers. Overall five-year survival is 37 per cent for women with ovary, fallopian tube and primary peritoneal carcinomas.[1] Standard treatment involves surgery and chemotherapy, with chemotherapy either post-surgery or neoadjuvant. In the majority of cases the disease returns after first line treatment. At this point treatment is no longer curative

[1] Public Health England (2020) The Ovarian Cancer Audit Feasibility Pilot. Available at: http://www.ncin.org.uk/cancer_type_and_topic_specific_work/cancer_type_specific_work/gynaecological_cancer/gynaecological_cancer_hub/ovarian_cancer_audit_feasibility_pilot_outputs

experience when caring for someone with the condition?	and each further recurrence and subsequent round of platinum based chemotherapy a woman goes through increases her chance of becoming platinum resistant; at which point very few treatment options remain and prognosis is extremely poor. The prospect of recurrence casts a shadow over the lives of many women. Fears around recurrence are compounded by the knowledge that there are pitifully few treatment options for ovarian cancer. *"I feel now and when I was going through my treatment that ovarian cancer is the poor relation of women's cancers. No screening programme, reduction in research funding, with a high recurrence. Having ovarian cancer doesn't fill you with high hopes by the time you are diagnosed*." Woman with ovarian cancer. An ovarian cancer diagnosis can have a negative impact on many aspects of an individual's life. Perhaps most notably are the practical implications of debilitating treatments rendering individuals unable to work or take part in regular day-to-day life.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There are a limited number of treatments available on the NHS for women with ovarian cancer. We recently asked women their thoughts on current treatment and care: *"I'm not BRCA, everything seems targeted at those with a genetic mutation"* Woman with ovarian cancer *"I was tested and told that I couldn't access olaparib until the cancer came back, surely prevention is better"* Woman with ovarian cancer *"Very limited options, with limited success, new treatments are urgently needed*" Woman with ovarian cancer *"Women are still being subjected to devastating chemotherapy drugs and have to undergo at least two chemotherapy courses before accessing a PARP inhibitor"* Woman with ovarian cancer

	We also asked women what their experience with treatment with niraparib *"Great, kept (ovarian cancer) at bay for a year"* Woman who had taken niraparib *"Still taking after 6 months, some side effects but generally ok"* Woman who had taken niraparib *"200 mg dose too high resulting in 3 blood transfusions. Dose reduced to 100 mg after 4 week break. Still on it 15 months later. CA125 increasing but Niraparib keeping it slow."* Woman who had taken niraparib *"I have been taking niraparib since September 2019 (200mg per day). No major side effects initially but currently am on a week's break due to a drop in my blood count."* Woman who had taken niraparib *"Stared at 300mg, then 200mg now 100mg doing ok lots of side effects but better than chemo"* Woman who had taken niraparib
8. Is there an unmet need for patients with this condition?	Treatment for ovarian cancer currently involves chemotherapy and surgery. Once ovarian cancer has recurred, curative treatment is no longer an option. Therefore, any treatment aimed at improving women's response to first-line treatment is to be welcomed. In recent years there have been some limited advancement in treatment: • Bevacizumab (Avastin®) has been made available through the Cancer Drugs Fund for women with advanced disease and sub-optimal debulking. • Olaparib (Lynparza®) for women with a BRCA mutation from the first and second lines of treatment on the cancer drugs fund and in routine commissioning from the third line onwards. • Niraparib (Zejula®) is currently available through the Cancer Drugs Fund for all women with recurrent disease (restricted to second-line treatment only for women with a BRCA mutation). • Rucaparib (Rubraca®) is available on the Cancer Drugs Funds as a maintenance treatment from second line onwards for all women with recurrent disease. While these all mark progress, there are still few first line treatment options.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	**Increased treatment options:** By providing a targeted treatment for women with advanced stage disease niraparib would increase treatment options for a patient population who as highlighted above currently have poor prognosis and limited treatment options. Currently only women with a BRCA mutation can access a PARP inhibitor from the first line of treatment so this indication would expand the range of treatment options available to all women as part of first line treatment. **Better quality of life:** As a maintenance treatment that increases the period between disease progression, niraparib offers women a better quality of life with longer intervals without chemotherapy.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	**Side effects** Side effects are associated with niraparib. The side effects experienced by each individual and the extent to which they are experienced will be unknown until treatment. commences, however, there are a range of approaches that a woman can discuss with her clinical team to reduce the impact of the side-effects while continuing to benefit from the treatment. *"Initially fine no problems, after not having it for a week as out of stock, when I started taking it again I became very breathless, abdominal pain, and bowel problems, but continuing on it for now."* Woman who had taken niraparib *"Started on 2 x 100mg a day but could not tolerate 200mg so been on 100mg for over a year. Experienced breathlessness and platelets too low."* Woman who had taken niraparib *"Low platelets on 300mg with daily nausea/sickness so reduced to 200mg. (Now) no side effects"* Woman who had taken niraparib

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Quality of life impact: the threat of recurrent disease looms large over the lives of women with ovarian cancer, the emotional, practical and physical implications for women and their family are significant. This makes it hard for women to plan events and activities that would have a positive impact on their quality of life.
- Limitations of current treatment: platinum-based chemotherapy is the primary treatment for first-line treatment of ovarian cancer. The majority of women with advanced disease will develop a recurrence and receive subsequent platinum-based chemotherapy. However, the risk of developing platinum resistance is high. Treatment for platinum-resistant disease is extremely limited.
- Benefits of first-line maintenance treatment: by introducing a first line treatment available to the majority of women with ovarian cancer, more women would have the possibility of no recurrence.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1680]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Shibani Nicum**
2. Name of organisation	**NCRI Gynaecology Group Lead**

NICE National Institute for Health and Care Excellence

3. Job title or position	**Consultant Medical Oncologist** The Cancer Centre, Oxford
4. Are you (please tick all that apply):	**X** an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with this condition? **X** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted	**X** yes

after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is to prevent disease progression and maintain quality of life by reducing disease related symptoms. There is the potential that patients who derive benefit may be cured by the intervention.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An extension of progression free survival and as a result symptom free survival/ quality of life would be an important outcome for this patient group. There is the potential for an improved overall survival and also in a subgroup that this intervention may result in cure. Progression free, overall survival and improved quality of life are all extremely important and relevant outcomes for a group of patients who have advanced ovarian cancer, which naturally results in patients needing to have repeated rounds of chemotherapy. This repeated recurrence and treatment has a significant impact on quality of life and also increases the potential for the development of resistance.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a significant unmet need for women with advanced ovarian cancer, which is the most lethal gynaecological cancer. The majority of patients will present with advanced disease as there is no affective screening intervention to diagnose this condition in the early stages (stage 1), where cure rates are over 80%. The majority of women will present with incurable advanced disease (stage 3 or 4 and will require repeated rounds of chemotherapy to control their cancer (80% relapse rate within 12-18 months)- this is a significant psychological and clinical burden for patients and also directly impacts

	local cancer services (clinic time/ chemotherapy delivery/inpatient care/ treatment of bowel obstruction. PARP inhibitor maintenance therapy has been demonstrated to impact on progression free, overall survival and improved quality of life - all extremely important and relevant outcomes for a group of patients who have advanced ovarian cancer.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	The majority of patients will require a combination of primary chemotherapy and radical debulking surgery. Patients meeting the CDF criteria will be able to access maintenance treatment with bevacizumab (Stage IV ovarian cancer/stage 3c with residual disease/inoperable) for a maximum of 18 treatments. Women who have had a response to primary treatment (chemotherapy/surgery) and carry a BRCA mutation will be able to access olaparib adjuvant therapy for up to 2 years. Patients who do not meet the criteria for olaparib or bevacizumab treatment will have no therapy and will be followed up clinically for relapse – which will occur in around 80% of patients within 12 months depending on the extent of residual disease.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Current international clinical care guidelines include ASCO and ESMO guidelines for patient treatment. National guidelines determine the availability of new treatments (CDF/NICE criteria) and the devolved nations also have guidelines impacting the use and availability of new agents.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is	There is consensus among UK clinicians regarding the treatment pathway I have outlined in section 10, but there may be local restrictions (e.g devolved nations) regarding the availability of a particular agent e.g bevacizumab is not available in Scotland in the front line setting.

from outside England.)	
• What impact would the technology have on the current pathway of care?	Niraparib is a new treatment option for all women with newly diagnosed advanced ovarian/fallopian tube/primary peritoneal cancer who have had a response to front line treatment regardless of their BRCA/HRD status. Currently olaparib is available for use in women in the good prognostic group, who carry a BRCA mutation.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The PRIMA trial demonstrated the benefit of niraparib maintenance therapy following chemotherapy in women with advanced ovarian cancer regardless of BRCA/HRD status in the front line setting. The magnitude of benefit was greatest in those women with a BRCA mutation or homologous recombinant deficiency (HRD) but was also demonstrated in the group who were HRD negative. We support the use of maintenance niraparib in all women with newly diagnosed advanced ovarian/fallopian tube/primary peritoneal cancer who have had a response to front line treatment regardless of their BRCA/HRD status or residual disease status. Currently olaparib is available for use in women in the good prognostic group, who carry a BRCA mutation, Bevacizumab is available in England for the poor prognostic group (Stage IV ovarian cancer/stage 3c with residual disease/inoperable). Based on the outcomes in the PRIMA trial, niraparib could be an efficacious alternative treatment option to bevacizumab. The benefits over bevacizumab is that this is an oral treatment option and this has significant implications in terms of patient acceptability and healthcare delivery, especially during the current COVID pandemic.
• How does healthcare resource use differ between the technology and current care?	As discussed above in point 11, oral niraparib treatment has some benefits compared to intravenous bevacizumab therapy (3 weekly for up to 18 treatments) – this has the potential to reduce healthcare resource- decreased pharmacy and chemotherapy unit resource- chair time and nursing capacity. This is particularly an issue due to the constraints on chemotherapy day units due to the increased use of maintenance therapies in all cancer groups and also the acute pressures associated with COVID 19.
• In what clinical setting should the technology be used? (For example,	Niraparib treatment should be administered via specialist oncology led/supervised clinics –supervision via a clinician trained in the use of PARP inhibitors and their toxicities is essential- generally this will be secondary/tertiary settings; with supervision by a Medical or Clinical Oncologist it would be appropriate to

primary or secondary care, specialist clinics.)	advanced nurse practitioner/pharmacy led treatment clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Local training of all staff involved in the prescribing/ dispensing/ supervision of treatment is essential, but this can be achieved within current clinical practices. Many centres/ units will already have this in place as PARP inhibitors have been in widespread use in the recurrent and front line therapy over the past 5 years.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes Although the some of the are currently immature for niraparib (overall survival), current evidence indicates the effects of PARP inhibitors are a class effect in the frontline (SOLO1/ PRIMA/PAOLA/ Abbvie) and relapsed setting (NOVA/SOLO2/Ariel 3) and so the data seen with olaparib in the SOLO1 trial recently presented at ESMO are likely to be indicative for niraparib in the frontline setting, taking into account some of the different eligibility criteria of the trials (SOLO1/ Olaparib- BRCA mutant patients only- indicates that after 5 years, 48.3% of patients treated with olaparib had not experienced disease progression and were still living with stable disease vs 20.5% of those taking placebo. Progression free survival was 56 months (olaparib), compared with 13.8 for individuals who received standard treatment only.)
• Do you expect the technology to increase length of life more than current care?	Yes – as the results from the PRIMA trial demonstrate improved progression free survival in all patients receiving niraparib compared to placebo (13.8 mo vs 8.2 mo HR 0.62); with magnitudes of benefit dependent on BRCA and HRD status. This benefit is also demonstrated in other trials of PARP inhibitor therapy e.g SOLO1 and the PAOLA trial (combination PARP inhibitor therapy).
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, as data from the PRIMA trial indicate that maintenance niraparib is predicted to increase the disease free progression of patients we would expect patients to remain well without symptoms for longer and thus have an improved quality of life, particularly as chemotherapy is offset- which also has a significant negative impact on quality of life.

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The PRIMA trial demonstrated the benefit of niraparib maintenance therapy following chemotherapy in women with advanced ovarian cancer regardless of BRCA/HRD status in the front line setting. The magnitude of benefit was greatest in those women with a BRCA mutation or homologous recombinant deficiency (HRD) but was also demonstrated in the group who were HRD negative. We support the use of this agent in all these group of patients in the front line setting as a maintenance therapy following primary chemotherapy/surgery.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It is unlikely that there will be significant additional implications for the implementation of this technology as many centres/ units will already have this in place as PARP inhibitors have been in widespread use in the treatment of ovarian cancer in the recurrent and front line therapy over the past 5 years. Olaparib (alternative PARP inhibitor) is already available via the Cancer Drugs Fund in England for newly diagnosed patients who have responded to first line chemotherapy. Local training of all staff involved in the prescribing/ dispensing/ supervision of treatment is essential, but this can be achieved within current clinical practices.
15. Will any rules (informal or	Formal starting rule: patients would need to fulfil NICE/CDF criteria- ie – newly diagnosed patients with

formal) be used to start or stop treatment with the technology? Do these include any additional testing?	ovarian/fallopian tube/primary peritoneal cancer who have responded to front line chemotherapy; adequate baseline bloods for starting niraparib. Additional tests: Regular monitoring of blood test is required – weekly in month one and then on a monthly, 2 or 3 monthly basis once patients are established on maintenance therapy. Stopping rule: Indications to stop maintenance niraparib would include - patient with evidence of progression; patient requiring second line chemotherapy for disease relapse – in both these scenarios a CT scan is likely to be performed- but this would be a standard of clinical care intervention and not due to niraparib therapy.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Unsure
17. Do you consider the technology to be innovative in its potential to make a	Yes. The majority (80%) of patients with ovarian/fallopian tube/ primary peritoneal cancer have poor outcomes as they present with advanced incurable disease ovarian cancer. Maintenance PARP inhibitor therapy has the potential to significantly impact the progression free survival of these patients and for some

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	may offer a potential cure. Although the data currently immature for niraparib, current evidence indicates the effects of PARP inhibitors are a class effect in the frontline (SOLO1/ PRIMA/PAOLA/ Abbvie) and relapsed setting (NOVA/SOLO2/Ariel 3) and so the data seen with olaparib in the SOLO1 trial recently presented at ESMO are likely to be indicative for niraparib in the frontline setting, taking into account some of the different eligibility criteria (Olaparib- BRCA mutatnt patients only- indicates that after 5 years, 48.3% of patients treated with olaparib had not experienced disease progression and were still living with stable disease vs 20.5% of those taking placebo. Progression free survival was 56 months (olaparib), compared with 13.8 for individuals who received standard treatment only.) It is clear that PARP inhibitors are a significantly step forward in the treatment of this disease, with the potential for long term survival that has not been seen with any other therapy to date. Furthermore the benefits of these oral treatments extend beyond the time that patients are taking the therapy reducing the burden on patients and potentially healthcare costs –in the relapsed setting patients remain on medication until progression rather than a defined period in the front line setting. Preventing relapse is an essential outcome, as once relapsed generally this patient group are considered incurable.
• Is the technology a 'step-change' in the management of the condition?	Please see response above
• Does the use of the technology address any particular unmet need of	Please see response above.

the patient population?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main side effects of niraparib seen in clinical practice (as within the trials) have been haematological ad an effect on blood pressure. This requires increased initial monitoring in terms of blood tests (weekly for 1 month and then extending to monthly/2 or 3 monthly once patients have been on a tolerable dose). The majority of patients will monitor their own BP/ BP checked when attend clinic and the GPs/oncology teams can efficiently manage this. Neither of these factors have had a significant impact on patient compliance or acceptability/QOL in practice. Furthermore there is extensive experience of the use of niraparib in the relapsed setting in the UK. The use of an individualised starting dose has been widely adopted and led to a significant decrease in initial toxicity seen with flat dosing at 300 mg. The majority of patients, once on a suitable dose have tolerated niraparib well, with low rates of discontinuation (rates were higher in the trial due to flat dosing in 2/3 of the trial population). Niraparib is generally well tolerated and as it has the potential to delay recurrence, quality of life is improved due to a decrease in disease related symptoms.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes- the PRIMA trial reflects current UK practice. However we feel that the population with no residual disease after primary surgery should also be able to access niraparib in the front line setting. The PRIMA trial predominantly focused on a group of women with advanced ovarian cancer with a poorer prognosis: ie those patients who had residual disease after primary surgery or required neoadjuvant chemotherapy due to the initial inoperability of their disease. As a significant benefit in median progression free survival has been demonstrated even in this poorer prognostic subgroup we would extrapolate due to a class effect of PARP inhibitors that the benefit for

	women with no residual disease after primary surgery would also be seen (as has been demonstrated in the 2 other front line PARP inhibitor trials : SOLO1 –olaparib and PAOLA – olaparib and bevacizumab.
• If not, how could the results be extrapolated to the UK setting?	We feel that the population with no residual disease after primary surgery should also be able to access niraparib in the front line setting. The PRIMA trial predominantly focused on a group of women with advanced ovarian cancer with a poorer prognosis: ie those patients who had residual disease after primary surgery or required neoadjuvant chemotherapy due to the initial inoperability of their disease. As a significant benefit in median progression free survival has been demonstrated even in this poorer prognostic subgroup we would extrapolate due to a class effect of PARP inhibitors that the benefit for women with no residual disease after primary surgery would also be seen (as has been demonstrated in the 2 other front line PARP inhibitor trials : SOLO1 –olaparib and PAOLA – olaparib and bevacizumab.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes of progression free survival and quality of life/tolerability have been answered in the PRIMA trial and the assessment of overall survival continues. There was also a breakdown across BRCA/HRD subgroups that was important in further analysising the degree of benefit.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light	None known

subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world experience compare with the trial data?	There is extensive experience of the use of niraparib in the relapsed setting in the UK. The use of an individualised starting dose has been widely adopted and led to a significant decrease in initial toxicity seen with flat dosing at 300 mg. The majority of patients, once on a suitable dose have tolerated niraparib well, with low rates of discontinuation (rates were higher in the trial due to flat dosing in 2/3 of the trial population). As niraparib has the potential to delay recurrence quality of life is improved due to a decrease in disease related symptoms. The MONITOR trial (Banerjee et al) has just begun in the UK to assess the real world experience of olaparib –in terms of QOL and adverse events.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
23. In clinical practice, what is the estimated proportion of people with advanced ovarian, fallopian tube or peritoneal cancer who have responded to first-line platinum-based chemotherapy who have stage III disease with no visible residual disease: irrespective of type of debulking surgery; following interval debulking surgery and following primary debulking surgery?	This is difficult to accurately estimate for the whole of the UK as there is significant site specific variation with regards to primary and interval debulking after 3-4 cycles of chemotherapy and rates of complete cytoreduction. In some sites primary surgery rates may be 80% with the majority (60-70%) achieving complete resection (NRVD); other sites may have 70-80% neoadjuvant chemotherapy and achieve NRVD. These will be sites that are carefully defining operability and undertaking supra-radical multivisceral surgery. Across the UK there remains considerable variation and in some sites complete cytoreduction rates may be approximately 40% or less with either approach. The BGCS are due to release an audit of UK resection rates in October 2020. The EORTC and CHORUS trials reported a decade ago demonstrated significantly lower complete cytoreduction rates in the UK -EORTC12% and CHORUS 17% (primary surgery) and 39% (interval)- however the general consensus is that surgical resections rates have improved over the past decade
24. Do patients with stage III	There is conflicting data regarding the benefits of primary or delayed surgery. The 2 clinical trials completed

ovarian, fallopian tube or peritoneal cancer with no visible residual disease following debulking surgery have any difference in prognosis depending on whether they received primary debulking surgery or interval debulking surgery?	a decade ago (EORTC –Vergote et al and CHORUS – Kehoe et al) demonstrated a non inferiority of interval debulking surgery. However the criticism of both trials were the low rates of complete cytoreduction (NRVD) seen- 12 and 17 % respectively. The TRUST trial has now completed recruitment and this will assess the role of primary vs delayed primary surgery where the radicality of surgery is not a confounding factor- as it has been conducted only in international and UK supra- radical centres. A number of trials have demonstrated that achieving no residual visible disease is the most important factor for patients, and the timing of surgery may be less important. However others believe that the progression free survival rates are significantly better in those patients who undergo primary surgery, the results of the TRUST trial are awaited. It is possible that the use of maintenance therapies may be important in defining outcomes in these patients beyond the timing of surgery.
25. Is it plausible that people given niraparib would have a constant survival advantage over people on routine surveillance over a 39-year time horizon?	Yes. Patients may derive significant benefit and it is plausible that the survival advantages would persist with time; and may even be greater for some subgroups (BRCA and HRD deficient groups).
26. For this population, after	The majority of relapses would be expected to occur within 5 years in this group of patients. Data from an

how many years with progression-free disease can long-term remission be assumed?	audit in Edinburgh indicate that there is a small likelihood of relapse at 5-7 years and after that (7-10years) there is a significant decrease in the likelihood of relapse (*Gourley et al – pers comm*).
27a. Which groups of people with advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy eligible for treatment with niraparib would be expected to continue treatment after 3 years? 27b. What length of time is it reasonable to assume niraparib would continue to be given to people who did not discontinue treatment at 3 years?	27a The PRIMA trial targeted a poor prognostic group- those with targeted a Those groups of patients who still have residual visible disease could continue until progression. 27b – this would be a small group who had visible but controlled disease and did not require any alternative treatment. I am not sure how long-the additional use of niraparib may be required- but an estimate may be 1-2 years at most- but likely to be small percentage of patients.

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Key messages
28. In up to 5 bullet points, please summarise the key messages of your statement. • Important new treatment option for women with newly diagnosed ovarian/fallopian tube/primary peritoneal cancer • Potential to effect cures in a previously incurable disease • Oral, well tolerated therapy • Benefit regardless of BRCA and HRD status- although there were differences in magnitude of benefit • PARP inhibitor class effect and benefit likely even in better prognostic subgroup who have PDS and no residual disease

Thank you for your time.

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BMJ TAG

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy

Single Technology Assessment Report

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Mariana Bacelar	Critical appraisal of the company's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Rebecca Boffa	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Gemma Marceniuk	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

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List of Abbreviations

1L	First line
2L	Second line
AA	Aplastic anaemia
AACR	American Association for Cancer Research
ADP	Adenosine diphosphate
ADR(s)	Adverse drug reaction(s)
AE(s)	Adverse event(s)
AIC	Akaike information criterion
AML	Acute myeloid leukaemia
AR	Adverse reaction
ARCAGY	Association de Recherche Cancers Gynécologiques
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
AZ	AstraZeneca
BD	Twice daily
BER	Base excision repair
BGCS	British Gynaecological Cancer Society
BIC	Bayesian information criterion
BICR	Blinded independent central review
BID	Twice daily
BMI	Body mass index
BNF	British National Formularly
BoR	Best objective response
BRCA	Breast cancer susceptibility gene
BRCAm	Breast cancer susceptibility gene mutation
BRCAwt	Breast cancer susceptibility gene wild type
BSA	Body surface area
CA	Cancer antigen
CADTH	Canadian Agency for Drugs and Technologies in Health
CDF	Cancer Drugs Fund
CI(s)	Confidence interval(s)
CMU	Commercial Medicines Unit
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRF	Case report form
CS	Company submission
CSP	Clinical study protocol
CSR	Clinical study report

CTCAE	Common terminology criteria for adverse events
DCO	Data cut-off
DNA	Deoxyribonucleic acid
DSB(s)	Double-strand break(s)
DSU	Decision support unit
ECG(s)	Echocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EACR	European Association for Cancer Research
EED	Economic evaluation database
EMA	European Medicines Agency
ENGOT	European Network for Gynaecological Oncological Trial Groups
EORTC	European Organisation for the Research and Treatment of Cancer
EoT	End of treatment
EPAR	European public assessment report
EQ-5D-5L	EuroQoL five dimensions, five level
ERG	Evidence Review Group
ESGO	European Society for Gynaecological Oncology
ESMO	European Society of Medical Oncology
ESS	Effective sample size
FACT-O	Functional Assessment of Cancer Therapy – Ovarian Cancer
FAS	Full analysis set
FDA	Food and Drug Administration
FIGO	International Federation of Gynaecology and Obstetrics
FOSI	Functional Assessment of Cancer Therapy-Ovarian Symptoms Index
gBRCAm	Somatic breast cancer susceptibility gene mutation
GCIG	Gynaecologic Cancer Intergroup
GI	Gastrointestinal
GOTIC	Gynecologic Oncology Trial and Investigation Consortium
GPs	General practitioners
HER2	Human epidermal growth factor receptor 2
HGSOC	High-grade serous ovarian cancer
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRQoL	Health-related quality of life
HRR	Homologous recombination repair
HS1/2	Health state ½
HSUV	Health state utility value
HTA(i)	Health Technology Assessment (International)
IA	Investigator assessed

ICER	Incremental cost-effectiveness ratio
ICH / GCP	International Conference on Harmonisation Good Clinical Practice
ICTRP	International Clinical Trials Registry Platform
IDS	Interval debulking surgery
ILD	Interstitial lung disease
INCa	French National Cancer Institute
IPD	Individual patient data
IQR	Interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC(s)	Indirect treatment comparison(s)
ITT	Intention-to-treat
IVRS/IWRS	Interactive Voice Response System/International Web Response System
KM	Kaplan-Meier
LGS	Low-grade serous
LoE	Loss of exclusivity
LYG	Life years gained
MA	Marketing authorisation
MDS	Myelodysplastic syndrome
MDTs	Multidisciplinary teams
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
MMS	Monthly Index of Medical Specialities
NACT	Neoadjuvant chemotherapy
NCRAS	National Cancer Registration and Analysis Service
NCRI	National Cancer Research Institute
NE	Not estimated
NED	No evidence of disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NNT	Number needed to treat
NR	Not reported
NVRD	No visible residual disease
Olap+bev	Olaparib in combination with bevacizumab
OLS	Ordinary least squares
ORR	Overall response rate
OS	Overall survival
PAIC	Population-adjusted indirect comparison
PAITC	Population-adjusted indirect treatment comparisons
PARP	Poly ADP-ribose polymerase
PARPi	Poly-ADP ribose polymerase inhibitor

PAS	Patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PD	Progressed disease
PD-1	First progressed disease
PD-2	Second progressed disease
PDS	Primary debulking surgery
PFS	Progression-free survival
PFS2	Time to second progression/second progression-free survival
PLD	Pegylated liposomal doxorubicin
PLDH	Pegylated liposomal doxorubicin hydrochloride
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRES	Posterior reversible encephalopathy syndrome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
Q3W	Once every three weeks
QALY(s)	Quality-adjusted life-year(s)
QLQ-C30	Quality of Life Questionnaire for Cancer Patients (Core 30 item module)
QLQ-OV28	Quality of life Questionnaire for Ovarian Cancer Patients
RA	Regression-adjusted
RCT(s)	Randomised controlled trial(s)
RECIST	Response evaluation criteria in solid tumours
RD	Residual disease
RF	Replication fork
ROC	Receiver operating characteristic
SAE(s)	Serious adverse events(s)
SAP	Statistical analysis plan
SAS	Safety analysis set
sBRCAm	Somatic breast cancer susceptibility mutation
ScHARRHUD	School of Health and Related Research Health Utilities Database
SD	Standard deviation
SD	Stable disease
SGO	Society of Gynaecologic Oncology
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMDM	Society for Medical Decision Making
SmPC	Summary of product characteristics
SSB(s)	Single-strand break(s)
STA	Society for Medical Decision Making
tBRCA	Tumour breast cancer susceptibility gene

tBRCAm	Tumour breast cancer susceptibility gene mutation
TCGA	The Cancer Genome Atlas
TDT	Time to treatment discontinuation or death
TEAE	Treatment-emergent adverse event.
TFST	Time to first subsequent therapy
TNM	Tumour-Node-Metastasis
TSD	Technical support document
TSST	Time to second subsequent therapy
TTD	Time to treatment discontinuation
UDS	Upfront debulking surgery
ULN	Upper limit of the normal range
UK	United Kingdom
US NIH	United States National Institutes of Health
USA	United States of America
VEGF	Vascular endothelial growth factor
VRD	Visible residual disease
VUS	Variant of uncertain significance
WHO	World Health Organization

1 Executive summary

1.1 Critique of the decision problem in the company's submission

Evidence in support of the clinical effectiveness of the poly(ADP-ribose) polymerase inhibitor (PARPi) niraparib as maintenance therapy for people with advanced ovarian cancer and a complete or partial response to first line platinum-based chemotherapy is derived from two key analyses in the company submission (CS). The first is based on the intention to treat (ITT) population of the PRIMA trial ('ITT population'), which does not include stage III patients with no visible residual disease (NVRD) after primary debulking surgery (PDS). The second analysis ('MA population') combines data from the PRIMA trial with data from additional sources on people with stage III NVRD after PDS. This is intended to estimate the effectiveness of niraparib in this population and cover the full population in the NICE final scope and marketing authorisation (MA) for niraparib. The ERG does not agree that there is a discrepancy between the expected MA for niraparib and the population in PRIMA as the trial includes a substantial proportion of patients with stage III NVRD. Due to this, the ERG considers the rationale for conducting the company's MA population analysis to be flawed, and the ITT analysis of PRIMA to be the most robust and appropriate evidence to inform the clinical effectiveness of niraparib for the anticipated MA and the appraisal of niraparib by NICE. The ERG acknowledges that there could be differences in the proportion of NVRD patients seen in routine UK clinical practice compared with PRIMA, and that this could be addressed by adjustment of the PRIMA ITT results. However, the company's analysis has severe limitations due to the large number of assumptions, the use of indirect evidence, and the method of estimating treatment effects. The ERG instead considers it reasonable to perform a sensitivity analysis adjusting the PRIMA population to more closely reflect a possible different patient population in routine clinical practice.

The key applicability issues of PRIMA to the decision problem are:

- Population:
    - Stage III patients with NVRD after PDS were excluded, which may represent a large proportion of patients seen in UK clinical practice. Nonetheless, stage III patients with NVRD after interval debulking surgery (IDS) were included, as well as all stage IV patients with NVRD;
    - The ERG consider that this could be addressed by conducting sensitivity analysis of the PRIMA trial, whereby the proportion of patients with NVRD are reweighted to reflect UK practice (see section 2.4.3).
- Intervention:

- Participants were initially randomised to fixed dosing (300mg per day) but a protocol amendment during the trial introduced individualised dosing (based on specific patient clinical characteristics) of either 200 or 300 mg per day. The ERG notes that the expected MA of niraparib will include only individualised dosing. The company provides subgroup analysis of fixed versus individualised dosing. This is a *post-hoc* subgroup analysis and should be considered exploratory (see section 1.2.1 below);
- PRIMA employed a 3-year cap on niraparib treatment, although continuation of treatment after this was allowed (based on clinical judgement). The expected MA for niraparib is not expected to state a maximum treatment duration of 3 years.

- Comparator: the comparator in PRIMA was placebo, which the ERG considers an appropriate substitute for routine surveillance (RS).
- Outcomes: all outcomes outlined in the scope reported, however data for second progression (PFS2) and overall survival (OS) are immature.

1.2 Summary of the key issues in the clinical effectiveness evidence

1.2.1 PRIMA

In PRIMA, patients were randomised to niraparib 300mg per day or placebo, though, due to a high number of adverse events (AEs) leading to dose reductions the trial protocol was amended (on 27 November 2017) to individualised dosing (section 2.2). Individualised dosing was based on weight and platelet count, whereby participants started on a lower dose of 200mg per day if they weighed <77kg or had a baseline platelet count <150,000/µL. In order to explore the extent to which the overall results may be driven by the effectiveness in patients who started on the 300 mg dose, the company provided progression-free survival (PFS) subgroup data based on fixed and individualised dosing at the clarification stage.

Just under two thirds (64.8%) of patients enrolled in PRIMA started on the fixed 300 mg dose, and 35.2% started on individualised dosing. Maintenance therapy with niraparib resulted in a longer median PFS both in the fixed ([redacted] months) and individualised dosing ([redacted] months) groups compared with placebo ([redacted] months for both fixed and individualised dosing), though the subgroup analyses indicate that niraparib may be slightly less effective on individualised dosing compared with fixed dosing (section 2.3.1). That is, the ITT analysis may overestimate the efficacy of niraparib expected in clinical practice as the proportion of patients starting on the 300 mg dose was higher in the trial than would be expected in clinical practice, where all patients will be offered individualised dosing. However, these subgroup analyses should be considered exploratory in nature, because they

are *post-hoc* non-stratified subgroup analyses, the difference between the subgroups were not statistically significant but PRIMA was also not powered to detect a difference between these groups. Importantly, individualised dosing led to fewer dose interruptions and dose reductions due to adverse events (AEs) than the fixed dose (section 2.3.3).

In PRIMA, PFS2 and OS data were very immature with only [redacted] and [redacted] having experienced a second progression in the niraparib and placebo arm, respectively, and 9.9% and 12.6% of people having died in the niraparib and placebo arms at the time of analysis (section 2.3.2), respectively. The lack of mature data for the long-term outcomes has important impacts on the economic modelling approach as described below in section 1.3; section 4.2.4; and section 4.2.6.

1.2.2 The company MA analysis

Although the ERG considers PRIMA to adequately reflect the population of the MA for niraparib, it acknowledges that the proportion of patients with stage III NVRD in PRIMA may be lower than in UK clinical practice, which could be addressed by adjustment of the PRIMA ITT results. In order to adjust the ITT results the company estimated the following data, which were subsequently applied in the economic model:

1. The proportion of patients in the MA population with stage III and NVRD (section 2.4.2). This estimate was based on a cohort of patients in the Edinburgh Ovarian Cancer Database and the PAOLA-1 trial (a randomised controlled trial [RCT] assessing the efficacy of olaparib and bevacizumab vs bevacizumab as maintenance therapy after first-line chemotherapy). The estimate of [redacted] based on the Edinburgh dataset is for stage III NVRD after IDS or PDS, rather than limited to only those who had had PDS, which is the population excluded from PRIMA. An estimate for stage III NVRD irrespective of type of surgery is of limited value for informing this appraisal as it is different from the population excluded from PRIMA. However, as an estimate of stage III NVRD irrespective type of surgery, it is likely to be an underestimate. The ERG's clinical experts estimate that the proportion of patients with stage III and NVRD is likely to be closer to 50-60% in the UK, and highlight that the proportion of patients with NVRD after surgery varies across the UK. Basing this estimate on one small region in the UK may therefore not be representative of the surgical outcomes seen across the country. In addition, the company did not conduct a systematic literature review (SLR) to identify other relevant sources to inform this proportion. Data from PAOLA-1 supports the assumption that stage III NVRD after PDS may constitute [redacted] of the MA population. However, the ERG's

clinical experts advised that this may also be an underestimate as the proportion of patients with stage III NVRD after PDS may be from 25% to 40% of the population.

2. 'NVRD effect' - The difference in outcomes between patients with stage III NVRD after PDS compared with populations similar to the ITT population of PRIMA based on PAOLA-1 and SOLO-1 (RCT assessing the efficacy of olaparib as maintenance therapy compared with placebo after first-line chemotherapy in patients with a BRCA mutation) (section 2.4.4). The ERG notes that the 'NVRD effect' estimated by the company based on PAOLA-1 and SOLO-1 has limited generalisability to PRIMA due to confounding caused by substantial differences in populations, interventions and trial design which have not or can not be adjusted for. The ERG has concerns about the appropriateness of applying a hazard ratio (HR) estimated from one trial and applying it directly to the PFS curves in PRIMA, particularly when PHs have been demonstrated not to hold for PFS in PRIMA. The company provided no justification for the approach taken.
3. A potential PARPi specific 'treatment effect' in patients with stage III NVRD after PDS compared with populations similar to the ITT population of PRIMA, based on PAOLA-1 and SOLO-1 (section 2.4.4). The evidence in support of an increased PARPi specific treatment effect in patients with stage III NVRD is sparse, uncertain, and of limited generalisability to PRIMA due to confounding. As for the 'NVRD effect', the ERG has concerns about the appropriateness of applying a HR, in this case estimated for a different treatment, in one trial and applying it directly to the PFS curves in PRIMA. This relies on the assumption of a class effect, i.e. that any relative treatment effect observed with olaparib will be the same for niraparib. An assumption for which the company has not provided support (as the relevant data are not available for niraparib to enable a comparison between PARPis).

1.2.3 The ERG's approach for adjusting PRIMA

Although the ERG considers PRIMA to adequately reflect the MA for niraparib, it acknowledges that the proportion of patients with stage III NVRD in PRIMA (stage III NVRD after IDS was [redacted] and NVRD irrespective of stage was 47%) may be lower than in UK clinical practice. As described above, the company has not provided a robust estimate of the proportion of patients with stage III NVRD after PDS (excluded from PRIMA) or of patients with stage III NVRD irrespective of type of surgery. Data from Hall *et al*. 2019, from two UK centres, show that the proportion of patients with NVRD after surgery (irrespective of stage of disease) ranges between 59% and 85%, depending on surgical expertise, and Vergote *et al*. 2010 showed that the proportion of patients with NVRD was 19% and

51% after PDS and IDS, respectively. As mentioned above, the ERG's clinical experts estimate that the proportion of patients with stage III NVRD irrespective of type of surgery is likely to be 50-60% and the proportion of patients with stage III NVRD following PDS to be between 25-40% in UK clinical practice.

The ERG therefore advises the company to explore the impact on results of re-weighting the proportion of patients with stage III NVRD after IDS in PRIMA to be reflective of the proportion of patients with stage III NVRD (irrespective of type of surgery) in clinical practice (section 2.4.3). There are several methods that can be employed for this, e.g. in a previous NICE appraisal (TA558) the corrected group prognosis method was used in preference to the average covariate method; however, the ERG is aware that the inverse probability of treatment weights (IPTW) may also be used.

The approach of reweighting outcome data for patients within PRIMA has several advantages over the methods used by the company for extrapolating the outcomes of PRIMA (sections 2.4.2 and 2.4.4). The ERG's approach relies solely on data from the key trial rather than estimating effects from other trials and applying them to PRIMA. Issues around comparability between trials due to differences in patient characteristics, interventions, and study design are therefore avoided and do not need to be considered or adjusted for. The approach of reweighting PRIMA data also avoids the assumption of a PARPi class effect for which there is limited evidence. The proposed approach also benefits from relying on individual patient data (IPD) rather than pseudo IPD or aggregate data. In addition, there is no need to estimate a separate 'NVRD effect' and 'treatment effect' as for the company approach.

Similar to the company's approach, the ERG's approach relies on a robust estimate of how big the proportion of patients excluded from PRIMA can be expected to make up of the patient population in clinical practice. In addition, the ERG acknowledges that the certainty of the clinical effectiveness results based on the suggested approach is reliant on the assumption of similar prognosis for patients with stage III NVRD after PDS and IDS. Vergote *et al.* 2010 has shown that there is no significant difference in PFS and OS based on type of surgery, i.e. PDS or IDS, and although subgroup analyses indicate that there might be a difference in prognosis between patients with NVRD after PDS and IDS, the evidence is not conclusive. Therefore, based on the opinion of the ERG's clinical experts, the prognosis of patients with stage III NVRD after PDS and IDS can be considered equivalent.

1.3 Alterations to the ERG's report as a result of the corrections made by the company after the factual accuracy check stage

As a result of the factual accuracy check (FAC), the company submitted a corrected model (hereafter referred to as the company's post-FAC model). This correction pretrained to the "goal seek" analysis in Excel used to estimate the HR between the RS and niraparib OS curves.

NICE requested that the ERG incorporated the results of the company's post-FAC model in the original ERG report. Therefore, the ERG has updated this report to include all the relevant results obtained from the company's post-FAC model (presented in Section 5). The ERG also notes that the error related to the use of the "goal seek" analysis described in Section 3.2.6 of the ERG report has been resolved in the company's post-FAC model.

The ERG found additional errors in some of the scenario analyses included in the company's post-FAC model. The scenarios for varying the assumption of the number of years after which PFS patients stop incurring disease management costs were not working in the company's post-FAC model. After correcting these, however, the ERG notes that given the extreme time constraint to provide this update to the ERG report, it could not undertake a thorough review of the company's post-FAC model.

1.4 Summary of the key issues in the cost effectiveness evidence

The key issues identified in the economic and clinical evidence used in the economic analysis relate to:

1. The use of the MA population in the model;
2. Assuming patients are cured in the economic analysis;
3. Use of niraparib PFS as a surrogate measure of OS for niraparib;
4. The dose of niraparib used in PRIMA;
5. Immaturity of subsequent treatment data; and second progression data in PRIMA;
6. Immaturity of OS KM data from PRIMA.

Use of the MA population in the model

The ERG considers that the ITT population in PRIMA is representative of niraparib's MA as the study includes 47% of patients with NVRD after PDS or IDS. Given that the company's rationale for generating an MA population is mainly based on the fact that NVRD patients have better outcomes than patients with VRD (section 3.4), the ERG considers that PRIMA does not only provide sufficient

evidence to address this issue, but is also the most robust source of evidence available to estimate the cost-effectiveness of niraparib vs RS.

Furthermore, given the conclusions presented in the ESMO guidelines for newly diagnosed and relapsed epithelial ovarian carcinoma that patients with stage IIIC and IV have similar outcomes after IDS and PDS, the ERG argues that the clinical outcomes for patients undergoing IDS in PRIMA are representative of the outcomes that would be observed in patients undergoing PDS in clinical practice.

However, the ERG acknowledges that because PRIMA excluded patients with stage III, NVRD after PDS, the overall proportion of patients with NVRD in PRIMA (47% in total; consisting of [redacted]% stage III NVRD and [redacted]% stage IV NVRD) might have been lower than in UK clinical practice, where the total proportion of patients with NVRD after surgery can range between 50% and 80%, depending on surgical expertise. Therefore, the ERG recommends that the company adjust the PRIMA results to reflect a higher proportion of patients with stage III, NVRD (as explained in section 3.4).

Assuming patients are cured in the economic analysis

The ERG considers the method used by the company to estimate cure in the model unfit for decision making. The latter relies on a weak methodology, given that both the proportion of patients cured and the cure threshold were exogenously chosen by the company. The company justified not undertaking a more methodologically robust approach to estimating cure in the model, such as a mixed cure model (MCM), due to the lack of long-term data from PRIMA or individual patient-level data from real-world sources. The ERG notes that the lack of mature OS data should not be used to justify employing a methodologically weaker alternative to estimating cure in the model.

Furthermore the ERG considers that: 1) if PRIMA does not provide mature enough evidence to substantiate a MCM approach, then neither does it provide a robust source of evidence to substantiate modelling a cure approach with niraparib or RS in the model; and 2) external sources of evidence are not robust enough to suggest when a cure threshold would be reached for niraparib, although there does seem to be some evidence to support the idea that patients receiving RS who are PF at 5 years (and therefore also at 7 years) are at low risk of recurrence.

Use of niraparib PFS as a surrogate measure of OS for niraparib

The ERG does not consider that enough robust evidence exists to substantiate the use of PFS as a surrogate measure of OS in the OC setting. There is however, some literature suggesting that if the

effect of a treatment for OC extends PFS by x months, it is reasonable to estimate that the treatment will also extend OS by x months, meaning that, "*the magnitude of the improvement in PFS is the magnitude of the improvement in OS.* [Therefore], *PFS is simply a measure of a drug's effect on tumour growth while it is administered and is not a surrogate for OS*".

Most importantly, the results generated from the company's approach to estimating an OS curve for niraparib are inconsistent with the OS data observed in PRIMA. Firstly, the HR of [redacted] used by the company in the ITT model to generate the 1:2 ΔPFS:ΔOS relationship suggests a much higher relative treatment effect for niraparib vs RS than that observed in PRIMA – HR of 0.70 (95% CI: 0.44 to 1.11). Secondly, at 19 months, the modelled niraparib and RS OS curves are on a [redacted] trajectory, suggesting that the relative treatment effect for niraparib does not diminish over time, while the underlying KM data from PRIMA shows a possible [redacted] in the curves. Given the company's methodology relies on applying a HR to the OS RS arm to estimate OS for niraparib, the benefit of niraparib over RS will be generated over the lifetime of patients. However, the ERG notes that there is no real evidence to substantiate the latter assumption.

Finally, the ERG notes that the estimation of OS for niraparib in the model was based on the equation: niraparib mean OS = (RS mean OS + [Mean PFS difference between niraparib and RS x 2]). This equation not only implies that the OS benefit for niraparib is based on the PFS to OS ratio used in the model (1:2), but also that this is based on the mean PFS difference estimated through the extrapolated PFS curves in the company's base case. Therefore, any overestimation of the relative treatment effect of PFS is doubled in the OS curves. Not surprisingly, this means that the PFS to OS ratio employed in the model to generate the OS curves is the key model driver.

In summary, the ERG notes that the cure approach (applied to both the PFS and the OS curves in the model) affects the estimation of the niraparib OS curve via two different routes (Figure A). This is because:

- The cure approach used in the model affects the mean difference in the PFS curves as from year 7 all PFS patients accrue the general population mortality and there is a higher; percentage of patients in the PFS niraparib curve at 7 years compared with the RS PFS curve;
- Any mean difference between the niraparib and RS PFS curves is doubled in the estimation of the difference between the niraparib and RS OS curves;

- The cure approach used in the model also affects the OS curves as the latter are composed of weighted survival by the number of patients cured (determined by the PFS curves).

Figure A. Impact of the cure approach on PFS and on the PFS to OS ratio in the ITT model to estimate OS for niraparib

The dose of niraparib used in PRIMA

The ERG notes that from month 7 in PRIMA, [redacted]. The ERG's clinical experts were surprised by the large proportion of patients reduced to a 100mg dose in PRIMA due to the lack of published evidence on the effectiveness of a 100mg dose. The ERG therefore, notes the potential relevance of further investigation of the lower dose of niraparib (100mg) and its impact on clinical outcomes for OC patients.

Immaturity of subsequent treatments data and second progression data in PRIMA

In PRIMA, there were 232 progression events in the niraparib arm and 154 progression events in the RS arm. When compared to the number of patients receiving 2L chemotherapy, the proportion of patients who progressed who also received subsequent chemotherapy in PRIMA amount to 85% and 81% for niraparib and RS, respectively. The ERG notes that the number of patients receiving subsequent treatments in PRIMA is lower than what is expected in UK practice and lower than what has been reported in other trials for the same disease area. For example, the ERG in TA598 reported

that the CSR for SOLO-1 suggests that 90% and 93% of the patients who progressed received subsequent chemotherapy in the olaparib and placebo arms, respectively.

Nonetheless, the ERG acknowledges that the PRIMA data are immature and therefore the available data on subsequent treatments needs to be interpreted with caution. The ERG stresses the importance of interpreting the future results for more mature OS data together with the more mature data on subsequent treatments received in PRIMA. The ERG also notes that analysis of PFS2 in PRIMA resulted in a non-statically significant HR of 0.82 (95% CI: 0.577 to 1.139). [redacted]; however, it is not possible to ascertain if niraparib is associated with a delay in second progression events without having more mature PFS2 data.

Immaturity of OS data in PRIMA

During the clarification stage, the ERG requested that the company fitted parametric models to the niraparib OS KM data from PRIMA. The company replied that the niraparib KM data in PRIMA are too immature (10%) and therefore inappropriate to fit parametric models. However, the ERG notes that the RS KM data in PRIMA are equally immature (13%) and the company used these data to fit a log-logistic curve to estimate RS OS in the model. The company's approach and justification are, therefore, highly inconsistent.

Given the uncertainty around the survival benefit associated with niraparib, the ERG does not have a preferred base case ICER and instead suggested three plausible exploratory analyses.

The ERG acknowledges that the immaturity of the OS KM data could potentially lead to modelling issues such as obtaining valid long-term survival predictions. Nonetheless, there are options to make survival curves flexible and adjust long-term survival estimates to achieve clinically valid tails, without having to use HRs, and thus assuming a constant survival benefit between treatment arms.

1.5 Summary of the ERG's assumptions and resulting ICER

The ERG proposes three sets of exploratory analysis combining different scenarios. The common preferred assumptions for the three scenarios in the economic model are listed below:

1. Use of the ITT population in the model;
2. Removal of the cure approach from the model and assuming PFS patients stop incurring disease management costs at 10 years;
3. Applying age-related utility decrements in the model;
4. Assuming no treatment discontinuation with niraparib as per the SmPC;
5. Including the cost of heart rate and blood pressure monitoring;
6. Using alternative resource use estimates for PFS.

In addition to the changes listed above, the ERG undertook three different sets of combined scenarios:

a) Use of a PFS to OS ratio of 1:0.66 as proposed in the company in TA598;
b) Use of a PFS to OS ratio of 1:1;
c) Use of a HR between RS OS and niraparib OS of 0.70 as observed in PRIMA.

Results of these analyses are reported in Table A for the ITT population. When the PFS to OS ratio of 1:0.66 is used in the model, the ICER amounts to £79,077 per QALY gained. When it is assumed that the magnitude of the improvement in PFS with niraparib is the same as the magnitude of the improvement in OS (i.e. using a PFS to OS ratio of 1:1), the ICER decreased to £45,226 per QALY gained.

The ERG notes that the OS HR for niraparib vs RS observed in PRIMA was of 0.70 (95% CI: 0.44 to 1.11), albeit not statistically significant. When a HR of 0.70 is used in the model, this leads to an ICER of £38,252 per QALY gained. This, in its turn corresponds to a PFS to OS ratio of 1:1.13 (1 month of extra PFS lead to 1.13 months of extra OS). However, given the lack of maturity and statistical significance of the HR in PRIMA, and the shape of the OS curves (see section 4.2.6.1.1), it is possible that the survival benefit with niraparib is much smaller. Given the lack of maturity of the data, it is also possible that the survival benefit of niraparib is higher than that observed in PRIMA.

When it is assumed that niraparib and RS have the same OS, the ITT ICER increases to £950,200 per QALY gained. The ERG concludes that without having more mature OS data from PRIMA it is not

possible to make inferences on the survival benefits of niraparib without a paramount level of uncertainty.

For all the analyses conducted by the ERG, it was assumed that niraparib has a constant survival advantage over RS for the entire time horizon of the analysis (given the use of a HR). The ERG considers that given the availability of OS KM data for niraparib from PRIMA, the company could have presented an option in the model to use these data, instead of using PFS as a surrogate outcome to estimate OS, and instead of forcing an assumption of a constant relative treatment effect for niraparib.

Finally, the ERG notes that while fitting an independent OS curve to the niraparib arm of the model would not solve the problems associated with the lack of maturity of OS data, it could provide an estimate long-term survival without having to assume a constant survival benefit between treatment arms.

Table A. Results of ERG's exploratory analysis for the ITT population

		Niraparib	RS	Inc. value
1	**Use of a PFS to OS ratio of 1:0.66 as per TA598**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			£79,077
2	**Use of a PFS to OS ratio of 1:1**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER	-	-	£45,226
3	**Use of a HR between RS OS and niraparib OS of 0.70**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			£38,252
	Abbreviations: ICER. Incremental cost-effectiveness ratio; Inc. incremental; ITT, intention to treat; OS, overall survival; PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life year; RS, routine surveillance; TA, technology appraisal			

Introduction and background

1.6 Introduction

Herein is a critique of the evidence submitted to the Single Technology Appraisal (STA) in support of clinical and cost effectiveness of niraparib (Zejula®; GlaxoSmithKline) as a regimen to maintain response to first-line platinum-based chemotherapy for adults with newly diagnosed advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (hereafter, collectively referred to as ovarian cancer).[1]

1.7 Background

Within section B.1.3 of the CS, the company provides an overview of ovarian cancer, including diagnosis, staging and management of advanced ovarian cancer (section B.1.3). The ERG considers the CS to present accurate overviews of ovarian cancer that are relevant to the decision problem. Additionally, based on advice from its clinical experts, the ERG considers the CS to provide an accurate description of the current treatment algorithm for the management of people with ovarian cancer.

In short, surgery is typically the preferred initial treatment, the goal of which is to excise all macroscopic disease (cytoreduction), irrespective of stage of disease. In cases where the clinician deems that complete or optimal cytoreduction of the tumour is achievable, primary debulking is recommended (Figure 1).[2] In cases where complete cytoreduction is not thought to be feasible, chemotherapy can be administered prior to surgery (neoadjuvant chemotherapy), with the objective of shrinking the tumour to facilitate complete excision and improve the probability of removal of all macroscopic disease: when surgery is performed following administration of neoadjuvant chemotherapy it is referred to as interval debulking surgery.[2]

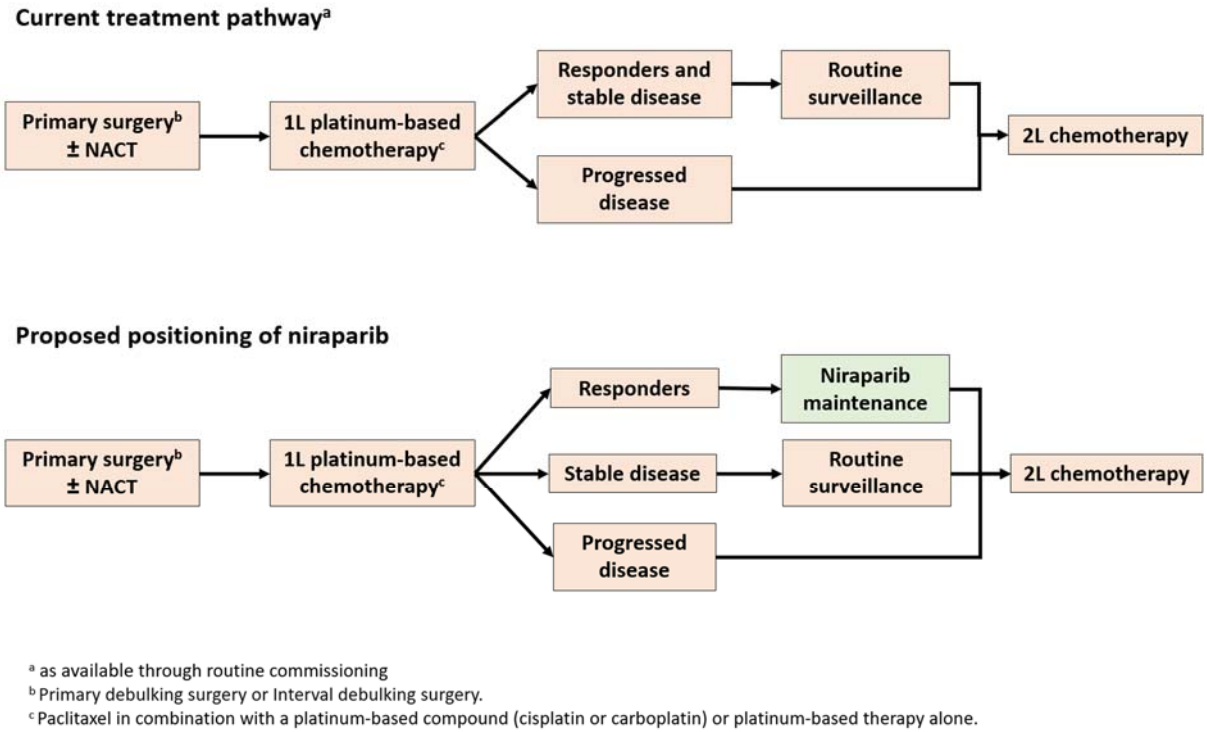
First-line chemotherapy is the first round of chemotherapeutic treatment a patient receives, whether it is as a neoadjuvant treatment before surgery or an adjuvant treatment following surgery. Second and subsequent line treatment is for those who have either relapsed after first-line chemotherapeutic treatment or experienced progression of their disease while receiving chemotherapy requiring a change in treatment regimen.

At the time of writing, national guidelines recommend cytotoxic chemotherapy after surgery, to reduce the risk of disease recurrence, with carboplatin in combination with paclitaxel typically the preferred chemotherapy regimen in this setting.[2] On completion of first line chemotherapy, people are followed up to monitor for recurrence of disease, with no further treatment available through

routine commissioning (routine surveillance; Figure 1) until relapse. However, maintenance treatments are available through the Cancer Drugs Fund (CDF) with olaparib for patients with a BRCA mutation (BRCA+) and with bevacizumab for patients at high risk of progression (stage III and RD ≥ 1cm, stage IV, or stage III requiring neoadjuvant chemotherapy).[3]

The proposed positioning of niraparib is as a treatment to maintain response to first-line chemotherapy, and, more specifically, a complete response (CR), partial response (PR) or no evidence of disease (NED) must have been achieved at completion of first-line platinum-based chemotherapy (Figure 1). The ERG and its clinical experts consider the proposed position of niraparib in the treatment pathway to be appropriate. Thus, if recommended by NICE, niraparib would be placed as a maintenance treatment option after one line of platinum-based chemotherapy.

Figure 1. Clinical pathway



[a] as available through routine commissioning
[b] Primary debulking surgery or Interval debulking surgery.
[c] Paclitaxel in combination with a platinum-based compound (cisplatin or carboplatin) or platinum-based therapy alone.

1.8 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by NICE together with their rationale for any deviation from the final scope (Table 1. Summary of decision problem (adapted from the CS Table 1). The company considers that the population within the evidence underpinning the CS (the PRIMA trial)[4] differs both from the NICE final scope[1] and the anticipated marketing authorisation (MA), because it did not include people with stage III OC with no visual residual disease (NVRD) after

primary debulking surgery (PDS). The company conducted further analyses using evidence from additional studies to estimate the clinical and cost-effectiveness of niraparib in the MA population. The ERG does not agree that there is a discrepancy between the expected MA and the population in PRIMA. The ERG instead considers that there could be differences in the proportion of NVRD patients seen in routine UK clinical practice compared to with PRIMA. This is discussed in in further detail in section 1.8.1.

The differences between the decision problem addressed in the CS and the scope are discussed in more detail in the sections that follow.

Table 1. Summary of decision problem (adapted from the CS Table 1)

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	ERG comment
Population	People with advanced ovarian, fallopian tube, or primary peritoneal cancer that has responded (complete or partial) to first-line platinum-based chemotherapy.	Cost-effectiveness analyses are presented for the expected marketing authorisation population, as per scope. The cost-effectiveness results for the marketing authorisation (MA) population, which is defined as the ITT population in the PRIMA trial plus patients with stage III patients with no visible residual disease after primary cytoreductive surgery (NVRD). Cost-effectiveness results are also presented for the ITT PRIMA population to provide additional confidence in the MA results.	It is anticipated that the MA for niraparib in the first-line maintenance setting will consist of adult patients with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line PBC. The anticipated licensed population includes patients with NVRD; this group of patients has a better prognosis than patients with visible residual disease. The submission explicitly considers the impact of incorporating this population into the analyses. Evidence from additional studies was used to demonstrate this difference in prognosis and to inform the cost-effectiveness analyses in the MA population.	The ERG notes that the CS involves two key analyses. The first is based on the PRIMA trial ('ITT population'), which does not include Stage III patients with NVRD after PDS. The second analysis ('MA population') combines data from the PRIMA trial with data from additional sources for people with Stage III NVRD after PDS. This is intended to estimate the effect of niraparib in this population and cover the full population in the NICE scope and marketing authorisation. The ERG does not agree that there is a discrepancy between the expected MA and the population in PRIMA. The ERG instead considers that there could be differences in the proportion of NVRD patients seen in routine UK clinical practice compared with PRIMA. This is explored below.
Intervention	Zejula (niraparib)	As per scope	N/A	The clinical evidence underpinning the CS involved participants either starting on fixed dosing (300mg per day) or individualised dosing (based on specific patient clinical characteristics) of either 200 or 300 mg per day. This was due to a protocol change in the trial. The ERG notes that the expected MA of niraparib will involve only individualised dosing.

				The company provides subgroup analysis of fixed versus individualised dosing, although the ERG note this is a *post-hoc* subgroup analysis and should be considered exploratory.
Comparator(s)	Routine surveillance	As per scope	N/A	The comparator in PRIMA was placebo, which the ERG considers an appropriate substitute for routine surveillance.
Outcomes	• overall survival (OS) • progression-free survival (PFS) • progression-free survival 2 (PFS2) • time to first subsequent therapy • adverse effects of treatment • health-related quality of life.	As per scope	N/A	All outcomes outlined in the scope reported, however data for PFS2 and OS are immature.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the	As per scope	N/A	The ERG notes that a commercial arrangement with a simple discount is currently in operation for the second-line indication or niraparib [redacted]

	intervention or comparator technologies will be taken into account.				
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • subgroups by BRCA mutation status	Clinical efficacy data from the PRIMA trial is presented, including results for the ITT population, as well as by BRCAmut subgroup. Cost-effectiveness analyses are not presented by BRCAmut subgroup.	The clinical data from the PRIMA trial showed that both the BRCAmut population and non-BRCAmut population benefited from a statistically significant PFS HR for niraparib compared with placebo. Patients in both patient populations should thus be considered in discussions around access to this medicine.	The CS presents subgroup data for people with and without BRCA mutation, but the ERG notes that randomisation was not stratified by BRCA mutation status (although it was stratified by HRD status) and that the subgroup analysis is considered exploratory in nature.	
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	There are no special considerations relating to issues of equity or equality.	N/A		

Abbreviations: BRCA, breast cancer susceptibility gene; CS, company submission; ERG, evidence review group; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to treat; MA, marketing authorization; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NVRD, no visible residual disease; OC, ovarian cancer; OS, overall survival; PBC platinum-based chemotherapy; PDS, primary debulking surgery; PFS, progression-free survival; UK, United Kingdom

1.8.1 Population

Clinical effectiveness data for niraparib are derived from the PRIMA trial, a multicentre international RCT with the participating centres based in 20 countries across 181 clinical sites, including 10 centres in the UK. The trial enrolled adults with newly diagnosed advanced (FIGO stage III to IV) high-grade serious or endometrioid tumours of the ovary, peritoneum or fallopian tube and a complete or partial response to first line platinum-based chemotherapy. People with no visual residual disease (NVRD) after primary debulking surgery (PDS) were excluded. The ERG's clinical experts consider the trial population largely representative of those seen in UK practice, with the exception of the exclusion of people with NVRD after PDS. The company concludes that, as the anticipated licensed population includes patients with NVRD, the PRIMA population is not fully representative of the expected MA population nor of the full NICE scope. In order to address this gap in the evidence, the company presents two different approaches, one in accordance with the PRIMA trial population and the other intending to address the full NICE scope and MA population:

- ITT population analysis (including only the PRIMA population);
- MA population analysis (including estimated treatment effects in people with NVRD after PDS in addition to the PRIMA population).

However, the ERG notes that PRIMA includes both stage IV patients with NVRD after PDS or interval debulking surgery (IDS), as well as stage III patients with NVRD after IDS. Due to this, the ERG considers the PRIMA population to be fully representative of the MA population. However, the ERG considers that there could be possible differences between PRIMA and the population seen in routine UK clinical practice, in terms of the proportion of patients with NVRD. The implications of this are discussed in sections 2.4 and 3.2.2.

The clinical evidence generation for the MA population involved four key assumptions:

- Patients with stage III NVRD after PDS have a better prognosis than patients with stage III/IV VRD;
- PARP inhibitors demonstrate improved clinical outcomes in patients with stage III NVRD
- Stage III patients who have NVRD constitute [redacted] of the MA population;
- Patients with stage III NVRD are at risk of recurrence and death and therefore have a high unmet need.

The estimated treatment effect of niraparib in people with NVRD after PDS was based on estimates of PFS from PAOLA-1, an RCT comparing olaparib + bevacizumab versus placebo + bevacizumab in women with ovarian cancer.[5] Subgroup analyses of the trial were used, which compared PFS in people with stage III NVRD after PDS versus the rest of the trial population. Similar subgroup analyses were available from SOLO-1, an RCT comparing olaparib versus placebo in people with ovarian cancer who had a BRCA mutation.[6] The company used the PAOLA-1 data for their primary MA population analysis and used SOLO-1 data in a scenario analysis. Furthermore, the estimated prognosis of people with NVRD not on treatment was further based on a similar PAOLA-1 comparison of PFS in the placebo + bevacizumab arm of PAOLA-1 (as a substitute for routine surveillance). See section 2.4 for a full critique of these methods.

The CS based estimates of the prevalence of stage III NVRD following PDS in a subset of patients in the University of Edinburgh Ovarian Cancer Database. The company considers that this subset matched the inclusion criteria of PRIMA and a subset that matched the anticipated MA for niraparib. The database contains outcome data for patients diagnosed with OC in the South East region of Scotland. The clinical experts advising the ERG consider that the proportion of patients with NVRD can vary considerably across clinical practice. See section 2.4 for a full critique of these methods.

The ERG critiques both the ITT and MA analyses in the following sections. The ERG explores the validity and robustness of both analyses, paying particular attention to the methodology and underlying assumptions of each. In general, the ERG considers the MA population analysis to have severe limitations due to the large number of assumptions (see above), the use of indirect evidence and estimated treatment effects, and differences in the population and interventions between PRIMA and PAOLA-1 (see section 2.4). Moreover, the ERG considers the rationale and justification for conducting this approach is limited in itself, given that the PRIMA trial included stage III NVRD patients and is therefore representative of the full MA population.

The ERG considers that basing recommendations for niraparib on the ITT population would be a more robust approach as it is solely based on direct randomised trial evidence. The ERG considers that the additional uncertainty caused by including indirect evidence is unnecessary. Although the ERG considers PRIMA to adequately reflect the MA population it notes that the proportion of patients with stage III NVRD in PRIMA could be an underestimate compared with the proportion among patients in UK clinical practice. The ERG therefore considers it reasonable to perform a sensitivity analysis adjusting the PRIMA population to more closely reflect a possible different

patient population in routine clinical practice. A key assumption of this approach would be that the prognostic benefit of NVRD after IDS is equivalent to that of NVRD after PDS. Based on the opinion of the ERG's clinical experts, the prognosis of patients with stage III NVRD after PDS can be considered equivalent to patients with stage III NVRD after IDS (for which data are available in PRIMA). See section 3.4 for full details.

1.8.2 Intervention

The NICE final scope specifies the intervention of interest for this appraisal as treatment with niraparib, which is consistent with the evidence presented by the company. The ERG notes that the duration of treatment in PRIMA may not be consistent with clinical practice, whereby participants in PRIMA could be treated for up to 3 years in the trial, after which time continuation of treatment was based on clinical judgement. However, it is expected that the anticipated MA for niraparib will not specify that treatment be capped at 3 years. Clinical experts advising the ERG note that decisions to continue niraparib treatment after 3 years may vary in practice and be based on individual characteristics of the patient.

In PRIMA, patients were randomised to niraparib 300mg per day or placebo, though, due to a high number of adverse events (AEs) leading to dose reductions the trial protocol was amended (on 27 November 2017) to individualised dosing. Individualised dosing was based on weight and platelet count, whereby participants started on a lower dose of 200mg per day if they weighed <77kg or had a baseline platelet count <150,000/µL. Due to this, 64.8% of participants in PRIMA started on fixed 300mg dosing (prior to the protocol change) and 35.2% started on individualised dosing. The ERG notes that mean dose differed only slightly between fixed and individualised dosing (see section 2.3.3). The ERG notes that the expected MA of niraparib involves the same individualised dosing based on platelet counts and body weight.

There is therefore a discrepancy between dosing in PRIMA and in the expected MA of niraparib and thus dosing that would occur in clinical practice. PRIMA may include a larger proportion of people on a higher dose than expected in clinical practice, given that more people started on 300mg than is likely to occur in clinical practice via individualised dosing. section 2.3.1 and 2.3.3 explore the efficacy and safety evidence of the two dosing strategies. However, the ERG note that these subgroup analyses should be considered exploratory in nature, because they are *post-hoc* non-stratified subgroup analyses, and PRIMA was not powered to detect a difference between these groups.

1.8.3 Comparator

The NICE final scope specifies the comparator of interest for this appraisal as routine surveillance after first-line platinum-based chemotherapy, which is the treatment option available to patients through routine commissioning. The PRIMA trial compared niraparib with placebo, which the ERG considers an adequate substitute for routine surveillance.

1.8.4 Outcomes

All the outcomes listed in the NICE final scope were captured and reported in PRIMA. The health states in the economic model are informed by data for PFS, the primary endpoint of the trial, and the secondary outcomes PFS2 and OS, although data for PFS2 and OS were immature.

Health-related quality of life (HRQoL) was captured using the standardised health measure, EQ-5D-5L.

2 Clinical effectiveness

2.1 Critique of the methods review

The company undertook systematic literature reviews (SLRs) to identify existing clinical, cost-effectiveness, health related quality-of-life (HRQoL) and cost and resource use evidence in first-line maintenance therapy of ovarian cancer. Full methods and results of the clinical SLR are reported in Appendix D of the company submission (CS). A summary of the methods, together with the ERG's critique of the appropriateness of the methods adopted, is presented in Table 2. The SLRs of cost-effectiveness, HRQoL, costs and resources are reviewed in section 3.1.

The clinical SLR was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[7] and following the reporting requirements published by the University of York Centre for Reviews and Disseminations[8] and the National Institute of Health and Care Excellence.

The company reported that 50 references met the inclusion criteria for the review: a list of included studies is provided in Appendix D (Table 8 in Appendices) of the CS. One study (5 references), PRIMA, was retrieved evaluating niraparib as a treatment to maintain response to first-line platinum-based chemotherapy.[4] The remaining references evaluated other interventions as maintenance therapy after first line chemotherapy.

Overall, the ERG considers the company's search strategies, and methods followed for study selection to be of reasonable quality and deems it likely that the SLR has identified all studies of potential relevance to inform the decision problem.

Table 2. Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Data sources	Appendix D.1, A.1	**The ERG considers the sources searched to be comprehensive**. Search date February 2019, update February 2020 Electronic databases: Embase, Medline and Medline ® In-Process, CENTRAL, ScHARRHUD, EuroQol, CRD NHS HTA and EED Trial registries: clinicaltrials.gov

		Conference proceedings: ESMO, ESGO, ASCO, SGO, NCRI, EACR, ISPOR. Searched over the two years prior to February 2020 Other sources: Google Scholar, NICE, PBS, CADTH, SMC, the manufacturer's repository of evidence, websites of manufacturers of comparator products. Searched previous two years to April 2019
Literature searches	Appendix D.1, A.4	**The ERG is satisfied that searches would have retrieved records for all RCTs relevant to the decision problem.** Search strategies combined medical subject headings relevant to each database and free text terms for the population, intervention, and comparators. As highlighted by the company, because the SLR was designed to be broad, search terms are included for interventions that are not of interest to the decision problem and for RCTs as well as observational studies. The ERG does not consider inclusion of terms for treatments outside the decision problem or study designs other than RCTs to affect the robustness of the search. Language or date restrictions were not applied to the search.
Inclusion criteria	Appendix D.1, A.3	**The ERG considers it likely that no relevant evidence was excluded based on the eligibility criteria used.** In terms of population and outcomes specified inclusion criteria were in line with the final scope issued by NICE. In terms of intervention and comparators any maintenance therapy for ovarian cancer was included. In addition, RCTs, non-randomised trials and observational studies were included. A list of excluded studies was available.

Abbreviations: ASCO, American Society of Clinical Oncology; CADTH, Canadian Agency for Drugs and Technologies in Health; CS, company submission; EACR, European Association for Cancer Research; EED, Economic Evaluation Database; ERG, Evidence Review Group; ESGO, European Society of Gynaecological Oncology; ESMO, European Society for Medical Oncology; HTA, health technology assessment; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; NCRI, National Cancer Research Institute; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PBS, Pharmaceutical Benefits Scheme; RCT, randomised controlled trial; ScHARRHUD, School of Health and Related Research Health Utilities Database; SGO, Society of Gynaecologic Oncology; SLR, systematic literature review; SMC, Scottish Medicines Consortium;.

2.2 Critique of trials of the technology of interest, the company's analysis and interpretation

In this section the ERG focuses on aspects of trial design, conduct and internal validity of PRIMA that are of importance to this single technology appraisal (STA). The ERG's critique is summarised in Table 3. The ERG agrees with the company's assessment of PRIMA as being at overall low risk of bias for analysis of the primary outcome, PFS, based on the full trial population (section B.2.3 of the CS).

Table 3. Summary of ERG's critique of the design and conduct of PRIMA, the trial evaluating the technology of interest to the decision problem

Aspect of trial design or conduct	Section of CS in which information is reported	ERG's critique
Randomisation	B.2.3.1	**Appropriate** People randomised 2:1 to niraparib:placebo. Randomisation was stratified by use of neoadjuvant chemotherapy (yes or no), best response to platinum therapy (CR or PR), and homologous recombination deficiency test status (positive or negative/not determined)

Concealment of treatment allocation	B.2.3.1	**Appropriate** An Interactive Web Response System (IWRS) was used to allocate patients to the two study arms.
Eligibility criteria	B.2.3.1	Newly diagnosed, FIGO stage III or IV, high-grade serous or endometrioid ovarian, fallopian tube or primary peritoneal cancer in complete or partial response to first-line PBC. Patients with stage III disease were eligible to enrol if they had visible residual tumour after primary debulking surgery (PDS), interval cytoreductive surgery or inoperable disease. Patients who had complete cytoreduction (NVRD) after PDS were excluded from the trial.
Biomarker analyses	B.2.3.1	Tumour BRCA status and HRD status were both determined by pre-randomisation BRCA testing using Myriad myChoice HRD test. A positive Myriad HRD status was determined either by presence of a tumour BRCA1/2 mutation, or by an HRD score at or above a pre-specified cut-off of 42 in the absence of a BRCA1/2 mutation.
Baseline characteristics	B.2.3.2	**Patient characteristics were generally well balanced** between treatment arms in the ITT population.
Masking appropriate	B.2.3.1	**Appropriate** Patients, investigators, and study centre staff were blinded to treatment allocation throughout the study.
No difference between groups in treatments given, other than niraparib and placebo	Reported in CSR only	[redacted]
Dropouts (high drop out and any unexpected imbalance between groups)	B.2.3.2	**Low rate of withdrawal from study; similar between arms** 18.6% of patients randomised to niraparib and 22.5% patients randomised to placebo had discontinued from the study by the time of data cut-off. The reasons for discontinuation from study were death ([redacted]% for niraparib and [redacted]% for placebo), withdrawal of consent ([redacted]% for niraparib and placebo), lost to follow-up ([redacted]% for niraparib and [redacted]% for placebo), and other ([redacted]% in niraparib and [redacted]% in placebo).
Outcomes assessed	B.2.3.1 and CSR	**All clinically relevant outcomes were assessed appropriately.** No evidence to suggest that additional outcomes were assessed and not reported. See further details below in section 2.2.1.
ITT analysis carried out	B.2.4.1	**ITT analysis were reported for all efficacy outcomes**
Subgroup analyses	B.2.7	Pre-specified subgroup analyses were carried out based on stratification factors, clinical characteristics and biomarker subgroups. Subgroup analysis was also conducted for individualised versus fixed dosing, which was not pre-specified (because it was due to a protocol alteration that occurred during the trial); see further details in section 2.2.2 below.

Statistical analysis plan		
Sample size and power	B.2.4.2 and CSR	**Appropriate** The study was powered to identify an interaction treatment effect in both people who were HRD positive and in the full ITT population. See section 2.2.3 for further details.
Analysis for estimate of effect	B.2.4.3-B.2.4.4 and CSR	**Appropriate** A hierarchical testing for the PFS endpoint was used to control the overall Type I error rate, whereby testing for statistical significance was first conducted in the HRD population followed by the ITT population as appropriate. The ERG generally considered this appropriate (see section 2.2.4 for further details).

Abbreviations: BICR, blinded independent central radiology review; BRCA, breast cancer susceptibility gene; CR, complete response; CSR, clinical study report; CS, company submission; DRS-P, disease-related symptoms–physical; ERG, Evidence Review Group; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency; ITT, intention to treat; NVRD, no visible residual disease; PARPi, poly(ADP-ribose) polymerase inhibitor; PBC, platinum-based chemotherapy; PDS, primary debulking surgery; PFS, progression-free survival; PFS2, time to second progression; PR, partial response; OS, overall survival.

2.2.1 Outcome assessment

The primary endpoint of PRIMA was progression-free survival (PFS), which was defined as time from the date of treatment randomisation to the date of first documentation of progression or death. This was assessed by blinded independent central review (BICR), defined either by radiological assessment as per RECIST v1.1 or by clinical criteria. The ERG considers this to be appropriate. Clinical criteria were defined as either one of the following:

- CA-125 progression according to Gynecologic Cancer Intergroup (GCIG)-criteria AND additional diagnostic tests (e.g. histology/cytology, ultrasound techniques, endoscopy, positron emission tomography [PET]) which may identify new lesions or determine existing lesions qualify for unequivocal progressed disease (PD);
- CA-125 progression according to GCIG criteria AND definitive clinical signs and symptoms of PD unrelated to non-malignant or iatrogenic causes, such as: [1] intractable cancer-related pain; [2] malignant bowel obstruction/worsening dysfunction or [3] unequivocal symptomatic worsening of ascites or pleural effusion.

Investigator assessed (IA) PFS was also presented as a sensitivity analysis.

The secondary outcomes were defined as follows:

- TFST: time from the date of randomisation to the date of the first subsequent anticancer therapy or death, whichever occurred first;
- PFS2: time from the date of randomisation to the date of progression on the next anticancer therapy following study treatment or death by any cause, whichever occurred first;
- OS: time from the date of randomization to the date of death by any cause.
- Health-related quality of life: as assessed by validated patient-reported outcome scales (EQ-5D-5L, EORTC-QLQ-C30, EORTC-QLQ-OV28).

OS was assessed using any acceptable means of data collection, including telephone contact. All patients that discontinued treatment were followed every 12 weeks to capture information for PFS2, TFST and OS. PFS2 was determined by the investigator via clinical and radiographic assessment using the same criteria as used to determine progression on niraparib/placebo.

2.2.2 Individualised versus fixed dosing subgroup analysis

In PRIMA, patients were randomised to niraparib 300mg per day or placebo, though, due to a high number of adverse events (AEs) leading to dose reductions the trial protocol was amended (on 27 November 2017) to individualised dosing. Individualised dosing was based on weight and platelet count, whereby participants started on a lower dose of 200mg per day if they weighed <77kg or had a baseline platelet count <150,000/µL. Due to this, 64.8% of participants in PRIMA started on fixed 300mg dosing (prior to the protocol change) and 35.2% started on individualised dosing. The ERG considers the rationale for the protocol change appropriate. Nonetheless, these subgroup analyses should be considered exploratory in nature, because they are *post-hoc* non-stratified subgroup analyses, and PRIMA was not powered to detect a difference between these groups.

2.2.3 Sample size and power

The study was primarily powered to identify an interaction treatment effect in people who were HRD positive. It was determined that, to detect an expected benefit corresponding to a hazard ratio of 0.5 with 90% power, 99 PFS events were required. It was projected that approximately 50% of all subjects randomised were HRD. Therefore, enrolment of approximately 620 subjects (310 with HRD) was needed to complete the study in approximately 44 months. However, the sample size was also sufficiently powered (with at least 90% power) to detect an expected benefit corresponding to hazard ratio of 0.65 in the full ITT population (assuming a median PFS of 14 months for all placebo subjects, a total of approximately 270 PFS events were expected for the final analysis). The ERG notes that the rationale to base sample size calculations primarily on the HRD subgroup rather than the full ITT population was due to a protocol amendment. Original inclusion criteria for the trial was limited to HRD positive patients (whereby the primary objective of the trial was to evaluate the effectiveness of niraparib in this population). This was expanded on 1 December 2016 to include patients irrespective of HRD status, and the primary objective of the trial was thus revised to evaluate the effectiveness of niraparib in the full ITT population. Therefore, although the sample size was primarily powered for the HRD population, the ERG considers the subsequent power calculations for the ITT population to be sufficient.

Furthermore, loss to follow-up was also taken into account, assuming that 15% of subjects would not provide a PFS event for the primary endpoint due to loss to follow-up or discordance between investigator and central reviewer.

2.2.4 Analysis for estimate of effect

2.2.4.1 Primary outcome: PFS

A hierarchical testing for the PFS endpoint was used to control the overall Type I error rate. First, the analysis of PFS was conducted in HRD patients at the 1-sided alpha level of 0.025. If the result was positive, PFS analysis was conducted in the ITT population with the 1-sided alpha level of 0.025; otherwise, PFS analysis was to become exploratory in the ITT population. PFS was compared between treatment groups using a stratified log rank test using the randomisation stratification factors (i.e. administration of neoadjuvant therapy, best response to platinum therapy, and HRD test status). The hazard ratio (HR) and 2-sided 95% confidence interval (CI) were derived from a stratified Cox proportional hazards model to estimate treatment effect.

The ERG considers this appropriate, although notes that the rationale to conduct hierarchical significance testing was likely due to a protocol amendment. Original inclusion criteria for the trial was limited to HRD positive patients, but this was expanded on 1 December 2016 to include patients irrespective of HRD status (see above section 2.2.3).

2.2.4.2 Secondary outcomes

[redacted]. TFST and PFS2 were analysed in the same way as PFS. Initial analysis in HRD patients showed statistical significance for TFST (p-value<0.0001), but not for PFS2 (p-value=[redacted]). Therefore, the subsequent analysis presented for PFS2 in the ITT population should be considered exploratory by nature, due to the risk of Type 1 error.

2.3 Clinical effectiveness results

2.3.1 Primary outcome – progression-free survival

The primary endpoint of PRIMA is PFS determined by blinded independent central review (BICR) either by radiological assessment as per RECIST v1.1 or by clinical criteria.[4] As described in section 2.2, a hierarchical testing for the PFS endpoints was used in PRIMA. The PFS results are therefore

presented in the order specified in the analysis plan, that is, HRD population followed by the ITT population, as if statistical significance was not achieved for the HRD population, the PFS analysis was to become exploratory in the ITT population

At the time of data cut (17 May 2019), the study met its primary efficacy objective; in patients with HRD median PFS was 21.9 months in the niraparib arm and 10.4 months in the placebo arm (HR 0.43, 95% CI: 0.31 to 0.59, p<0.0001). The study also met the primary objective for the ITT population; median PFS was 13.8 months in the niraparib arm and 8.2 months in the placebo arm (p<0.0001) with 47.6% and 63.0% of patients having progressed or died in the niraparib and placebo arm, respectively (Table 4). The Kaplan–Meier curves for PFS show a clear benefit with niraparib treatment over placebo in ITT population (

Figure 2). However, the company presented an assessment of the proportional hazards (PHs) assumption for PFS in the ITT population based on an inspection of plots of the log cumulative hazards and Schoenfeld residual (CS, section B.3.3, ITT population, PFS). Assuming PHs means that the relative difference identified holds for the entire period. The company concludes that the relative hazards are likely to vary over time and the assumption of proportional hazards is unlikely to hold for PFS for the ITT population. The ERG therefore emphasizes that the HR with accompanying 95% confidence interval (CI) is difficult to interpret and potentially misleading.

Table 4. Progression-free survival based on BICR in the ITT population (reproduced from CS, Table 11)

PFS based on BICR (months)	Niraparib (N=487)	Placebo (N=246)
Median (95% CI)	13.8 (11.5,14.9)	8.2 (7.3,8.5)
Censored observations, n (%)	255 (52.4)	91 (37.0)
Event rate, n (%)	232 (47.6)	155 (63.0)
p-value	<0.0001	
Hazard ratio (95% CI)	0.62 (0.502,0.755)	

Source: CSR
Abbreviation: BICR, blinded independent central review; CI, confidence interval; CSR, clinical study report; PFS, progression free survival

Figure 2. Kaplan-Meier plot of PFS for the PRIMA ITT population (reproduced from clarification response, question A3)

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival

As described in section 2.2, the dosing of niraparib was changed from a fixed dose of 300 mg per day to individualised dosing (patients starting on 300 mg or 200 mg depending on weight and platelet count) due to the high number of dose reductions and adverse events on the fixed dose. In order to explore the extent to which the overall results may be driven by the effectiveness in patients who started on the 300 mg dose, the company provided PFS subgroup data based on fixed and individualised dosing at the clarification stage.

Just under two thirds (475/733) of patients enrolled in PRIMA started on the fixed 300 mg dose, and 35% (258/733) started on individualised dosing (Table 5). According to the CSR, of the 258 patients starting on individualised dosing, 255 received at least 1 dose of the study drug.[1]

. Maintenance therapy with niraparib resulted in a longer median PFS both

[1] Factual inaccuracy identified after appraisal committee meeting 1. Correct information is "According to the CSR, of the 258 patients starting on individualised dosing, received niraparib and received placebo. "

in the fixed and individualised dosing groups compared with placebo, though the difference in median PFS was larger in the fixed compared with the individualised dosing group (Table 5). The impacts of individualised versus fixed dosing on drug exposure and dose intensity are explored in section 2.3.3.

The company highlights that due to shorter duration of follow up in the individualised dosing subgroup there was a smaller number of PFS events and therefore more uncertainty around the results. The ERG notes that as PHs are unlikely to hold for PFS in the ITT population, so the assumption may not hold in these subgroups either. The ERG therefore notes that the HRs for the subgroups are best interpreted with caution. The company reports that the test of treatment interaction between starting dose subgroups was not statistically significant at the pre-specified 0.10-level (p=0.2957); indicating that there was no evidence of treatment difference between fixed and individualised dosing regimens. The ERG notes that tests for subgroup interaction is almost always underpowered to detect a statistically significant difference.

Table 5. Progression-Free Survival Based on BICR Assessment by Starting Dose Group (ITT Population) (adapted from clarification response, question A4)

PFS based on BICR	Fixed		Individualised	
	Niraparib (N=317)	Placebo (N=158)	Niraparib (N=170)	Placebo (N=88)
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Censored observations, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Event rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]		[redacted]	
HR (95% CI)	0.59 (0.457, 0.757)		0.69 (0.481, 0.982)	

Abbreviations: BICR, blinded independent central review; CI, confidence interval; CR, complete response; HR, hazard ratio; ITT, intention-to-treat; NE, not estimated; PFS, progression-free survival; PR, partial response.

The company presents results of several sensitivity analysis of PFS, including investigator assessed PFS, all of which showed similar results to the primary analysis (Appendix 5.6). A summary of PFS data in the pre-specified subgroups of the PRIMA ITT population, based on stratification factors (first-line treatment outcome, receipt of neoadjuvant chemotherapy and HRD status), clinical characteristics, and biomarker subgroups, is provided in Appendix 5.6. A PFS benefit with niraparib versus placebo was observed regardless of first-line treatment outcome, neoadjuvant chemotherapy and HRD status, and across all pre-specified clinical characteristics.

The ERG notes that for several subgroups there are differences in the mean estimates potentially indicating differences in the efficacy of niraparib between subgroups, including for stage of disease and BRCA mutation status, a subgroup specified as of interest in the NICE scope.[1] For the subgroup of patients with a BRCA mutation, the HR for PFS is 0.40 (95% CI: 0.265 to 0.618) and for the BRCA wild type subgroup it is 0.69 (95% CI: 0.541 to 0.882). Similarly, there is a difference between the subgroup of patients with stage III (HR 0.54, 95% CI: 0.419 to 0.698) and stage IV (HR 0.79, 95% CI: 0.554 to 1.118) disease. The company uses the difference between the subgroups by disease stage as validation when extrapolating the PRIMA ITT results to the MA population (see section 2.4.4.3). The ERG notes that, although these subgroups were pre-specified, it is unlikely the trial was powered to investigate significant differences between subgroups. In addition, the confidence intervals are overlapping and similarly to the subgroup analysis by fixed or individualised starting dose, it is unlikely that the difference between these subgroups are statistically significant. The data in support of the extrapolation to the MA population is discussed in detail in section 2.4.

2.3.2 Secondary outcomes

At the date of the primary analysis (17 May 2019), patients randomised to niraparib had a statistically significant improvement in TFST compared with patients on placebo (HR 0.65, 95% CI: 0.521 to 0.802, Table 6). PFS2 and OS data were very immature with only [redacted] and [redacted] having experienced a second progression in the niraparib and placebo arm, respectively, and 9.9% and 12.6% of people having died in the niraparib and placebo arms at the time of analysis. Median OS was [redacted] months in the niraparib arm, but not reached in the placebo arm. At this timepoint there was no statistically significant difference between the treatment arms for PFS2 (HR 0.81, 95% CI: 0.577 to 1.139) or OS (HR 0.70, 95% CI: 0.442 to 1.106).

Table 6: Secondary efficacy endpoint efficacy outcomes for the ITT population, reproduced from CS, table 13

	Niraparib (N=487)	Placebo (N=246)
Time to First Subsequent Therapy		
Median TFST (95% CI)	18.6 ([redacted])	12.0 ([redacted])
Censored observations, n (%)	[redacted]	[redacted]
Event rate, n (%)	[redacted]	[redacted]
p-value	0.0001	
Hazard ratio (95% CI)	0.65 (0.521,0.802)	
Progression-Free Survival 2		

Median PFS2 (95% CI)	[redacted]	[redacted]
Censored observations, n (%)	[redacted]	[redacted]
Event rate, n (%)	[redacted]	[redacted]
p-value	[redacted]	
Hazard ratio (95% CI)	0.81 (0.577,1.139)	
Overall Survival		
Median OS (95% CI)	[redacted]	[redacted]
Censored observations, n (%)	[redacted]	[redacted]
Event rate, n (%)	48 (9.9)	31 (12.6)
p-value	[redacted]	
Hazard ratio (95% CI)	0.70 (0.442,1.106)	

Source: CSR [57]

Abbreviation: CI, confidence interval; ITT, intention-to-treat; NE, not estimable; OS, overall survival; PFS2, progression-free survival 2; TFST, time to first subsequent therapy

Figure 3. Kaplan-Meier plot of TFST for the PRIMA ITT population (reproduced from clarification response, question A.3)

Abbreviations: CI, confidence interval; ITT, intention-to-treat; TFST, time to first subsequent treatment

Figure 4: Kaplan-Meier plot of PFS2 for the PRIMA ITT population (reproduced from clarification response, question A.3)

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PFS2, progression-free survival on subsequent therapy

Figure 5: Kaplan-Meier plot of OS for the PRIMA ITT population (reproduced from clarification response, question A.3)

Abbreviations: CI, confidence interval; ITT, intention-to-treat; OS, overall survival

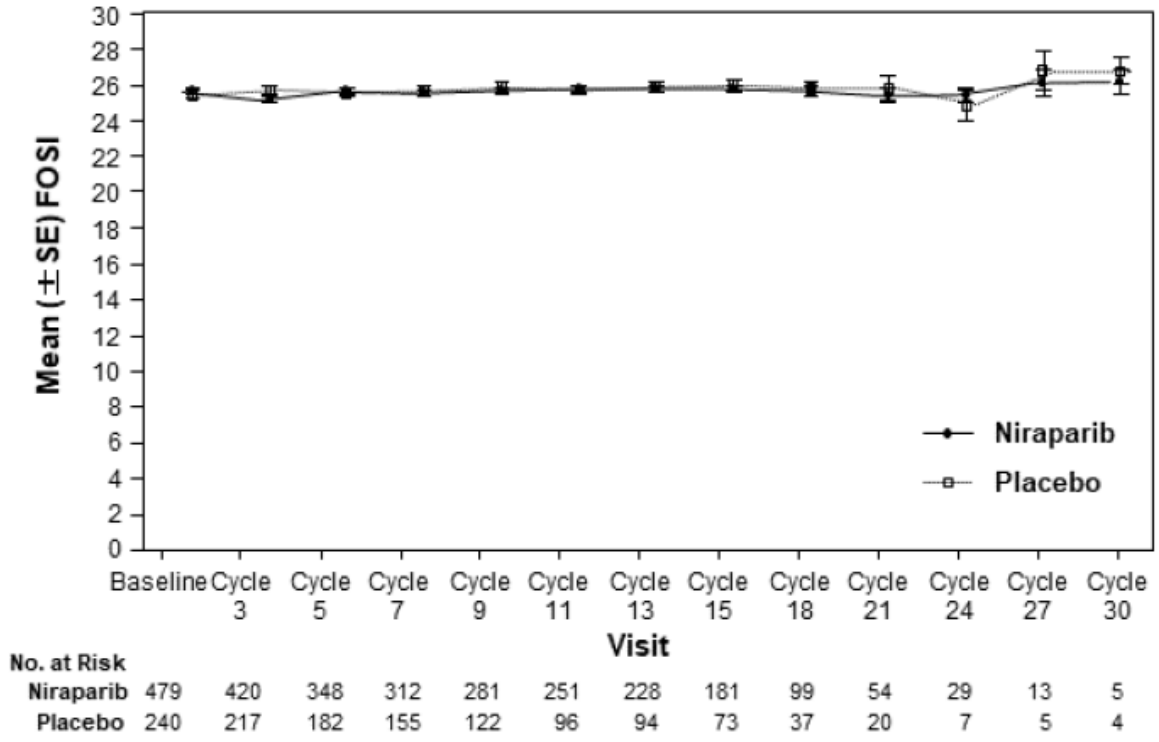
2.3.2.1 HRQoL

Changes over time in HRQoL were presented for the Functional Assessment of Cancer Therapy-Ovarian Symptoms Index (FOSI) and the European Quality of Life Scale 5-Dimensions (EQ-5D-5L). Baseline symptoms and quality of life, as measured by FOSI, were similar between the niraparib and placebo arms in the ITT population (overall FOSI mean: niraparib [redacted] versus placebo [redacted]). Similarly, there were no observed differences between the niraparib and placebo arms in changes from baseline over study visits during the follow-up period [redacted]

Figure 6).

[redacted]

Figure 6. Adjusted Means and Associated Standard Error for FOSI by Study Visit in ITT Population (reproduced from CS, Figure 11)

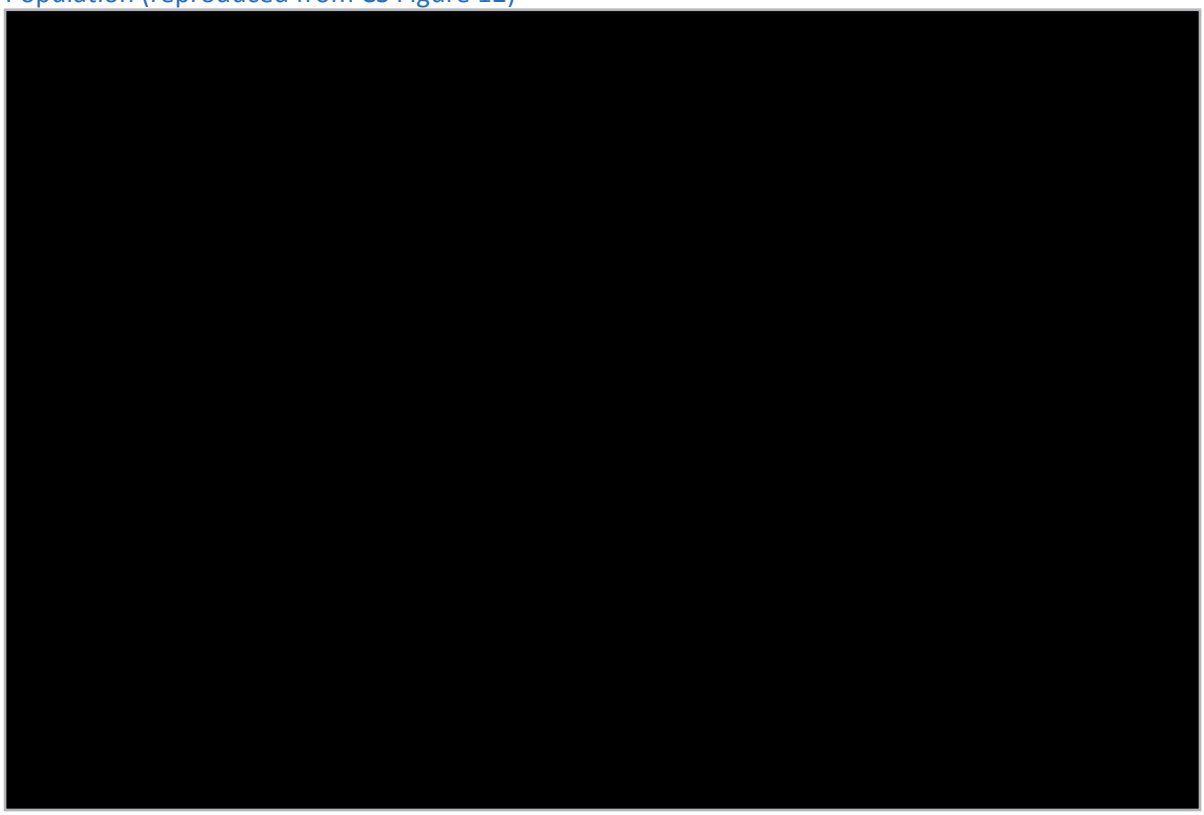


Source: CSR [57]
Abbreviations: FOSI, Functional Assessment of Cancer Therapy – Ovarian Symptom Index; SE, standard error

Baseline EQ-5D-5L scores were similar between niraparib and placebo patients in the ITT population (mean health utility index: [redacted] versus placebo [redacted] Similar results were observed throughout the study with no observed significant differences in changes from baseline between the niraparib and placebo arms during the follow-up period ([redacted]

Figure 7).

Figure 7. Adjusted Means and Associated Standard Error for EQ-5D-5L by Study Visit in ITT Population (reproduced from CS Figure 12)



Source: CSR [57]
Abbreviations: EQ-5D-5L, EuroQoL 5-dimensions 5-levels; SE, standard error

2.3.3 Safety

Safety data were derived from the full safety population, comprising 728 patients, who received at least one treatment dose (N=484 and N=244 in the niraparib and placebo arms respectively). The median drug exposure from first to last dose for niraparib and placebo treated patients was 11.1 months and [redacted] months, respectively. The full daily dose was 300mg and the mean dose intensity in the niraparib and placebo groups was [redacted] mg/day and [redacted] mg/day. However, an individualised dosing regimen was introduced during the study to allow patients with platelet count below 150,000/µL and/or weighing below 77kg to start on a lower dose of 200mg per day. Due to this, 64.8% of participants in PRIMA started on fixed 300mg dosing (prior to the protocol change) and 35.2% started on individualised dosing. Of these,

[redacted]

[redacted].[2] Nonetheless, mean dose between fixed and individualised niraparib differed only slightly at [redacted] per day for fixed dosing ([redacted]), and [redacted] per day for individualised ([redacted]). Median actual treatment exposure (defined as overall treatment exposure minus the duration of dose interruptions) differed only slightly between fixed versus individualised dosing ([redacted] versus [redacted] months respectively), even though median time in the study was longer on fixed dosing ([redacted] months) versus individualised ([redacted] months). The ERG notes that the difference between median time in the study between fixed and individualised dosing should be similar to the difference in median actual treatment exposure, given that this has been adjusted for dose interruptions. The implications of this discrepancy are unclear.

Adverse events for individualised versus fixed dosing are explored below. In the safety population, most subjects in both treatment groups experienced at least one treatment emergent adverse event (TEAE), including 478 (98.8%) of 484 subjects who received niraparib and 224 (91.8%) of 244 subjects who received placebo. In the niraparib group, 12.0% of AEs resulted in treatment discontinuation compared to 2.5% in the placebo group, and this did not differ broadly between fixed and individualised dosing (11.3% versus 10.5% respectively). In the niraparib group, 385 patients (79.5%) had at least one study drug interruption due to AEs versus 44 patients (18%) in the placebo group, and 362 patients (74.8%) in the niraparib group and 30 patients (12.3%) in the placebo group had a dose reduction. Dose interruptions caused by TEAEs were lower in individualised dosing compared to fixed dosing (71.6% versus 83.8% respectively). Dose reductions were also lower in individualised (61.5%) versus fixed (75.9%).

[2] Factual inaccuracy identified after appraisal committee meeting 1. Correct information is "Of these, [redacted]

Figure 8 highlights the proportion of participants on each dose of niraparib throughout the trial, whereby [redacted] of participants were on the maximum 300mg dose by month 12, and [redacted] of participants were receiving 200mg ([redacted]) or 100mg ([redacted]).

Figure 8. Percentage of patients in Safety population of PRIMA ITT receiving either 100 mg, 200 mg or 300 mg of niraparib QD at each month of treatment (reproduced from CS, Figure 7)

Most of the common TEAEs were reported at a higher incidence in the niraparib arm compared with the placebo arm (see appendix 5.7 for a full list of the common adverse events in the trial), but most common TEAEs were reported at a lower incidence in patients who received an individualized starting dose compared to patients who received a fixed starting dose (

Table 7). Furthermore, 341 (71%) of 484 patients who received niraparib and 46 (19%) of 244 patients who received placebo experienced a Grade 3 or 4 TEAE. Among the most common grade ≥3 adverse events in the niraparib group were anaemia (31.0% of the patients), thrombocytopenia (28.7%), decreased platelet count (13.0%), and neutropenia (12.8%). Grade 3 or higher TEAEs were reduced in patients who received the individualised starting dose as compared with those who received the fixed starting dose, particularly for blood and lymphatic disorder TEAEs. See

Table 7 below for full summary of adverse events. There were two deaths attributed to TEAEs in the niraparib arm, and 1 in the placebo arm.

Table 7. Summary of adverse events, adapted from clarification response A12 and A13

Event	Niraparib			Placebo
	All n (%) N=484	Individualised n (%) N=169	Fixed n (%) N=315	All n (%) N=244
Any TEAE	478 (98.8)	[redacted]	[redacted]	224 (91.8)
Any TEAE with CTCAE Grade ≥3	341 (70.5)	102 (60.4)	239 (75.9)	46 (18.9)
Grade ≥3 Treatment-emergent Adverse Events Reported in ≥5% of Patients in Either Treatment Subgroup				
Blood and lymphatic system disorders	255 (52.7)	[redacted]	[redacted]	6 (2.5)
Thrombocytopenia	139 (28.7)	25 (14.8)	114 (36.2)	1 (0.4)
Anaemia	150 (31.0)	38 (22.5)	112 (35.6)	4 (1.6)
Neutropenia	62 (12.8)	16 (9.5)	46 (14.6)	3 (1.2)
Investigations	99 (20.5)	[redacted]	[redacted]	8 (3.3)
Platelet count decreased	63 (13.0)	12 (7.1)	51 (16.2)	0
Neutrophil count decreased	37 (7.6)	9 (5.3)	28 (8.9)	0
Vascular disorders	32 (6.6)	[redacted]	[redacted]	4 (1.6)
Hypertension	29 (6.0)	[redacted]	[redacted]	3 (1.2)
General disorders and administration site conditions	21 (4.3)	[redacted]	[redacted]	4 (1.6)
Fatigue	9 (1.9)	[redacted]	[redacted]	1 (0.4)

Abbreviations: CSR, clinical study report; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

2.3.3.1 *Adverse events of special interest*

The ERG notes that adverse events of special interest related to niraparib include haematologic adverse reactions (particularly thrombocytopenia), myelodysplastic syndrome/acute myeloid leukaemia, hypertensive crisis, and posterior reversible encephalopathy syndrome (PRES).[9] 28.7% of patients in the niraparib group had thrombocytopenia, compared to 0.4% in the placebo group (although this reduced to 14.8% on individualised dosing). There was 1 case of myelodysplastic syndrome, which occurred in a patient in the fixed dosing niraparib group, and resulted in discontinuation. Hypertension was a common adverse event occurring in ≥10% of patients, although it is unclear how many of these events were hypertensive crises. PRES cases were not reported,

[redacted].

2.4 Extrapolation to the MA population

Patients with stage III and NVRD after PDS were excluded from the PRIMA trial;[4] however, the anticipated marketing authorisation (MA) for niraparib includes these patients. For reasons set out below the company considers it is important to include these patients within the evidence underpinning a NICE recommendation:

- Patients with stage III NVRD following PDS constitute approximately [redacted] of the MA population;
- Patients with stage III NVRD following PDS have a better prognosis than patients with stage III/IV VRD, irrespective of the treatment received;
- Patients with stage III NVRD are still at risk of recurrence and death and therefore have a high unmet need;
- PARPis demonstrate improved clinical outcomes in patients with stage III NVRD – i.e. a treatment specific effect of PARPi in patients with stage III NVRD compared with patients with VRD or stage IV disease.

In support of the assertions listed above the company presented a package of activities in the CS (section B.2.14), with the aim of bridging the gap between the ITT and MA populations. In the following sections the ERG provides a review and critique of the company's evidence in support of their assertions and of the company's MA analysis (as mentioned in section 1.8.1). Specifically, the ERG provides a description and critique of the data sources, methods, results and uncertainty around:

- the estimate that stage III patients with NVRD constitute approximately [redacted] of the MA population;
- the 'NVRD effect' - an indirect estimates of the difference in outcomes between patients with stage III NVRD after PDS compared with populations similar to the ITT population of PRIMA; and
- the 'treatment effect' - an indirect estimates of a potential treatment specific effect of PARPi in patients with stage III and NVRD compared with patients with VRD or stage IV disease.

As highlighted in section 1.8.1, the ERG considers the PRIMA population to be representative of the expected MA population and that it provides robust evidence for the safety and efficacy of the use of niraparib in the MA population. Although patients with stage III NVRD following PDS were excluded from PRIMA, the trial does include a substantial proportion of patients with stage III NVRD following IDS. As highlighted in the ESMO guidelines[10] and as shown in a study by Vergote *et al.*,[11] there is no significant difference in PFS and OS based on type of surgery, i.e. PDS or IDS. However, the ERG acknowledge that the outcomes may differ between the subgroup of patients with NVRD after IDS and PDS but notes that there is limited evidence to support this. Though, based on the opinion of the ERG's clinical experts, the prognosis of patients with stage III NVRD after PDS can be considered equivalent to patients with stage III NVRD after IDS (for which data are available in PRIMA), and the PRIMA ITT population adequately covers the full MA population.

However, the proportion of patients with stage III NVRD in PRIMA may differ to the proportion seen in UK clinical practice. This may therefore reduce the applicability of the results of PRIMA to the population seen in UK clinical practice. The ERG therefore considers it important to explore the uncertainty relating to the composition of the PRIMA trial compared with the patient population in UK clinical practice in a sensitivity analysis. For the reasons just stated, the ERG considers it more appropriate to refer to the company's additional analysis as informing the "extrapolation of the ITT population to the patient population in UK clinical practice" rather than an "extrapolation of the ITT population to the MA population".

The company's approach to extrapolation of the PRIMA ITT population requires several assumptions and estimates inferred from other sources, as described in section 1.8.1 and in more detail in the sections below (2.4.2 and 2.4.4). The ERG suggests an alternative approach for adjustments of the PRIMA population to more closely reflect the patient population in UK clinical practice. Compared with the company's approach, the ERG approach relies on fewer assumptions and it is informed solely by data from PRIMA, thereby avoiding several issues, both methodological and those caused by differences between trial populations and study designs. The ERG's approach for adjustments of the PRIMA population is described in section 2.4.3.

2.4.1 Literature review of PFS and OS associated with stage III NVRD

The company conducted a targeted literature review to determine the PFS and OS associated with NVRD and VRD after cytoreductive surgery in people with advanced (stage III/IV) ovarian cancer receiving first-line treatment. The review focused on studies in the USA and Europe which were

published in the last 10 years, as the definition of surgical outcome success has recently changed from <2cm as the best outcome to NVRD. The company identified 14 studies that report OS or PFS by RD status following ovarian cancer surgery. A summary table of the included studies is provided in Appendix 5.8. The studies show that PFS and OS are longer for patients with "complete cytoreduction" or "no RD" compared to those with VRD following surgery, and that this is irrespective of the treatment received in the first-line setting of ovarian cancer. Several studies reported a multivariate HR for the association between RD status and OS but none of the identified studies reported a HR for associations between VRD and PFS.

The ERG notes that the data presented from the identified studies are for NVRD vs VRD; that is, providing support to the statement that patients with stage III NVRD following PDS have a better prognosis than patients with stage III/IV VRD. None of the studies, however, provided data specifically on stage III patients with NVRD after PDS (patients excluded from PRIMA) compared with stage IV, stage III after IDS, and stage III VRD after PDS (the population included in PRIMA). That is, these studies provide some support for the assumption that the outcomes of the patients excluded from PRIMA may have a better prognosis than the patients included in PRIMA, but they don't provide any information on the magnitude of this difference. The ERG also notes that, based on the identified studies, the better prognosis of patients with NVRD than for patients with VRD seems to be irrespective of patients receiving PDS or IDS. However, the presented studies do not provide evidence in support of a difference in prognosis of NVRD achieved by PDS or IDS.

2.4.2 Real world evidence – Edinburgh dataset

In order to inform and validate the extrapolation of the PRIMA ITT population to the MA population the company conducted a retrospective database analysis using the University of Edinburgh Ovarian Cancer Database (please see CS, Appendix L for study protocol). This database contains outcome data for patients diagnosed with OC in the South East region of Scotland (N > 4,000). Three cohorts were identified from the database by applying inclusion and exclusion criteria similar to those of PRIMA (Appendix 5.9):

- the anticipated MA population for niraparib;
- a simulated-PRIMA ITT population (stage III/IV patients with inoperable disease or VRD after debulking surgery);
- a stage III population with NVRD (i.e. patients included in the MA population but not in the simulated-PRIMA cohort).

The ERG highlights that there are some key differences between the inclusion and exclusion criteria for the PRIMA-simulated cohort and the PRIMA trial; the PRIMA-simulated cohort was not restricted to a performance status of ECOG 0 or 1, and all patients with stage III NVRD were excluded, not just stage III NVRD following PDS as in PRIMA. Patient identification was restricted to patients diagnosed between the 1 January 2000 and the 21 December 2015 and followed up until last patient record or until January 2019. The results of the analysis were used to validate the findings from the targeted literature review described above, to estimate the proportion of patients of the MA population that were excluded from PRIMA, and to aid the selection of the appropriate OS distributions of the routine surveillance arm within the economic analysis.

There were 569 patients from the Edinburgh dataset included in the MA population, of which 427 were the simulated-PRIMA cohort and the remaining [redacted]. Thus, [redacted] of the MA population was classified as stage III NVRD. The ERG highlights that the proportion of patients with stage III NVRD estimated from the Edinburgh dataset will be different to the proportion of patients with stage III NVRD specifically after PDS, which is the patient group excluded from PRIMA. The ERG notes that in the CS, the company also reference the PAOLA-1 trial in support of the estimate of [redacted].[12] In PAOLA-1, which is a trial assessing the efficacy of maintenance therapy with olaparib and bevacizumab compared with bevacizumab alone in advanced ovarian cancer, the proportion of patients with stage III NVRD after PDS is approximately [redacted] of the full trial population.[5] The ERG's clinical experts advised that this may be an underestimate and that this proportion could be somewhere from 25% up to 40% in UK clinical practice, and the company's clinically experts were of the same view (estimating the proportion to be [redacted] The ERG notes that the proportion of patients with stage III and NVRD irrespective of PDS or IDS in PAOLA-1 is likely to be substantially higher.

Baseline characteristics from the simulated-PRIMA cohort (appendix 5.8) were generally similar to those observed in PRIMA (appendix 5.5) but with some important differences, mainly due to differences in the inclusion/exclusion criteria. The simulated-PRIMA population from the Edinburgh database is a more severe patient population with 30% of patients having an ECOG status of 2 or 3; a population excluded from PRIMA. The simulated-PRIMA population also had a [redacted] proportion of patients who had received neoadjuvant chemotherapy ([redacted]) compared with the placebo arm in PRIMA (67.9%) and the proportion of patients achieving NVRD after cytoreductive surgery differed substantially. In PRIMA [redacted] had NVRD irrespective of stage of disease and [redacted] of patients had stage III disease and NVRD after IDS. In the simulated-PRIMA

cohort, which only included stage IV NVRD, [redacted] had NVRD after cytoreductive surgery and in the MA simulated cohort, which included patients with stage III NVRD, [redacted] had NVRD irrespective of stage. The ERG's clinical experts advise that the proportion of patients with stage III and NVRD is likely to be closer to 50-60% in the UK, but highlight that the proportion of patients with NVRD after surgery varies across UK practice and basing this estimate on one small region in the UK may therefore not be representative of the surgical outcomes seen across the country. In comparison, in a study by Hall *et al*.[13], which compared the outcomes of patient treated within two neighbouring UK cancer centres for advanced ovarian cancer, the proportion of patients with NVRD after cytoreductive surgery (irrespective of stage of disease) was 59% and 85%, depending on surgical expertise, and Vergote *et al*. 2010 showed that the proportion of patients with NVRD was 19% and 51% after PDS and IDS, respectively. The ERG's clinical experts estimate that the proportion of patients with stage III NVRD irrespective of type of surgery is likely to be 50-60% and the proportion of patients with stage III NVRD following PDS to be between 25-40% in UK clinical practice.

The median OS was approximately [redacted] in the simulated-PRIMA group, compared with [redacted] in the stage III NVRD cohort, and approximately [redacted] for the MA population (Table 8 and

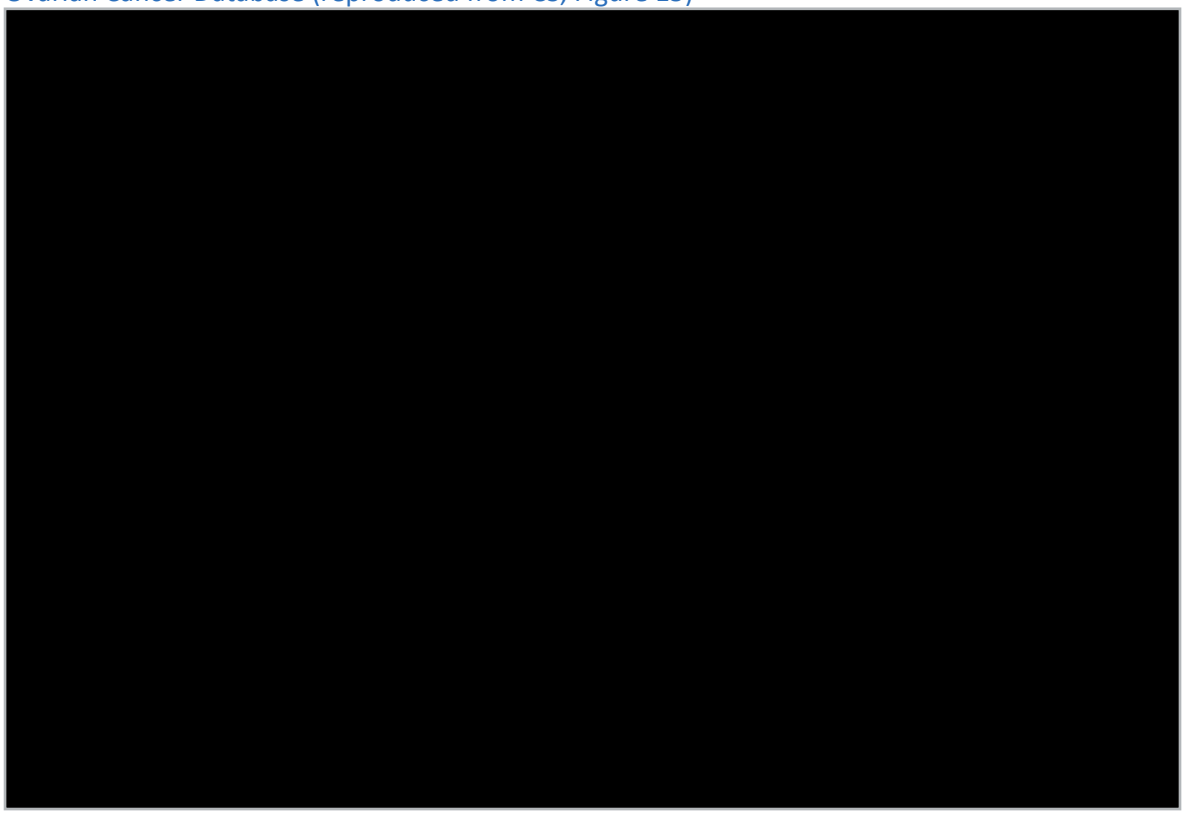
Figure 9). According to the data provided in the CS (Table 20), median TFST was [redacted] in the MA cohort ([redacted]) than the simulated PRIMA cohort ([redacted], Table 8). In section B.3.3 of the CS the company indicates that long-term PFS data were not available and therefore long-term data for TFST were used as a proxy to predict PFS in the economic model; at 5 and 10 years the data for the simulated PRIMA cohort show [redacted] and [redacted] of the patients are progression-free (have not started their first subsequent therapy), respectively (see Table 8).

Table 8. Survival outcomes of the MA cohort and simulated-PRIMA cohort from the University of Edinburgh Ovarian Cancer Database (adapted from CS Table 20)

Characteristic	MA cohort		Simulated-PRIMA cohort	
		95% CI		95% CI
Cases (n)	[redacted]	[redacted]	[redacted]	[redacted]
Median follow-up (years)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS (years)	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS (years)[a]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MA, marketing authorisation; OS, overall survival; PFS, progression-free survival; TFST, time to first subsequent treatment.
*a Median PFS is based on TFST as a proxy, because PFS data were unavailable.

Figure 9. Overall survival of the simulated-PRIMA, stage III NVRD and MA cohorts of the Edinburgh Ovarian Cancer Database (reproduced from CS, Figure 15)



Abbreviations: MA, marketing authorisation; NVRD, no visible residual disease

Based on the results of the three cohorts from the University of Edinburgh Ovarian Cancer database the company draws the following conclusions:

- Patients with stage III NVRD have improved OS compared to those in the simulated-PRIMA and MA cohorts, but are still at high risk of death over their lifetime – for this reason, the company considers that the population excluded from PRIMA should be accounted for by adjusting the ITT population to the MA population.
- Within the populations of interest, there are a proportion of patients who will remain progression free for an extended period of time and a proportion who will continue to live beyond 7 years – this is used as validation for the long-term remission assumption in the economic model (see section 3.2.4);

- The cohort of patients with stage III NVRD can be assumed to make up [redacted] of the MA population – this is used to estimate the degree of adjustment required to the results of the PRIMA ITT population to estimate the results of the MA population (see section 3.2.2).

The ERG agrees that the cohort of patients excluded from PRIMA is expected to do better in terms of PFS and OS than the PRIMA population or the patient population in UK clinical practice. However, the estimate based on the Edinburgh database that [redacted] of the MA population constituting patients with stage III NVRD is not directly relevant to the extrapolation of the PRIMA ITT population to the MA population as it is not limited to stage III NVRD after PDS (the population excluded from PRIMA). However, even the estimate of stage III NVRD irrespective of type of surgery is likely to be an underestimate according to the ERG's clinical experts. In addition, due to additional differences in inclusion and exclusion criteria between PRIMA and the PRIMA simulated cohort from the Edinburgh database, the PRIMA simulated cohort had more severe disease than the PRIMA population. For these reasons the survival for the PRIMA population is expected to be better than the survival for the MA simulated and the PRIMA simulated cohort.

The ERG notes that the company did not conduct a systematic, or a targeted literature review, in order to identify other relevant sources to inform the extrapolation to the MA population. The ERG's clinical experts estimate that the proportion of patients with stage III NVRD after PDS may be somewhere from 25% up to 40% of the population and the proportion of patients with stage III and NVRD irrespective of type of surgery is likely to be closer to 50-60% in the UK. The experts also highlight that the proportion of patients with NVRD after surgery varies across UK practice and basing this estimate on one small region in the UK may therefore not be representative of the surgical outcomes seen across the country. The ERG is also concerned about the use of the simulated PRIMA cohort to inform the extrapolation, as well as the curve choice and cure threshold for OS in the economic model.

2.4.3 ERG approach – re-weighting of PRIMA

The ERG reiterates its opinion that the PRIMA trial is representative of the full MA population but that the exclusion of patients with stage III NVRD after PDS from the trial could mean that the proportion of patients with stage III NVRD in PRIMA may not be representative of the patient population in UK clinical practice. Based on data from the targeted literature review conducted by the company (section 2.4.1) and supported by clinical expert opinion (both the ERG's and the

company's), there is a clear prognostic difference in survival outcomes (both PFS and OS) for patients with NVRD compared with patients with VRD after surgery. This prognostic effect is present both for patients who have had PDS and those who have had IDS. As highlighted in the ESMO guidelines[10] and as shown in a study by Vergote *et al*.,[11] there is no significant difference in PFS and OS based on type of surgery, i.e. PDS or IDS, but the ERG acknowledge that the outcomes may differ between the subgroup of patients with NVRD after IDS and PDS with NVRD potentially being a stronger prognostic factor for patients who have PDS than for those who have IDS, but notes that there is limited evidence to support this.[11] Based on the opinion of the ERG's clinical experts, it is reasonable to assume that the prognosis of patients with stage III NVRD after PDS is equivalent to patients with stage III NVRD after IDS.

As it is reasonable to assume that the prognostic benefit of NVRD between IDS and PDS is similar, the ERG recommends the company take advantage of the significant proportion of patients in PRIMA with stage III NVRD after IDS ([redacted], Table 9) to adjust the ITT results to the patient population likely to be treated in the UK. The ERG suggests the company reweight the results of patients with stage III NVRD after IDS in PRIMA to account for the patients with stage III NVRD after PDS, which were excluded from the trial. There are several methods that can be employed for this, e.g. in a previous NICE appraisal (TA558) the corrected group prognosis method was used in preference to the average covariate method; however, the ERG is aware that the inverse probability of treatment weights (IPTW) may also be used.

The reweighting of the PRIMA data is dependent on a reliable estimate of the size of the patient cohort excluded from PRIMA compared with the composition of patients expected in clinical practice. For this, the company uses the proportion of patients with stage III NVRD irrespective of type of surgery, as derived from the Edinburgh dataset, but also mentions the estimated proportion of patients equivalent to those excluded from PRIMA (stage III NVRD after PDS) as derived from PAOLA-1. The ERG notes the uncertainty around both of these estimates, as described in section 2.4.2, and noted that the company did not conduct a systematic literature review in order to identify other, potentially more relevant and robust sources to inform this estimate.

The approach of reweighting outcome data for patients within PRIMA has several advantages over the methods used by the company for extrapolating the outcomes of PRIMA, described in sections 2.4.2 and 2.4.4. The approach of reweighting PRIMA outcome data relies solely on data from the key trial rather than estimating effects from other trials and applying them to PRIMA. Issues around

comparability between trials due to differences in patient characteristics, interventions, and study design are therefore avoided and does not need to be considered or adjusted for. The approach of reweighting PRIMA data also avoids the assumption of a PARPi class effect for which there is limited evidence. The proposed approach also benefits from relying on individual patient data (IPD) rather than pseudo IPD or aggregate data. In addition, there is no need to estimate a separate 'NVRD effect' and 'treatment effect' as for the company approach.

However, the ERG acknowledges that the certainty of the clinical effectiveness results based on the suggested approach is reliant on the assumption of similar prognosis for patients with stage III NVRD after PDS and IDS. In addition, the results are directly affected by the estimate of how large the proportion the population excluded from PRIMA might be, but this limitation is also true for the company's approach.

Table 9. Surgical outcomes at baseline for patients in PRIMA (adapted from table provided at clarification)

	Cancer stage (FIGO) III			Cancer stage (FIGO) IV		
Parameter	Niraparib (N=318) n (%)	Placebo (N=158) n (%)	Overall (N=476) n (%)	Niraparib (N=169) n (%)	Placebo (N=88) n (%)	Overall (N=257) n (%)
Primary Debulking Surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No visible residual disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visible residual disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interval Debulking Surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No visible residual disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visible residual disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Debulking Surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FIGO, International Federation of Gynaecology and Obstetrics

2.4.4 *Review of PARP inhibitor treatment outcomes and their application to PRIMA data*

In order to estimate the treatment effect of niraparib in the population with stage III and NVRD after PDS, the company conducted another targeted literature review; this time to identify RCTs that have assessed PARPis in the first-line setting. No more details were provided about the methods of the targeted review. The ERG notes that any relevant trials should be captured within the 50 references

that met the inclusion criteria for the systematic literature review done to identify PRIMA (section 2.1). The company identified two studies, PAOLA-1[5, 12] and SOLO-1[6, 14], to inform the PFS and OS associated with PARPi therapy and NVRD among people with advanced ovarian cancer receiving first-line treatment. The company also explored if the PRIMA study outcomes could be used to inform the magnitude of the expected treatment effect in the stage III NVRD post PDS population. The different assumptions, methods and results for the extrapolation to the MA population using each of the three trials are discussed in the following sections.

In order to extrapolate the survival outcomes of the ITT population of PRIMA to the MA population, the company employed an adjustment method calculating an 'NVRD effect' and a PARPi-specific 'treatment effect' from PAOLA-1 and SOLO-1. For PAOLA-1 and SOLO-1 KM-data were digitised to produce pseudo patient level data. The data was subsequently analysed in R Studio using a simple Cox model to produce two HRs, one for the 'NVRD effect' and one for the 'treatment effect'. The NVRD effect was estimated between the two placebo curves and the treatment effect was estimated between the two treatment curves in each of the trials. To predict survival curves for PFS within the economic model the 'NVRD effect' HR and 'treatment effect' HR were then applied to the routine surveillance and niraparib PFS curves for the ITT population, respectively (section 3.2.4). The ERG has concerns about the appropriateness of applying HRs estimated from one trial and applying it directly to the PFS curves in PRIMA, particularly when PHs have been demonstrated not to hold for PFS in PRIMA. The company provided no justification for the approach taken (see section 2.3.1).

2.4.4.1 PAOLA-1

PAOLA-1 is a placebo controlled RCT comparing olaparib and bevacizumab with placebo and bevacizumab in patients with advanced ovarian cancer who are in response to first line platinum-based chemotherapy. Subgroup data are available from PAOLA-1 for the populations equivalent to the PRIMA population and the relevant patient population excluded from PRIMA (Table 10):

- stage III patients with residual disease following PDS, patients who had received NACT or stage IV patients; and
- stage III patients with PDS and no residual disease.

Baseline characteristics of patients in PAOLA-1 are relatively similar to those in PRIMA but with a larger proportion of patients with stage III disease in PAOLA-1 compared with PRIMA. PFS KM data, as assessed by BICR, from PAOLA-1 for the relevant subgroups are presented in Figure 10 and

Figure 11. Following the methods described earlier the company calculated the NVRD and treatment effect based on PAOLA-1 to be:

- 'NVRD effect': HR 0.490, 95% CI: 0.329 to 0.723;
- 'treatment effect': HR 0.340, 95% CI: 0.233 to 0.497.

At the clarification stage the company was asked to assess if proportional hazards hold for these HRs. The company provided KM-plots, log-cumulative hazards plots, Schoenfeld residual plots and p-values for the subgroup with stage III NVRD after PDS versus everyone else, separately for patients on placebo + bevacizumab and olaparib + bevacizumab, respectively. The results indicate that the assumption of proportional hazards cannot be rejected. However, as noted earlier, the ERG is concerned about the validity of the company approach of applying HRs estimated from PAOLA-1 and applying it directly to the PFS curves in PRIMA when PHs have been demonstrated not to hold for PFS in PRIMA.

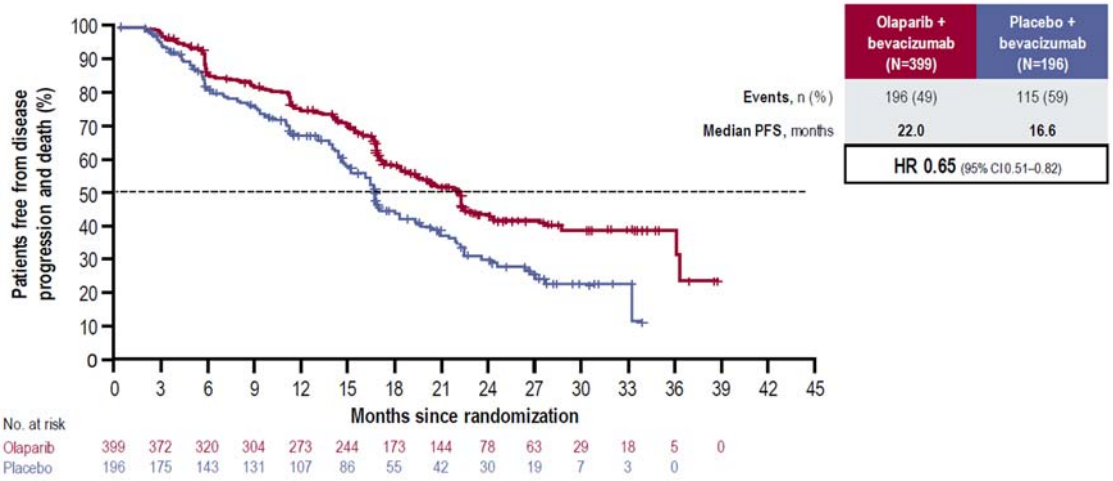
The calculated NVRD effect indicates that there is a substantial prognostic difference between the subgroup equivalent to those enrolled in PRIMA and the subgroup of patients equivalent to those excluded from PRIMA, and this prognostic difference is even greater in patients treated with olaparib + bevacizumab compared to those treated with placebo + bevacizumab (the treatment effect).

The company acknowledge that the populations in PAOLA-1 and PRIMA are not directly comparable due to differences in study design and patient characteristics, and the ERG highlights that no adjustments have been made for any differences between the trials. For the company's estimates of the NVRD and treatment effect from PAOLA-1 to be applicable to PRIMA, e.g. the baseline characteristics of patients within the subgroup of PAOLA-1 equivalent to the population in PRIMA and the PRIMA population have to be similar. Full baseline characteristics for the relevant subgroups of PAOLA-1 are not available but a breakdown of the proportion of patients in PAOLA-1 and PRIMA by disease stage, residual disease status and prior surgery is proved in Table 11. This shows that the proportion of patients with stage III and stage IV disease are relatively similar between the two trials, but PAOLA-1 has a larger proportion of patients who have not had surgery.

The ERG notes that several other factors are also likely to confound the estimates of the NVRD and treatment effect which limit their applicability for extrapolation of the PRIMA population. The calculated NVRD effect is confounded by all patients in PAOLA-1, including patients in the placebo

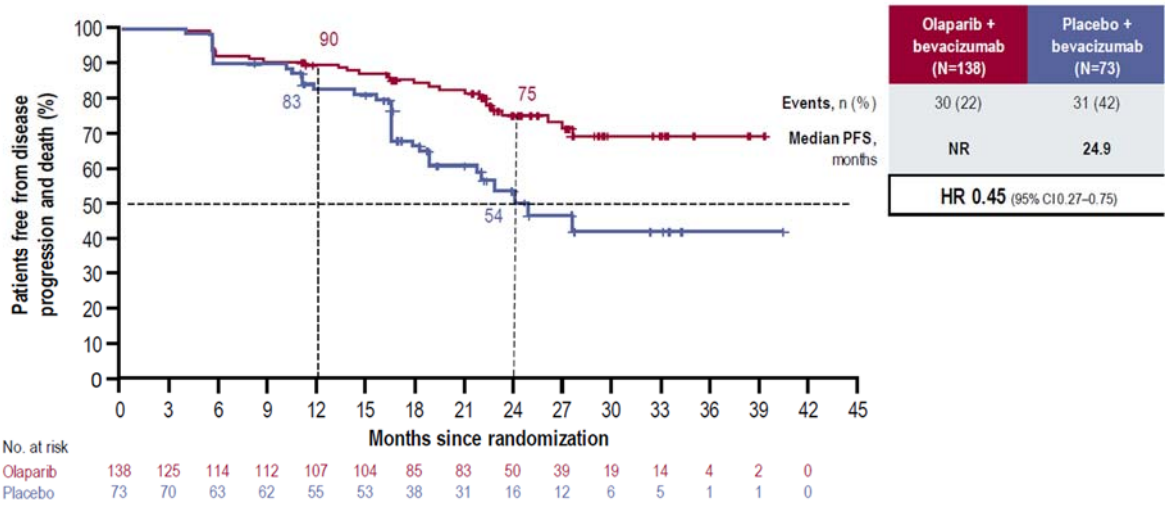
arm, receiving bevacizumab. Bevacizumab has been shown to be more effective compared with routine surveillance in patients at high risk of progression, defined as stage IV disease or stage III disease and >1.0 cm of residual disease after debulking surgery (similar to the inclusion criteria of PRIMA) than in patients at a lower risk of progression.[15] As the relative efficacy of bevacizumab is less in patients who are at low risk of progression (e.g. patients with stage III and NVRD) than high risk of progression, it would be expected that the relative improvement of patients treated with bevacizumab would be smaller in the subgroup of patients with stage III NVRD after PDS than in the rest of the PAOLA-1 population. This means that the NVRD effect calculated based on subgroups of the placebo arm in PAOLA-1 is likely to be an underestimate of the "true" NVRD effect. Similarly, the estimate of the 'treatment effect' is likely to be confounded; there may be a potential synergistic effect of maintenance treatment with PARPi and bevacizumab.[5, 16] The ERG therefore considers it possible that the concomitant bevacizumab use will confound the data and potentially provide an overestimate of the treatment effect. In addition, although the population in PAOLA-1 seems similar to that in PRIMA based on available baseline characteristics, there is likely to be unobserved differences that have not been adjusted for.

Figure 10. PAOLA-1 Kaplan-Meier estimate of PFS as assessed by BICR for stage III patients with PDS and residual disease, patients who had received NACT, stage IV patients82 (reproduced from the CS figure 30)



Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan Meier; PDS, partial debulking surgery; PFS, progression-free survival; NACT neoadjuvant chemotherapy

Figure 11. PAOLA-1 Kaplan-Meier estimate of PFS as assessed by BICR for stage III patients with PDS and no visible residual disease82 (reproduced from the CS figure 31)



Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan Meier; PDS, partial debulking surgery; PFS, progression-free survival

Table 10. PFS results from the PAOLA-1 trial (adapted from CS, table 21)

Population	Treatment arm	Median PFS (in months)	HR
Stage III patients with PDS and VRD, patients who had received NACT, stage IV patients	Olaparib + bevacizumab (n=399)	22.0	0.65 (95% CI 0.51-0.82)
	Placebo + bevacizumab (n=196)	16.6	
Stage III patients with PDS and NVRD	Olaparib + bevacizumab (n=138)	NR	0.45 (95% CI 0.27-0.75)
	Placebo + bevacizumab (n=73)	24.9	

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treatment; NACT, neoadjuvant chemotherapy; NVRD, no visible residual disease; PDS, primary debulking surgery; PFS, progression-free; VRD, visible residual disease

Table 11. Comparison of Non 'stage III NVRD after PDS' subgroup in PAOLA-1 and PRIMA

Patient characteristics	PAOLA-1 treatment arm (Olaparib and bevacizumab)	PRIMA treatment arm (Niraparib)	PAOLA-1 placebo arm (Placebo and bevacizumab)	PRIMA placebo arm (Placebo)
Stage IV and III VRD after PDS (N, %)	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV NVRD after PDS (N, %)	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV and III NVRD after IDS (N, %)	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV and III VRD after IDS (N, %)	[redacted]	[redacted]	[redacted]	[redacted]

No surgery (N, %)	[redacted]	[redacted]	[redacted]	[redacted]
Total (N)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IDS, interval debulking surgery; NVRD, no visible residual disease; PDS, primary debulking surgery; VRD, visible residual disease

2.4.4.2 SOLO-1

SOLO-1 is a placebo controlled RCT comparing olaparib with placebo in patients with advanced ovarian cancer and a BRCA mutation (BRCA+), and who are in response to first line platinum-based chemotherapy. Subgroup data from SOLO-1 are available for the populations equivalent to the MA population for niraparib (although limited to BRCA+ patients) and the patient population excluded from PRIMA (

Table 12):

- ITT population: stage III patients with and without residual disease following PDS, patients who had received NACT or stage IV patients; and
- Stage III patients with PDS and no residual disease.

Except for the difference in BRCA mutation status between the SOLO-1 and PRIMA populations, the trials also differ in the proportion of patients with stage III disease and complete or partial response to first line therapy. The NVRD and treatment effect for SOLO-1 was estimated using KM data for investigator-assessed PFS shown in

Figure 12 for the ITT population and Figure 13 for stage III patients with NVRD. The PFS results are also presented in

Table 12. However, the ERG has not been able to validate the subgroup data in

Table 12 based on the reference provided for the study in the CS.[6]

The company estimated the NVRD and treatment effect between the ITT curve and the placebo NVRD curve, in the olaparib arms and placebo arms respectively, to be:

- "NVRD effect": HR 0.753, 95% CI: 0.521 to 1.327;
- "treatment effect": HR 0.718, 95% CI: 0.491 to 1.393.

As for PAOLA-1, the company assessed if proportional hazards hold for the "NVRD effect" and "treatment effect" HRs based on SOLO-1, and similarly the log-cumulative hazards plots, Schoenfeld residual plots and p-values indicate that the assumption of proportional hazards cannot be rejected for either. As with PAOLA-1, the ERG's concerns remain about the validity of the company approach of adjusting the PRIMA ITT data for PFS by applying HRs to each of the treatment arms when the PHs assumption has been shown not to hold for PFS within PRIMA.

The estimated NVRD effect based on SOLO-1 is smaller than that based on PAOLA-1 data, and neither the NVRD effect or the treatment effect would be considered statistically significant. In addition, the treatment effect for SOLO-1 is similar to the NVRD effect indicating that there is little or no olaparib-specific treatment effect on top of the NVRD effect seen between the ITT population and subgroup given placebo.

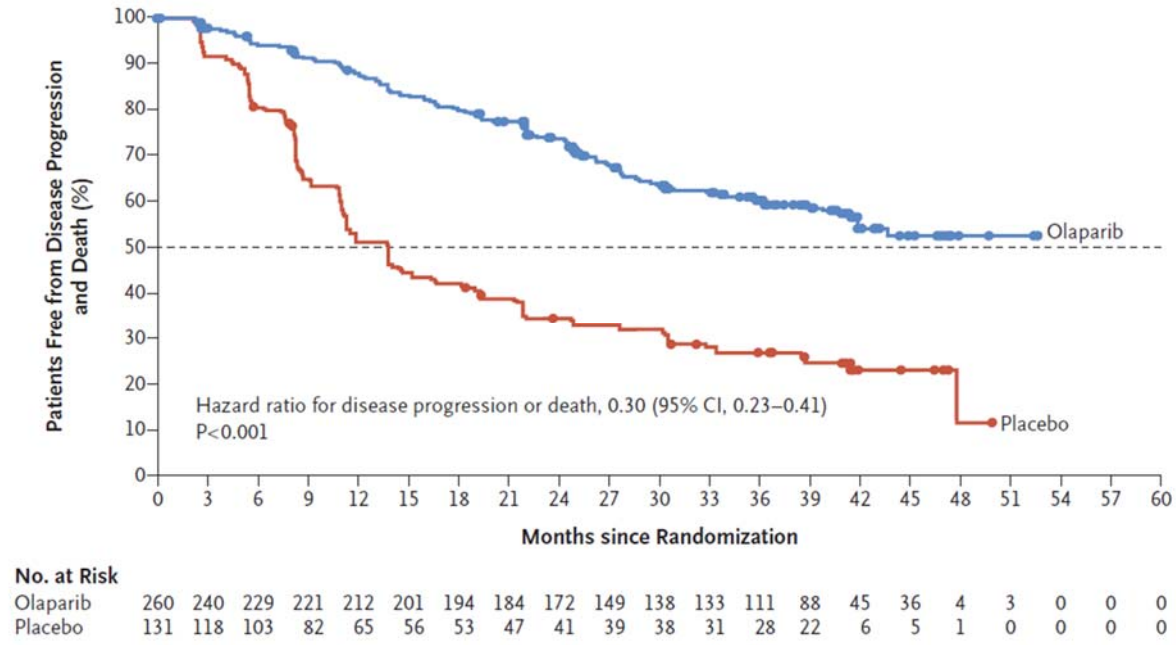
As for PAOLA-1, the populations in SOLO-1 are not directly comparable to the patients in PRIMA due to differences in study design, inclusion criteria and baseline characteristics, and the NVRD and treatment effects calculated based on SOLO-1 are confounded, both by known and likely unknown confounders. A comparison of the composition of the ITT populations of SOLO-1 and PRIMA shows that a similar proportion of patients had no surgery but all categories by residual disease and type of surgery differed substantially between the trials (Table 13).

The population of SOLO-1 is limited to patients with a BRCA mutation, who have a better prognosis than patients with BRCA wild type (BRCAwt) and the overall population. The PARPi specific treatment effect has also been established to be larger in the BRCA+ population than in BRCA- or the overall population. The impact on the NVRD effect of the SOLO-1 trial only including BRCA+ patients is not clear. As the BRCA+ subgroup overall has a better prognosis, it could potentially hide or obscure the true NVRD effect, or it may not have an impact on the relative NVRD effect at all. The impact of focusing on BRCA+ patients on the treatment effect on the other hand is likely to lead to

an overestimate of the effect as treatment with PARPis like olaparib and niraparib are known to lead to longer PFS compared with placebo in BRCA+ patients compared with BRCA- patients or a mixed population. This means that the very small difference between the NVRD and treatment effect for SOLO-1 is likely to be an overestimate of the true treatment effect. That is, the results based on SOLO-1 data, which are both non-significant, indicate that there is no NVRD effect or PARPi specific treatment effect.

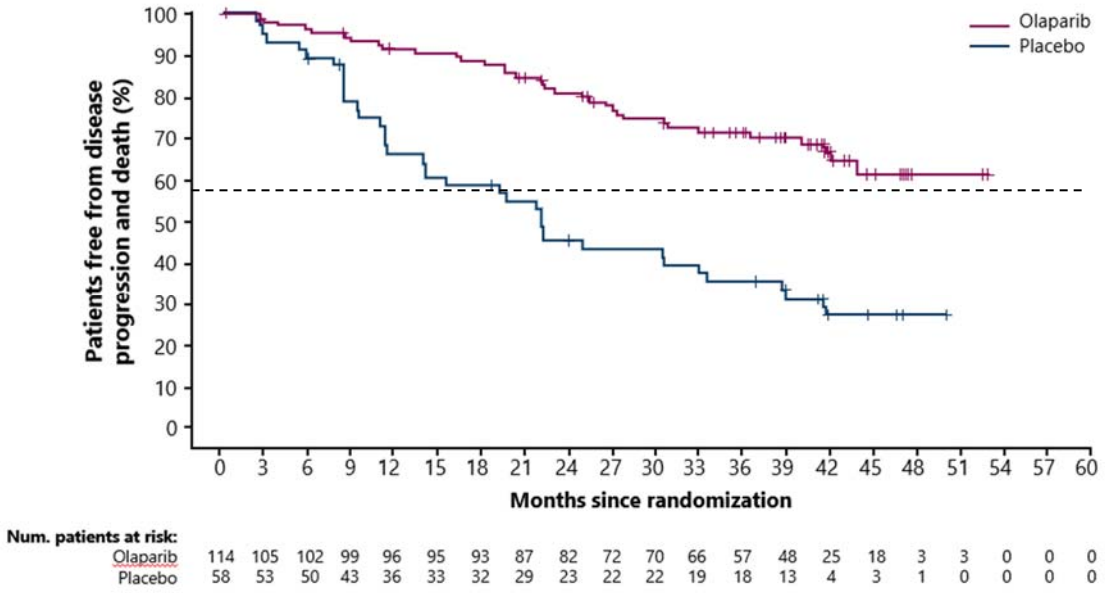
As highlighted above, the NVRD and treatment effect calculated for SOLO-1 are based on a comparison of the subgroup of patients with stage III disease and NVRD compared with the ITT population rather than the complementing subgroup as in PAOLA-1. This could lead to an underestimate of both the NVRD and the treatment effect as the ITT population includes the NVRD subgroup.

Figure 12. SOLO-1 Kaplan-Meier estimate of investigator-assessed PFS in the ITT population83 (reproduced from CS figure 32)



Abbreviations: CI, confidence interval; ITT, intention to treat; PFS, progression-free survival

Figure 13. SOLO-1 Kaplan-Meier estimate of investigator-assessed PFS in stage III patients who underwent upfront surgery and had no visible residual disease[83] (reproduced from CS, figure 33)



Abbreviations: PFS, progression-free survival

Table 12. PFS results from the SOLO-1 trial (adapted from CS, table 21)

Trial	Population	Treatment arm	Median PFS (in months)	HR
SOLO-1[43,83]	ITT	Olaparib (n=260)	NR	0.30 (95% CI 0.23–0.41)
		Placebo (n=131)	13.8	
	Stage III, upfront surgery, NVRD	Olaparib (n=114)	NR	0.32 (95% CI 0.20-0.51)
		Placebo (n=58)	21.9	

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treatment; PFS, progression-free; NR, not reached; NVRD, no visible residual disease

Table 13. Comparison of ITT population in SOLO-1 and PRIMA

Patient characteristics	SOLO-1 treatment arm (Olaparib)	PRIMA treatment arm (Niraparib)	SOLO-1 placebo arm	PRIMA placebo arm
Stage IV and III VRD after PDS (N, %)	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV and III NVRD after PDS (N, %)	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV and III NVRD after IDS (N, %)	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV and III VRD after IDS (N, %)	[redacted]	[redacted]	[redacted]	[redacted]
No surgery (N, %)	[redacted]	[redacted]	[redacted]	[redacted]
Total (N)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IDS, interval debulking surgery; NVRD, no visible residual disease; PDS, primary debulking surgery; VRD, visible residual disease

2.4.4.3 PRIMA

The company also explored outcomes of the PRIMA study to assess whether they could be used to inform the magnitude of the expected treatment effect in the population with stage III and NVRD after PDS. The company compared the niraparib treatment effect observed between stage III and IV patients within the PRIMA trial. The subgroup analyses indicated that niraparib is more effective in stage III (HR 0.54, 95% CI: 0.42 to 0.70) patients than in stage IV patients (HR 0.79, 95% CI: 0.55 to 1.12). The company therefore proposes that the treatment effect observed in the stage III cohort in PRIMA can be used as a minimum of the treatment effect for the cohort with stage III and NVRD following PDS and that this would be a conservative estimate. To model this within the economic analysis, the PFS for routine surveillance in the ITT population had an 'NVRD effect' applied using the

HR estimated from PAOLA-1 as described earlier, and then the stage III HR of 0.54 observed in PRIMA was applied to the achieve the niraparib NVRD efficacy.

The ERG highlights that the company uses the HR for niraparib versus placebo for the stage III subgroup of PRIMA rather than calculating a treatment effect using the same methods as for PAOLA-1 and SOLO-1. The ERG has concerns about the appropriateness of applying a HR directly to the PFS curves in PRIMA, when PHs have been demonstrated not to hold for PFS in PRIMA. How the PRIMA stage III subgroup HR was applied in the model is described in section 4.2.4.2.

The ERG notes that, if it is considered that the proportion of patients with stage III NVRD in PRIMA is substantially different from UK clinical practice, then to produce a more accurate estimate of the treatment effect of niraparib in this population, the company could use the subgroup of patients with stage III and NVRD after IDS rather than the stage III subgroup irrespective of residual disease status. If this is the case, the ERG has a strong preference for how the adjustment of the PRIMA ITT data is done, as described in section 2.4.3.

Table 14. PFS results from PRIMA (adapted from CS Figure 13)

Population	Treatment arm	HR
Stage III patients[a]	Niraparib (n=318)	0.54 (95% CI: 0.42 to 0.70)
	Placebo (n=158)	
Stage IV patients	Niraparib (n=169)	0.79 (95% CI: 0.55 to 1.12)
	Placebo (n=88)	

a. Patients with PDS and VRD, patients with IDS and VRD or NVRD, and patient with no debulking surgery
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treatment; NACT, neoadjuvant chemotherapy; NVRD, no visible residual disease; PDS, primary debulking surgery; PFS, progression-free survival; VRD, visible residual disease

2.4.5 Summary of company's MA approach

The company considers that a limitation of the PRIMA trial is the absence of patients with stage III NVRD following PDS. Due to the exclusion of these patients from the trial the company considers PRIMA not to fully reflect the MA population but that it is important to include these patients within the evidence underpinning a NICE recommendation. The ERG disagrees with the company and considers PRIMA to adequately reflect the MA population and the population in the NICE final scope (section 1.8.1). Although patients with stage III NVRD following PDS were excluded from PRIMA, the trial does include a large proportion of patients with stage III NVRD following IDS. As highlighted in the ESMO guidelines[10] and as shown in a study by Vergote *et al.*,[11] there is no significant difference in PFS and OS based on type of surgery, i.e. PDS or IDS. However, the ERG acknowledge that

outcomes may differ between the subgroup of patients with NVRD after IDS and PDS but notes that there is limited evidence to support this. Based on the opinion of the ERG's clinical experts, the prognosis of patients with stage III NVRD after PDS can be considered equivalent to patients with stage III NVRD after IDS. Therefore, the ERG considers the PRIMA ITT analysis the most relevant and robust evidence to inform the efficacy and safety of niraparib and does not consider an 'MA analysis' necessary to inform the decision problem.

Although the ERG considers PRIMA to adequately reflect the MA population it notes that the proportion of patients with stage III NVRD in PRIMA could be an underestimate compared with the proportion among patients in UK clinical practice. The ERG therefore advises the company to explore the impact on results of re-weighting the proportion of patients with stage III NVRD after IDS in PRIMA to be reflective of the proportion of patients with stage III NVRD (irrespective of type of surgery) in clinical practice.

The company's main conclusions in support of extrapolation of the PRIMA ITT data together with the ERG's main critique are summarised in the table below.

Table 15. Summary of 'MA population' analysis assumptions and ERG considerations

Company conclusion	Evidence cited by company	ERG view
Patients with stage III NVRD after PDS have a better prognosis than patients with stage III/IV VRD	• Targeted literature review • Edinburgh dataset • PAOLA-1 • SOLO-1	The ERG agrees with the company conclusion but notes that the 'NVRD effect' estimated by the company based on PAOLA-1 and SOLO-1 has limited generalisability for PRIMA due to confounding caused by differences in populations, interventions and trial design between PAOLA-1, SOLO-1 and PRIMA. The ERG also has concerns about the appropriateness of applying a HR estimated from one trial and applying it directly to the PFS curves in PRIMA, particularly when PHs have been demonstrated not to hold for PFS in PRIMA. The company provided no justification for the approach taken.
PARP inhibitors demonstrate improved clinical outcomes in patients with stage III NVRD	• PAOLA-1 • SOLO-1 • PRIMA	The evidence in support of an increased PARPi specific treatment effect in patients with stage III NVRD is uncertain and of limited generalisability to PRIMA due to confounding. As for the 'NVRD effect', the ERG has concerns about the appropriateness of applying a HR, in this case estimated for a different treatment, in one trial and applying it directly to the PFS curves in PRIMA. The estimated 'treatment effect' relies on the assumption of a class effect, i.e. that any relative treatment effect observed with olaparib will be the same for niraparib, an assumption for which the company has not provided support (as the relevant data are not available for niraparib to enable a comparison between PARPis).

Stage III patients who have NVRD constitute [redacted] of the MA population	• Edinburgh dataset • PAOLA-1	The estimate based on the Edinburgh dataset is for stage III NVRD rather than limited to those who had had PDS, which is the population excluded from PRIMA. As an estimate for stage III NVRD irrespective type of surgery, it is likely to be an underestimate. The ERG's clinical experts estimate that the proportion of patients with stage III and NVRD is likely to be closer to 50-60% in the UK. The proportion of patients with NVRD after surgery varies across UK practice and basing this estimate on one small region in the UK may not be representative of the surgical outcomes seen across the country. In addition, the company did not conduct an SLR to identify other relevant sources to inform this proportion. Data from PAOLA-1 supports the assumption that stage III NVRD after PDS may constitute [redacted] of the MA population. However, the ERG's clinical experts advised that this may also be an underestimate and that the proportion may be somewhere from 25% up to 40% of the population.
Patients with stage III NVRD are at risk of recurrence and death and therefore have a high unmet need	• Edinburgh dataset • PAOLA-1 • SOLO-1	The ERG agrees but notes that PRIMA includes a substantial proportion of patients with stage III NVRD and thus the population of PRIMA is representative of the full MA population.

Abbreviations: ERG, evidence review group; HR, hazard ratio; MA, marketing authorisation; NVRD, no visible residual disease; PARP(i); poly(ADP-ribose) polymerase (inhibitor); PDS, primary debulking surgery; PFS, progression-free survival; PH, proportional hazard; VRD, visible residual disease

2.5 Conclusions of the clinical effectiveness section

Evidence in support of the clinical effectiveness of niraparib as maintenance therapy for people with advanced ovarian cancer who have responded (CR or PR) to first line platinum-based chemotherapy, is derived from the PRIMA trial. PRIMA is a double-blind, multicentre placebo-controlled phase III randomised controlled trial providing comparative evidence on the clinical efficacy and safety of maintenance treatment with niraparib versus placebo. All patients were initially started on 300 mg niraparib once daily but due to high numbers of dose reductions due to adverse events (AEs) a protocol amendment was introduced. After the amendment, patients were given an individualised dose with patients with a weight of < 77kg or a baseline platelet count <150,000/µL starting on 200 mg niraparib once daily. In order to explore to what extent the overall results may be driven by the effectiveness in patients who started on the 300 mg dose, the company provided PFS subgroup data based on fixed and individualised dosing at the clarification stage.

Just under two thirds (64.8%) of patients enrolled in PRIMA started on the fixed 300 mg dose, and 35.2% started on individualised dosing. Maintenance therapy with niraparib resulted in a longer median PFS both in the fixed and individualised dosing groups compared with placebo, though the subgroup analyses indicate that niraparib may be slightly less effective in the subgroup on individualised dosing than in the fixed dose subgroup. That is, the ITT analysis may overestimate the

efficacy of niraparib expected in clinical practice as the proportion of patients starting on the 300 mg dose was higher in the trial than would be expected in clinical practice, where all patients will be offered individualised dosing. However, these subgroup analyses should be considered exploratory in nature, because they are *post-hoc* non-stratified subgroup analyses, the difference between the subgroups were not statistically significant and PRIMA was not powered to detect a difference between these groups. Importantly, individualised dosing led to fewer dose interruptions and dose reductions due to AEs than the fixed dose.

The results of the primary outcome of PRIMA, PFS determined by BICR in the ITT population, showed a statistically significant benefit of niraparib treatment compared with placebo (median PFS was 13.8 and 8.2 months in the niraparib and placebo arms respectively and p<0.0001). However, PHs are unlikely to hold and therefore the resulting HR with accompanying 95% CI is difficult to interpret and potentially misleading. Results of the secondary outcomes PFS2 and OS were consistent with the primary outcome results favouring niraparib over placebo but neither were statistically significant as the data were very immature. Only [redacted] and [redacted] had a second progression in the niraparib and placebo arm, respectively, and 9.9% and 12.6% of people had died in the niraparib and placebo arms at the time of analysis. Changes over time in HRQoL were captured using FOSI and EQ-5D-5L. These results of the HRQoL measures indicate that maintenance treatment with niraparib does not negatively impact on the HRQoL of patients. A greater proportion of patients on niraparib (71%) than on placebo (19%) experienced an adverse event of grade ≥3. Among the most common grade ≥3 adverse events in the niraparib group were anaemia (31.0% of the patients), thrombocytopenia (28.7%), decreased platelet count (13.0%), and neutropenia (12.8%).

The company considers that a limitation of the PRIMA trial is the absence of patients with stage III NVRD following PDS. Due to the exclusion of these patients from the trial, the company considers PRIMA not to fully reflect the MA population but that it is important to include these patients within the evidence underpinning a NICE recommendation. The ERG disagrees with the company and considers PRIMA to adequately reflect the MA population and the population in the NICE final scope. Although patients with stage III NVRD following PDS were excluded from PRIMA, the trial does include a substantial proportion of patients with stage III NVRD following IDS. As highlighted in the ESMO guidelines[10] and as shown in a study by Vergote *et al.*,[11] PFS and OS are similar irrespective of type of surgery, i.e. PDS or IDS. However, the ERG acknowledge that the outcomes may differ between the subgroup of patients with NVRD after IDS and PDS but notes that evidence to support this is not conclusive. Therefore, based on the opinion of the ERG's clinical experts, the prognosis of

patients with stage III NVRD after PDS and IDS can be considered equivalent. In conclusion, the ERG considers the PRIMA ITT analysis the most relevant and robust evidence to inform the efficacy and safety of niraparib and does not consider the company's 'MA analysis' appropriate to inform the decision problem.

Although the ERG considers PRIMA to adequately reflect the MA population it acknowledges that the proportion of patients with stage III NVRD in PRIMA (stage III NVRD after IDS was [redacted] and NVRD irrespective of stage was 47%) may be lower than in UK clinical practice, which the company's MA analysis could potentially inform. Data from two UK centres show that the proportion of patients with NVRD after surgery (irrespective of stage of disease) ranges between 59% and 85%, depending on surgical expertise, and Vergote *et al*. 2010 showed that the proportion of patients with NVRD was 19% and 51% after PDS and IDS, respectively.[11, 13] However, according to the ERG's clinical experts surgery has improved since the Vergote study and the proportion of patients with stage III NVRD irrespective of type of surgery is likely to be 50-60% in UK clinical practice.

The company's analysis has severe limitations due to the large number of assumptions, the use of indirect evidence and estimated treatment effects. In short, the company estimated an 'NVRD effect' and a 'treatment effect' based on data from the PAOLA-1 and SOLO-1 trials. These estimates have limited generalisability for PRIMA due to different issues relating to confounding, and it is not always clear in what direction the confounding may influence the results. The ERG also has concerns about the appropriateness of applying a HR estimated from one trial and applying it directly to the PFS curves in PRIMA, particularly when PHs have been demonstrated not to hold for PFS in PRIMA. The company provided no justification for the approach taken. The company also relies on the assumption of a PARPi specific class effect. The company also estimated the likely proportion that patients with stage III NVRD constitute of patients in clinical practice based on data from the Edinburgh Ovarian Cancer Database. This estimate is not fully aligned to the population excluded from PRIMA and it is possible that there are more robust information sources that are more representative of clinical practice across the UK, but this hasn't been explored.

The ERG considers a more robust and appropriate approach to assume that PFS outcomes are similar for patients with stage III NVRD after PDS and IDS; the company can then re-weight the subgroup of patient with stage III NVRD after IDS in PRIMA to adjust the ITT results in order to reflect the proportion of NVRD patients that would be seen in UK clinical practice. There are several methods that can be employed for this, e.g. in a previous NICE appraisal (TA558) the corrected group

prognosis method was used in preference to the average covariate method; however, the ERG is aware that the inverse probability of treatment weights (IPTW) may also be used

In summary, the PRIMA trial shows that maintenance therapy with niraparib significantly improves PFS in the ITT population but data for long-term outcomes are very immature and the magnitude of the survival benefit is therefore uncertain. A substantial proportion of patients on niraparib therapy experience grade ≥3 AEs on the fixed dose of 300mg per day but this was lowered by individualised dosing. Although, it is unclear to what extent the trial data may overestimate the efficacy of niraparib due to a larger proportion being given a starting dose of 300 mg than would be expected in clinical practice.

The ERG considers the PRIMA data to adequately represent the MA population but acknowledge that the proportion of patients with stage III NVRD in the trial may underestimate the proportion in routine clinical practice. The company can use the data within PRIMA to re-weight the proportion of stage III NVRD patients to explore this potential discrepancy, which is more methodologically robust than the company's approach.

3 Cost effectiveness

3.1 ERG comment on the company's review of cost effectiveness evidence

The company performed a systematic literature review (SLR) using a single search strategy to identify published studies reporting cost-effectiveness evaluations, health-related quality-of-life (HRQoL) data and resource use and cost data of patients with ovarian cancer (OC). The cost-effectiveness review focussed on maintenance interventions for OC while the other reviews considered all interventions for OC. Searches were initially run in February 2019 and were last updated in February 2020. A summary of the ERG's critique of the methods implemented by the company to identify relevant evidence is presented in Table 16. Due to time constraints, the ERG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 16. ERG's critique of company's systematic literature review

Systematic review step	Section of CS in which methods are reported			ERG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and cost evidence	
Search strategy	Appendix G	Appendix G	Appendix G	Appropriate. Electronic databases included: EMBASE, Medline, Medline (R) In-Process, CENTRAL, CRD, HTA, NHS EED, EconLit, ScHARRHUD and EuroQol. Other sources for "grey" literature included: HTA websites (NICE, PBS, CADTH and SMC), clinicaltrials.gov, ESMO, ESGO, ASCO, ASGO, SGO, NCRI, EACR, Google Scholar and ISPOR.
Inclusion/ exclusion criteria	Appendix G	Appendix G	Appendix G	Appropriate. Although no restriction on date was applied by the company. The ERG considers using a date restriction would have reduced the number of identified and included studies, as well as ensure the data extracted was the most recent and relevant.
Screening	Appendix G	Appendix G	Appendix G	Appropriate.
Data extraction	Appendix G and Table 22 in the CS. References were not extracted if they assessed the cost-effectiveness of bev where clinical data were sourced from trials that	Appendix H and Tables 32 to 35 in the CS. Extracted studies in which the intervention was a maintenance therapy to align with the licensing of niraparib.	Appendix I. Extracted studies in which the intervention was a maintenance therapy to align with the licensing of niraparib.	Appropriate. Due to the high volume of relevant studies, the ERG considers that appropriate and pragmatic decisions were made regarding their extraction.

	randomised patients prior to 1L chemotherapy (e.g. ICON-7, GOG-218).			
Quality assessment of included studies	Appendix G, using the Drummond and Jefferson criteria.	Appendix H, quality discussed alongside data extraction	Appendix I, quality discussed alongside data extraction	Appropriate.

Abbreviations: ASCO, American Society of Clinical Oncology; CS, company submission; EACR, European Association for Cancer Research; ERG, evidence review group; ESMO, European Society of Molecular Oncology; HRQoL, health related quality of life; ISPOR, The International Society for Pharmacoeconomics and Outcomes Research; NCRI, National Cancer Research Institute; SGO, Society of Gynaecological Oncology;

The SLR identified a total of 8,631 papers after de-duplication and based on title and abstract, a total of 389 papers were identified as potentially relevant to one or more of the three types of evidence the SLR aimed to identify. These papers were obtained for full text review. After assessment of the full texts, a total of 56 papers were included and extracted by the company including: 29 cost-effectiveness papers (24 unique studies), 23 HRQoL papers (21 unique studies) and 41 cost papers (39 unique studies).

Of the 29 cost-effectiveness papers, three studies were identified in the first line (1L) maintenance setting. This included two technology appraisals for olaparib in the maintenance treatment of ovarian cancer after 1L chemotherapy in the UK (TA598) and Canada (CADTH 2019), and one cost-effectiveness study for olaparib as maintenance treatment in Singapore (Tan 2019). The company considered these studies plus studies that assessed maintenance therapies in other settings (two lines of prior chemotherapy or more) to provide evidence on model structure as well as adverse event (AE), cost, and resource use inputs.

Of the 23 HRQoL papers, three included patients within the 1L maintenance setting (Friedlander 2018, CADTH 2019 and TA598). Three HTA appraisals for second line (2L) maintenance therapies were also identified by the company as being of relevance to the submission (TA528 for niraparib, TA620 for olaparib and TA611 for rucaparib). These studies reported PFS- and PD-state related utilities and AE disutilities. The company concluded that the mapped PRIMA EQ-5D-3L health state utility values (HSUVs) obtained through descriptive analyses of PRIMA data would be used to inform the base case analysis. These data were considered the most robust and applicable source of utility data, as they were directly collected in patients newly diagnosed advanced ovarian cancer following response to platinum-based chemotherapy. However, disutilities obtained through the published

literature were used to model the impact of AEs. Please refer to section 4.2.8 for further details on the HRQoL data applied in the model.

Of the 41 cost papers, five included patients who had received one prior line of chemotherapy at the start of the analysis: CADTH 2019, Gong 2019, TA598, Matsuo 2017 and Oaknin 2019. As shown in Table 17, the cost and resource use data applied in the model is largely informed by TA598. Please refer to section 4.2.9 for further details on the cost and resource use data applied in the model.

Table 17. Sources for base-case cost and resource use data in the model (reproduced from Table 22 of the clarification responses)

Category	Source	Identified in SLR
Treatment acquisition costs (maintenance and subsequent chemotherapy)	British National Formulary 2020	N/A Appropriate data source for the decision problem
Subsequent treatment resource use	UK expert opinion	N/A UK expert opinion were deemed an appropriate choice for subsequent chemotherapy regimens
Disease management unit costs	NHS Reference Costs 2018/19	Yes – code selection for unit costs were based on TA598 which was identified in the SLR
Disease management resource use	TA598	Yes
AE unit costs	NHS Reference costs 2017/18 and 2018/19	Yes – code selection for AE costs were based on methods adopted in TA528 and TA598 which was identified in the SLR
Terminal care unit cost and resource	Guest *et al.* 2006 Gao *et al.* 2013	Yes – Guest *et al.* and Gao *et al.* were referenced within TA598 and TA528 (Guest *et al.* only) which were both identified in the SLR.

Abbreviations: AE, adverse events; N/A, not applicable; SLR, systematic literature review; TA, technology appraisal; UK, United Kingdom

3.2 Summary and critique of company's submitted economic evaluation by the ERG

3.2.1 NICE reference case checklist

Table 18 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in section 2.

Table 18. NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes.
Perspective on costs	NHS and PSS	Yes.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The company's model adopts a 39-year time horizon. By this point, 100% of patients are dead in the RS arm of the model but 1% of patients are alive in the niraparib arm (when patients would be 100 years old). This is related to the overestimation of OS in the niraparib arm (discussed in section 4.2.4.3 and section 4.2.6.2).
Synthesis of evidence on health effects	Based on systematic review	Yes.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.

Abbreviations: ERG, evidence review group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year

3.2.2 Population

The company considered two populations in the economic analysis: the ITT population, which included the ITT population from the PRIMA trial; and the marketing authorization (MA) population, which the company defined as the ITT population from PRIMA plus patients with Stage III, no visible residual disease (NVRD) after primary debulking surgery (PDS).

The ITT population in PRIMA did not include Stage III patients with NVRD after PDS; however, it included Stage III patients with NVRD after interval debulking surgery (IDS) and Stage IV patients with NVRD (regardless of type of debulking surgery). The company considered that the ITT population in PRIMA only partially addresses the population defined in the NICE scope and in the actual MA for niraparib with the justification that, "*the anticipated licensed population includes patients with NVRD*".

In order to estimate outcomes for the MA population in the model, the company used hazard ratios (HRs) derived from the PAOLA-1 study which looked at progression-free survival (PFS) outcomes in patients with Stage III NVRD after PDS vs the patients in PAOLA-1 who had the same characteristics as the ITT PRIMA population. In their base case, the company assumed that [redacted]% of the MA population would consist on patients with Stage III NVRD after PDS (see section 3.4 and section 4.2.4.2 for more details).

The ERG's view is that PRIMA is representative of the MA population as it includes patients with NVRD after PDS or IDS (47% of the entire ITT population in PRIMA had NVRD). Given that the company's rationale for generating an MA population is mainly based on the fact that NVRD patients have better outcomes than patients with VRD (section 3.4), the ERG considers that PRIMA does not only provide sufficient evidence to address this issue, but is also the most robust source of evidence available to estimate the cost-effectiveness of niraparib vs RS.

Furthermore, the ERG notes that the company's approach of estimating treatment effects for patents with Stage III NVRD after PDS vs the patients in PAOLA-1 who had the same characteristics as the ITT PRIMA population lacks robustness. The company's approach effectively estimates outcomes for NVRD stage III after PDS vs the simulated PRIMA ITT in PAOLA-1 (which includes [redacted]% of NVRD patients), therefore confounding the analysis of NVRD vs VRD outcomes.

Even though this has not been explicitly stated by the company, the ERG hypothesises that the company's rationale was based on Stage III NVRD PDS patients having different outcomes from Stage

III NVRD IDS patients. In response to a clarification question, the company reported that according to Ledermann *et al*. 2013, IDS remains the treatment modality primarily used for patients with poor performance status at presentation, low albumin levels and in those with very extensive tumour dissemination.[10] Therefore, the company considered that the outcomes for the patients excluded from PRIMA (Stage III NVRD after PDS) would be better when compared to the outcomes for patients with Stage III NVRD after IDS, included in PRIMA.

The ERG reviewed the Ledermann *et al.* ESMO guidelines and notes that the authors report that, "*The timing of surgical cytoreduction in relation to chemotherapy is still debated. A large prospective trial showed that in advanced bulky stage IIIC or IV disease, three cycles of platinum-based neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to primary debulking surgery followed by chemotherapy. Surgical morbidity had a non-significant trend to be lower in the neoadjuvant arm. As a result of these data, the use of primary chemotherapy with interval surgery is becoming more widely accepted and is offered to patients with poor performance status at presentation, low albumin levels and in those with very extensive tumour dissemination. Validation of the results of this approach may come from further trials that are ongoing."* [10]

The ERG interprets the study conclusions differently to the company. The guidelines report that because there is evidence that patients with advanced bulky disease (Stage IIIC and IV) who received IDS do not have worse outcomes than patients who received PDS, the former is becoming more widely used in this group of patients. This does not mean that only patients with a poorer prognosis receive IDS.

The proportion of patients in PRIMA with Stage IIIC and IV amounts to 93% in the niraparib arm and to 92% in the RS arm. Given the ESMO conclusions that patients with Stage IIIC and IV have similar outcomes after IDS and PDS, the ERG argues that the clinical outcomes for patients undergoing IDS in PRIMA are representative of the outcomes that would be observed in patients undergoing PDS.

Nonetheless, the ERG notes that the ESMO analysis is based on the overall population (i.e. NVRD and VRD patients combined). The issue remaining thus, is the possibility that NVRD achieved through PDS yields better clinical outcomes than NVRD achieved through IDS. The ERG has not found evidence to provide a definite conclusion on this issue and therefore, it does not find it necessary to undertake any extra analysis to address this in the cost-effectiveness analysis.

However, the ERG acknowledges that because PRIMA excluded patients with Stage III, NVRD after PDS, the overall proportion of patients with NVRD in PRIMA ([redacted]% in total; Stage III NVRD amounting to [redacted]%; and Stage IV NVRD [redacted]%) might have been lower than in UK clinical practice, where the total proportion of patients with NVRD after surgery can range between 50% and 80%, depending on surgical expertise (according to the ERG's clinical experts' view and Hall *et al.* [13]).

In conclusion, the ERG considers that:

1. The company's approach of estimating treatment effects for Stage III NVRD after PDS vs the patients in PAOLA-1 who had the same characteristics as the ITT PRIMA population lacks a robust rationale and employs a flawed method;
2. There is no need to estimate an NVRD effect in the model and therefore, the ERG advises against using the MA population in the model;
3. The ERG considers that it is likely that the PRIMA ITT is reflective of the NICE final scope and of niraparib's MA;
4. The ERG acknowledges the overall proportion of patients with Stage III NVRD ([redacted]%) in PRIMA might have been lower than in UK clinical practice, therefore recommends that the PRIMA results are adjusted to reflect this discrepancy (see section 3.4).

More details on the estimation of the NVRD effect can be found in section 3.4, together with a discussion around how the company could adjust the PRIMA results to reflect a higher proportion of patients with Stage III, NVRD.

3.2.3 Interventions and comparators

The intervention included in the economic model was based on the PRIMA trial protocol. The original protocol started patients on 300mg of niraparib once daily; however, a subsequent protocol amendment (February 2018) allowed patients who weigh <77 kg and/or have a baseline platelet count < 150,000/µL, to initiate niraparib on 200 mg OD.

The company's base case model originally included the actual dose received in months 1 through 12 in the PRIMA ITT (therefore, it included a combination of patients on [redacted]). After the clarification stage, the company changed this to include months 1 to 18 in PRIMA.

	Proportion of patients across dose (mg) categories in PRIMA	Average dose

Cycle/Month	100	200	300	Weighted average (mg)
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]
18+	[redacted]	[redacted]	[redacted]	[redacted]

Table 19 shows the proportion of patients on the different treatment schedules and the resulting weighed dose per month in PRIMA (used in the economic analysis). The company assumed that the weighted average dose received in month 18 would be the same for the remainder of the treatment period with niraparib in the model. The clinical experts advising the ERG reported that at 18 months thee dose tolerated by each patient should be stable enough to be a good reflection of the rest of the treatment period.

	Proportion of patients across dose (mg) categories in PRIMA			Average dose
Cycle/Month	100	200	300	Weighted average (mg)
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]

11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]
18+	[redacted]	[redacted]	[redacted]	[redacted]

Table 19. Niraparib dose received in PRIMA and included in the company's base case model

[redacted]In the recent license variation (pending EMA approval) the recommended starting dose of niraparib was reduced from 300mg daily to 200mg OD in order to minimise the incidence of adverse events. However, for patients who weigh ≥ 77 kg and have baseline platelet count ≥ 150,000/µL, the recommended starting dose of niraparib remained 300 mg (three 100 mg capsules), taken once daily.

The ERG notes that only in month [redacted]. The ERG's clinical experts were surprised by the large proportion of patients reduced to a 100mg dose in PRIMA due to the lack of published evidence on the effectiveness of a 100mg dose. The ERG also notes the potential relevance of further investigation of reducing the licensed dose of niraparib to 100mg and its impact on clinical outcomes for OC patients.

[redacted].[3]

The comparator modelled was routine surveillance (RS), which is in agreement with the NICE final scope.

[3] Factual inaccuracy identified after appraisal committee meeting 1. Correct information is "[redacted]"

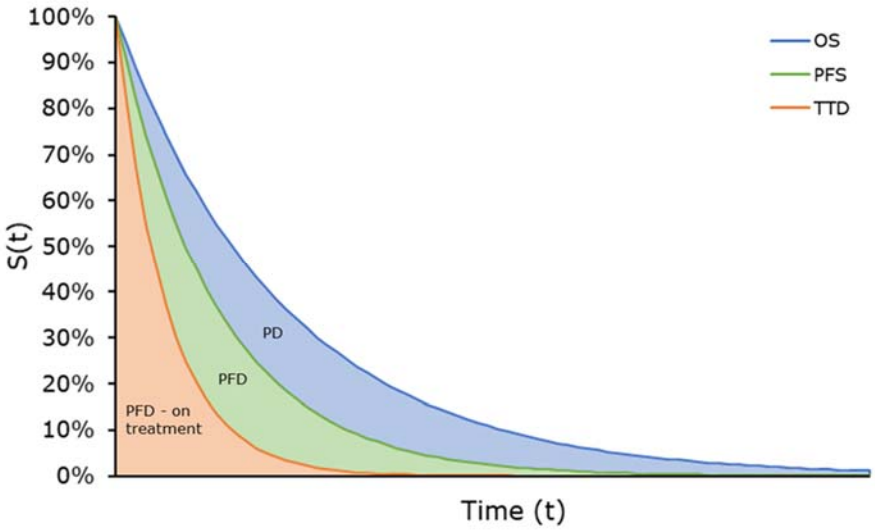
3.2.4 Modelling approach and model structure

As explained in section 2.3.1; section 3.4; and section 4.2.2, the ERG's view is that the PRIMA ITT population (and therefore the ITT model) is representative of the NICE final scope and of the MA for niraparib. Therefore, the ERG advises against the use of the MA model to determine the cost-effectiveness of niraparib vs RS. Nonetheless, for completeness purposes, the ERG described the company's modelling approach for both the ITT and the MA population for the updated model submitted after the clarification stage. The ERG also reports the company's results for the MA model; however, the ERG has not conducted any additional analyses using this population.

The company developed a *de novo* model in Microsoft Excel®. The model adopts a partitioned survival approach comprising of three health states: progression-free survival (PFS); disease progression (PD); and death -

Figure 14. Patients enter the model in the PFS state at a mean age of 61 years. Patients occupying the PFS state are at risk of disease progression or death and can also discontinue treatment before disease progression. The probability of being alive and free from disease progression was calculated using the cumulative PFS curve in the model, while the probability of being alive was calculated from the cumulative OS curve. Time on treatment with niraparib was estimated in the model through the use of time to treatment discontinuation (TTD) data from PRIMA.

Figure 14. Company's model (Figure 16 CS)



Abbreviations: PD, progressed disease; PFD, progression-free disease; PFS, progression-free survival; OS, overall survival; s(t), survival at time t; TTD, time to treatment discontinuation

The company incorporated a long-term remission assumption in their modelling approach. Based on clinical expert advice, the company chose 7 years as the point in the model when the survival rate for PFS patients was set to the all-cause general population mortality. The company applied the long-term remission assumption to the OS curves in the model for both niraparib and RS, and for both the ITT and the MA populations:

Equation 1:

$$OS(t) = \alpha \times \dot{OS}(\mathrm{t}) + \beta \times \widetilde{\mathrm{OS}}(\mathrm{t})$$

Where $OS(t)$ is the weighted survival probability for the full ITT or MA populations in the model, α is the proportion of PFS patients in the OS curve at 7 years in the model, β is the proportion of PD patients in the OS curve at 7 years in the model; and $\widetilde{\mathrm{OS}}(\mathrm{t})$ is the probability of survival for patients who achieve and who do not achieve long-term remission in the model, combined. $\dot{OS}(\mathrm{t})$ was estimated differently before and after 7 years in the model. Before year 7, $\dot{OS}(\mathrm{t})$ was estimated as the probability of survival for patients who achieve and who do not achieve long-term remission in the model combined, and therefore:

$$\dot{OS}(t < 7) = \widetilde{\mathrm{OS}}(\mathrm{t})$$

After 7 years in the model the company estimated $\dot{OS}(\mathrm{t})$ as:

$$\dot{OS}(t \geq 7) = \widetilde{\mathrm{OS}}(\mathrm{t}-1) \times [1 - Rgen(t)]$$

Where $Rgen(t)$ is the risk of death in the general population matched for age. The company's underlying assumption was that after 7 years in the model, patients who were still in the $\dot{OS}(\mathrm{t})$ curve would be patients who do not achieve long-term remission in the model.

The company also applied the general population survival to the PFS curves for both the niraparib and RS arms, and for both the ITT and the MA populations after 7 years in the model, where:

$$PFS(t < 7) = \widetilde{\mathrm{PFS}}(\mathrm{t})$$

Where $\widetilde{\mathrm{PFS}}(\mathrm{t})$ is the probability of progression-free survival for patients who achieve and who do not achieve long-term remission in the model combined (taken from PRIMA). After year 7 in the model, the company assumed that:

$$PFS(t \geq 7) = \widetilde{\mathrm{PFS}}(\mathrm{t}-1) \times [1 - Rgen(t)]$$

3.2.4.1 ITT population from PRIMA

PRIMA collected data on PFS, OS and TTD. Time to disease progression data in the niraparib and RS arms of the model were fitted with standard parametric curves in alignment with the Decision Support Unit technical support document 14 (DSU; TSD 14).[17] This was also the case for OS data in the RS arm; and for TTD data in the niraparib arm.

The company considered that the use of a standard parametric modelling approach was inappropriate to derive OS curves for niraparib as the PRIMA niraparib OS data was too immature. In order to derive an OS curve for the niraparib arm of the model, the company used Study 19. [18] They compared olaparib monotherapy with RS in BRCA+ patients for second line maintenance treatment, with a 7-year follow-up period. The company estimated the difference in mean PFS (0.16) between olaparib and RS, and then divided this by the difference in mean OS (0.48) between olaparib and RS. The company assumed a class effect for olaparib and niraparib and used the estimated ΔPFS:ΔOS ratio of 1:3 from Study 19 as the basis for a relative difference between niraparib and RS.

In their base case analysis, the company used a 1:2 ratio with the justification that the latter is a more conservative choice given that the 1:3 ratio was based on a different trial and different data. The company also conducted a range of scenario analyses to test different ratios (1:1, 1:1.25, 1:1.5, 1:1.75, 1:2.5, and 1:3). The hazard ratio (HR) estimated by the company between RS OS and niraparib OS to generate the ΔPFS:ΔOS relationship of 1:2 amounts to [redacted] and guarantees that:

Niraparib mean OS = (RS mean OS + [Mean PFS difference x 2])

The company then applied the [redacted] HR to the RS OS fitted curve in order to estimate the niraparib OS curve in the model.

3.2.4.2 MA population

In order to estimate PFS for the Stage III NVRD population, the company used the PFS curves derived from the ITT population and applied the hazard ratios (HRs) described in section 3.4 to reflect the NVRD effect (HR 0.490; 95% CI: 0.329 to 0.723) in the RS am and the treatment effect (HR 0.340; 95% CI: 0.233 to 0.497) in the niraparib arm. The company applied the HRs in the model through the following approach:

1. For the RS arm: the company applied the 0.49 HR to the RS PFS curve fitted to the RS PFS KM ITT data from PRIMA;
2. For the niraparib arm: the company applied the 0.34 HR to the niraparib PFS curve fitted to the niraparib PFS KM ITT data from PRIMA.

The company assumed that the "NVRD effect" did not directly impact OS outcomes in the model given the lack of published OS data for Stage III patients with NVRD.

For PFS; OS; and TTD curves the company assumed that [redacted] of the MA population had Stage III NVRD after PDS while [redacted] of the MA population was composed of the PRIMA ITT population. The curves were weighted by these proportions and respective outcomes (more detail on this in section 4.2.6).

The company stated that the [redacted] estimate was based on evidence from the Edinburgh database and the PAOLA-1 trial (for both niraparib and RS); however, the company highlighted that this is a relatively conservative estimate, as there are areas in England where this ratio is higher. Therefore,

the company conducted scenario analyses to assess the impact of changing the proportion of Stage III patients with NVRD to 30% and to 40% (see section 3.4 for more details).

3.2.4.3 ERG critique

The ERG is generally satisfied with the model structure, however, notes that PRIMA collected data on second progression events (PFS2) which could have been used to capture second progression-related costs and the impact of secondary events on women's quality of life. As a result of a clarification request from the ERG, the company reported that PFS2 data from PRIMA were too immature to be included in the model. Nonetheless, the ERG notes that PFS2 data were 20% mature at data cut-off, which compares to 13% maturity for the OS RS KM data from PRIMA, which the company has used to fit OS curves.

The main issues concerning the ERG in the company's modelling approach are:

1) The estimation of Stage III NVRD outcomes (covered in section 4.2.2);
2) The estimation of long-term remission in the model; and
3) The estimation of OS in the niraparib arm through the use of a PFS:OS ratio.

3.2.4.3.1 Company's modelling of long-term remission

Methodological approach

The company's long-term remission assumption means that patients who are free from disease progression at 7 years in the model do not relapse again and start incurring the general population mortality. It is, therefore, the ERG's view that the company's approach to modelling long-term remission is the equivalent of assuming that patients remaining in the PFS curves at 7 years are cured in the model.

The ERG considers that the estimation of cure in the model relies on a weak methodology, given that both the proportion of patients cured and the cure threshold were exogenously chosen by the company instead of being estimated through a robust method, such as a mixture cure model (MCM). The goal of a MCM is to depict long-term survivors whose risk of death becomes the same (or close to) that of a disease-free patient (Bullement *et al.* 2019[19] and Othus *et al*. 2017[20]). In such models, the proportion of cured patients is estimated through the model and there is no "cure threshold" as the survival trajectory of long and short-term survivors is also endogenously estimated in the MCM.

During the clarification stage the ERG proposed that, if the company deemed that a cure approach was justifiable, an MCM should be employed. In response, the company stated that the lack of long-term data from PRIMA or individual patient-level data from real-world sources to inform such model made it an unfeasible approach.

The ERG agrees with the company that the appropriate use of MCMs relies on the existence of mature data from studies with long follow-up times that far exceed the anticipated point of cure time, as well as sufficient numbers of patients at risk at the end of follow-up in order to robustly estimate a cure fraction.[21] However, advises that the lack of mature data should not be used to justify employing a methodologically weaker alternative to estimating a cure in the model.

Table 20 reports how the company has estimated the α parameter (the proportion of patients cured) and β (the proportion of patients not cured) in Equation 1 described in the previous subsection (and reported again below):

$$OS(t) = \alpha \times \dot{OS}(\mathrm{t}) + \beta \times \widetilde{\mathrm{OS}}(\mathrm{t})$$

As reported in Table 20, the proportion of patients cured in the RS arm ([redacted]) is higher than in the niraparib arm ([redacted]) at 7 years. As the company explained in response to clarification question B5: "*At the long-term remission base case of 7 years, PFS and OS are higher in the niraparib arm compared to the RS arm. However, as less people are alive within the RS treatment arm, the ratio of PF:PD is higher for RS ([redacted] for RS compared to [redacted] for niraparib). The chance of achieving long-term remission at 7 years is, as expected, higher in the niraparib arm ([redacted] than the RS ([redacted] arm."* The ERG maintains its view that using this simplistic approach is not only methodologically weak but also leads to parameters lacking face validity and therefore, unfit for decision making.

Furthermore, while α and β in the ITT population were taken from the ITT PFS and OS curves estimated in the model, the and α and β in the Stage III NVRD after PDS population were taken from the Du Bois study.[22] The study consists of an exploratory analysis of three prospective randomized trials investigating platinum-taxane based chemotherapy regimens in advanced OC conducted between 1995 and 2002, and the impact of complete surgical resection on clinical outcomes. In response to a clarification question, the company justified using the Du Bois study to estimate the proportion of patients cured in the NVRD population because of:

- *"Large sample size; n=3,129 OC patients from three prospective trials in Europe;*

- *Assessment of a range of surgical outcomes;*
- *Long follow-up period (144 months) allowing for PFS and OS data to be extracted at 5, 7 and 10 years. "*

Table 20. Proportion of patients assumed to be cured and not cured at 7 years in company's base case)

Parameter	α	β	Source
ITT population			
Niraparib	[redacted]	[redacted]	α – % of patients in the niraparib PFS ITT curve divided by the % of patients in the niraparib OS ITT curve at 7 years β – % of patients in the niraparib PD ITT curve divided by the % of patients in the niraparib OS ITT curve at 7 years
Routine surveillance	[redacted]	[redacted]	α – % of patients in the RS PFS ITT curve divided by the % of patients in the RS OS ITT curve at 7 years β – % of patients in the RS PD ITT curve divided by the % of patients in the RS OS ITT curve at 7 years
NVRD population			
Niraparib	[redacted]	[redacted]	α – % of PFS patients with stage IIIC, tumour size=0 divided by the % of OS patients with stage IIIC, tumour size=0 at 7 years in the Du Bois study.[22] β – % of PD patients with stage IIIC, tumour size=0 divided by the % of OS patients with stage IIIC, tumour size=0 at 7 years in the Du Bois study.[22]
Routine surveillance	[redacted]	[redacted]	Same as niraparib NVRD

Abbreviations: ITT, intention to treat; NVRD, no visible residual disease; PFS, progression-free survival; PD, progressed disease; OS, overall survival; RS, routine surveillance

The company did not provide any explanation as to why the proportion of patients cured for the Stage III NVRD population was not taken from the NVRD PFS curves estimated in the model, which would have been a consistent approach to that used to the ITT population. The ERG investigated this in the economic model and noted that a possible reason might be that because the Stage III NVRD population was not incorporated in the model with a robust methodology, the NVRD PFS curves cross the NVRD OS curves, therefore leading to negative numbers of patients with progressed disease in the model.

The company also did not provide any comparative analysis between the population in the De Bois study and the population in PAOLA-1 (from which the treatment effect for patients with Stage III NVRD after PDS was estimated), nor with the population in PRIMA. The company also did not provide any rationale for why the proportion of patients cured with niraparib and RS were assumed to be the same in the Stage III NVRD population but were different in the ITT population. This reinforces the ERG's concerns around the company's methods to estimating the cost-effectiveness

for the Stage III NVRD population, and the inconsistencies generated in the model parameters due to multiple sources being used to derive clinical parameters.

External validation of the long-term remission assumption

The company provided three external sources of evidence to support their cure assumption: 1) UK expert opinion; 2) TA598 (SOLO-1); and 3) the University of Edinburgh Ovarian Cancer database.

Clinical expert opinion provided to the ERG, and clinical expert opinion reported in TA598, is somewhat consistent in reporting that if RS patients are PF at 5 years they are less likely to relapse.[16] However, there is no evidence to substantiate that this time point is exactly 5 years and not any longer, or even that this represents a point of definite cure.

There are some external long-term data for chemotherapy followed by RS that can be used for validation of RS model outcomes. For example, the CHORUS trial had a 9-year follow-up period where 96% of the trial population had stage III or IV newly diagnosed OC. Women were randomised to primary surgery followed by six cycles of chemotherapy; or to three cycles of primary chemotherapy, then surgery, followed by three more cycles of completion chemotherapy.[23] The CHORUS OS data suggest that PFS patients might be at a lower risk of relapse approximately at 7 years from the point of primary surgery.

The company did not provide any external literature sources to validate long-term survival outcomes for niraparib. The company mentioned TA598 and SOLO-1, which compared olaparib monotherapy vs RS in BRCA+ patients for first line maintenance treatment. The ERG in TA598[16] concluded that without sufficiently mature trial data from SOLO-1, a possibility remained that olaparib may just delay the point at which women are at a much lower risk of experiencing a recurrence and as such, it might not be appropriate to make the assumption that olaparib and RS have a similar cure threshold of 5 years. The same is applicable for the current submission, where there are no sufficiently mature data to substantiate that niraparib cures a higher proportion of patients than RS at 7 years, instead of delaying the point at which women are at a much lower risk of experiencing a recurrence.

Lambert *et al*. 2007 used data from the England and Wales cancer registrations for 33,874 females with cancer of the ovary to estimate a MCM.[21] The data follow-up period was restricted to 10 years as the authors considered this to be a sufficient timeframe to observe the cure fraction. The ERG notes that the follow-up in PRIMA was approximately 2 years and considers this time period to be

too short to derive robust conclusions on the anticipated point of cure for patients receiving niraparib.

Therefore, the ERG considers that: 1) PRIMA does not provide a sound evidence base to substantiate a cure threshold for niraparib; and 2) external sources of evidence are not robust enough to suggest when a cure threshold would be reached for niraparib, although there does seem to be some evidence to support the idea that patients receiving RS who are PF at 5 years (and therefore also 7 years) are at low risk of recurrence.

3.2.4.3.2 Company's modelling of OS based on PFS to OS relationship

The DSU conducted a review on studies examining the relationship between PFS and OS outcomes in advanced or metastatic cancer.[24] The review concluded that even where robust evidence supporting a correlation between the treatment effect on PFS and OS is available, it remains unclear how that should be converted into a quantified relationship between the surrogate and the final outcome within a cost-effectiveness model. The DSU review based its definition of robust evidence on the Elston and Taylor definition where, "*evidence demonstrating treatment effects on the surrogate correspond to effects on the patient-related outcome (from clinical trials)*". All the studies included in the DSU review employed statistical methods to estimate the strength of the relationship between surrogate and final outcome. A high number of studies used linear regression methods, while several papers reported other measures of correlation between treatment effects such as spearman's rank correlation coefficients. Most relationships analysed were based on median PFS/OS; HRs for PFS/OS; or individual patient-level data.

In response to the ERG's clarification questions, the company has provided a spearman's rank correlation test to assess the statistical association between PFS and OS outcomes observed in Study 19. The company reported using the proportion of patients who were progression-free and alive up to 12 months (a time point where data for both PFS and OS were available) from both the olaparib and placebo arms of the Study 19 trial. The company estimated a spearman's rank coefficient of 0.95. The ERG notes that the company did not provide any confidence intervals or p-values for the spearman's rank correlation coefficient. Furthermore, the ERG notes that the spearman's rank coefficient of 0.95 indicates that an improvement in mean PFS is correlated with an improvement in OS, however it does provide any indication of the magnitude of this relationship beyond 12 months or how said relationship should be quantified.

The ERG in TA598 (olaparib for first-line maintenance treatment of BRCA+ ovarian, fallopian tube and peritoneal cancer) undertook a brief scoping search and identified a systematic review (searches run between 1 January 1996 to 30 June 2012) on the relationship between PFS and OS in epithelial ovarian cancer.[16] The review found a modest relationship between the HRs for PFS and OS (r2 =0.52), and a moderate association between median PFS and median OS (r2 = 0.72). The ERG in TA598 noted therefore, that the relationship between median times to PFS and OS in this population do not mean there is an equivalent relationship between the HRs for these two outcomes. The committee for TA598 concluded that: "*No significant differences in overall survival have been observed between the olaparib and placebo arms in SOLO1. Given the magnitude of the effect on PFS, it would be reasonable to expect that olaparib will extend life, but the size of that effect is uncertain*."

The ERG notes that the company in TA598 proposed a relationship of PFS to OS of 1:0.66 (i.e. 1 month of incremental PFS translates to 0.66 months of incremental OS), which is a conservative assumption against the 1:2 ratio proposed by the company in the current submission. Furthermore, while NICE appraisals have contemplated that PARP inhibitors in the platinum-sensitive relapsed OC setting might be associated with a PFS to OS benefit at a ratio of 1:>1, there is no established or accepted measure for this relationship. Therefore, consistent with TA598, the ERG has conducted a scenario analysis where the relationship of PFS to OS was 1:0.66 in the model.

The ERG also notes that while reviews of the correlation between median PFS and median OS; and PFS HR and OS HRs are available in OC literature, the ERG has not identified any studies investigating the strength of the correlation between mean PFS and mean OS.

In summary, the ERG does not consider that enough robust evidence exists to substantiate the use of PFS as a surrogate measure of OS in the OC setting. There is however, some literature suggesting that if the effect of a treatment for ovarian cancer extends PFS by x months, it is reasonable to estimate that the treatment will also extend OS by x months, meaning that, "*the magnitude of the improvement in PFS is the magnitude of the improvement in OS. PFS is simply a measure of a drug's effect on tumour growth while it is administered and is not a surrogate for OS*".[25, 26] Therefore, the ERG has run a scenario analysis where the PFS to OS ratio is 1:1. Results are presented in section 6. This issue is further discussed in section 4.2.6.2.

3.2.5 Perspective, time horizon and discounting

A lifetime horizon of 39 years was adopted in the model and time was discretised into monthly cycles (30.44 days) with a half-cycle correction applied. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.

At 39 years, 100% of patients are dead in the RS arm of the model but 1% of patients remain alive in the niraparib arm (when patients would be 100 years old). This is related to the overestimation of OS in the niraparib arm (discussed further in section 4.2.6.3).

3.2.6 Treatment effectiveness

To assess the relative goodness-of-fit of the different models fitted to the ITT PFS; TTD; and OS KM data from PRIMA the company: (1) generated combined Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics for the niraparib and RS arms; (2) visually assessed the parametric curves against the KM curves; (3) assessed the clinical plausibility of model extrapolations and compared the latter with relevant literature data.

The company also produced cumulative hazard plots and Schoenfeld residual plots to assess whether proportional hazards (or odds of accelerated failure time) could be assumed.

Standard parametric distributions, including the exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma distributions were fitted independently to the niraparib and RS PFS arms; to the TTD niraparib arm; and to the OS RS arm data.

3.2.6.1 Time to first progression

ITT population

According to the AIC and BIC criteria (Table 25, CS) provided for the KM PFS ITT data in PRIMA (Figure 17, CS), the company chose the generalised gamma curve as the best-fitting model. The company also reported that based on clinical expert opinion, the “fat tail” produced by the gamma curve was reflective of patients’ disease progression course in the first-line setting.

The company also undertook a comparative analysis of PFS predictions across the different parametric models fitted to the PFS KM data in PRIMA; the PRIMA KM PFS data; and time to first

subsequent treatment (TFST) data from the University of Edinburgh Ovarian Cancer Database at 5 and 10 years. The company used the TFST data as a proxy to predict PFS.

3.2.6.1.1 ERG critique

Table 21 provides PFS estimates at different points in time for three alternative options to modelling PFS in the model: the MA population curves; the ITT population curves; and the generalised gamma curve fitted to the PRIMA KM PFS data. The latter excludes the cure assumption included in the company's base case model and is based on the PRIMA ITT population.

During the clarification stage, the ERG asked the company to include the CHORUS PFS data in the comparisons made with the estimated PFS RS curves in the model. The company deemed the comparison between CHORUS and PRIMA inappropriate as patients in CHORUS were older (median age 65 years) and the proportion of women with poor performance status in CHORUS was greater than in other similar trials. The ERG notes that the median age in PRIMA (62 years) was not dissimilar to the median age in CHORUS and that 19% of patients had an ECOG performance status of 2 or 3. This is lower than the 30% of patients who had an ECOG status of 2 or 3 in the Edinburgh Ovarian Cancer populations, which the company used several times to validate long-term model predictions. Therefore, the ERG considers CHORUS a relevant source.

The ERG notes that the company's fitted generalised gamma to the RS ITT PRIMA KM PFS data (i.e. without assuming a cure approach) still provides consistently higher PFS values than CHORUS (with the exception of year 1) (

Table 21).

Regarding the niraparib estimated curves, the ERG notes that when the cure approach is removed from the ITT PFS curves, there is still a long-term treatment effect from niraparib vs RS, albeit a more conservative one when compared to the company's base case approach (Figure 15 and

Figure 16). The ERG presents the model results when the ITT generalised gamma curves for RS and niraparib are used in section 6.

Table 21. Progression-free survival data comparisons

	Median (months)	Years						
		1	2	3	5	7	8	10
Routine surveillance								
PRIMA	8.2	35%	23%	-	-	-	-	-
CHORUS*	10.7	44%	15%	13%	8%	5%	3%	-
Company's base case for MA population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's base case for ITT population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's fitted generalised gamma to PRIMA KM PFS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Niraparib								
PRIMA	13.8	53%	32%	-	-	-	-	-
Company's base case for MA population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's base case for ITT population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's fitted generalised gamma to PRIMA KM PFS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Estimates provided for these studies are only approximations and based on visual inspection of KM curves by the ERG
Abbreviations: ITT, intention to treat; KM, Kaplan Meier; MA, marketing authorisation; PFS, progression-free survival; OS, overall survival

Figure 15. Progression-free survival in company's base case (MA population, long-term remission assumption)

Figure 16. Progression-free survival in company's generalised gamma model (ITT population, no long-term remission assumption)

3.2.6.2 Overall Survival

ITT population

The company fitted a log-logistic model to the OS RS KM data from PRIMA. Similar to PFS, the company undertook a comparative analysis of OS predictions across the different parametric models fitted to the RS OS KM data in PRIMA; the KM OS data; and RS OS data from the University of Edinburgh Ovarian Cancer Database at 1,5, 10, and 15 years.

The niraparib KM data were deemed too immature to use in a fitting exercise as discussed in section 4.2.4. In order to estimate the niraparib OS curve, the company applied a HR of [redacted] to the OS RS curve as to generate the 1:2 ΔPFS:ΔOS relationship.

Patients with Stage III NVRD after primary debulking surgery

Even though the company assumed that the NVRD effect did not impact OS outcomes in the model, the ITT OS curves are indirectly impacted by applying the NVRD effect to the PFS curves in the model, and therefore the ITT OS and Stage III NVRD OS curves are not the same due to two factors:

1. When the MA population is chosen in the model, the ITT PFS curves are adjusted to generate Stage III NVRD PFS curves (see section 4.2.6.1), therefore, the proportion of "cured" patients

(taken from the Stage III NVRD PFS and PD curves) also change. These proportions are used to estimate the Stage III NVRD OS curves for RS and niraparib;

2. In order to maintain the PFS:OS relationship of 1:2 in the company base case, the HR applied to the RS OS curve of the model also changes, and so does the niraparib OS curve.

3.2.6.2.1 ERG critique

ITT population

During the clarification stage, the ERG requested that the company fitted parametric models to the niraparib OS KM data from PRIMA. The company replied that the niraparib KM data in PRIMA are too immature (10%) and therefore inappropriate to fit parametric models. However, the ERG notes that the RS KM data in PRIMA are equally immature (13%) and the company used these data to fit a log-logistic curve to estimate RS OS in the model. The company's approach and justification are, therefore, highly inconsistent.

The ERG does not disagree with the company that the OS data from PRIMA (

Figure 17) are highly immature. The ERG adds that OS data from PRIMA show a non-statistically significant survival benefit for niraparib (which could to be related with the lack of maturity in the OS data) and therefore, any estimations of a survival benefit with niraparib made in the model should be interpreted with extreme caution.

Most importantly, the results generated from the company's approach are inconsistent with the OS data observed in PRIMA. Firstly, the HR of [redacted] used by the company in the ITT model to generate the 1:2 ΔPFS:ΔOS relationship suggests a much higher relative treatment effect for niraparib vs RS than that observed in PRIMA - HR of 0.70 (95% CI 0.44, 1.11). Secondly, Figure 18 shows that at [redacted] months, the RS and niraparib curves [redacted] ([redacted]% alive in the RS arm and [redacted]% alive in the niraparib arm). At this point there are [redacted] patients (out of 467) in the niraparib arm, and approximately [redacted] patients (out of 236) in the RS arm. The ERG notes that the number of patients at risk is low and therefore, results should be interpreted with caution; however, these still represent around [redacted]% of the niraparib patients and [redacted]% of the RS patients. Nonetheless, at 19 months, the modelled niraparib and RS OS curves are on a [redacted] trajectory, suggesting that the relative treatment effect for niraparib does not diminish over time. This is an implication of applying a HR to the RS arm to estimate OS for niraparib, such an approach ensures that a benefit of niraparib over RS will be generated over the lifetime of patients.

Furthermore, the company's base case curve predicts that [redacted] of patients would be alive at 30 years in the model, when they would be 91 years old (

Table 22). This estimate compares with [redacted] in the company's curve for the ITT population (and [redacted] with no cure assumption).

Furthermore, the company applied a HR to a log-logistic model. From a methodological point of view, the application of an HR to a log-logistic model (i.e. to a non-PHs model) is not appropriate. Based on the AIC and BIC statistics provided by the company, the lognormal; log-logistic; Weibull and generalised gamma all provided satisfactory fits to the OS RS KM data from PRIMA. Using the Weibull or the generalised gamma curves (which can be PHs models) to fit the RS KM OS data would have resolved this methodological issue (

Table 22).

The company stated and the ERG agrees that the Weibull curve is likely to considerably underestimate long-term survival (100% of patients in the RS arm are dead at 8 years -

Table 22), while the generalised gamma would considerably overestimate it (10% of patients in the RS arm are alive at 20 years -

Table 22). Given the discrepancy in the OS predictions generated with the Weibull curve and with the generalised gamma, the ERG did not conduct an analysis using either of these curves. Nonetheless, the ERG notes that this issue could have potentially been resolved if more flexible models had been fitted to the RS KM OS data (such as spline), or if the company had used the niraparib KM OS data from PRIMA to fit a survival curve.

The ERG also considers that given the availability of OS KM data for niraparib, the company should have presented an option in the model of using these data, instead of only using a surrogate outcome to estimate OS.

Overall, the ERG emphasises the immaturity of OS data in PRIMA and therefore, the high level of uncertainty related to any estimation of a potential survival benefit in the economic analysis.

Figure 17. Overall survival KM data from PRIMA (Figure 5 in PRIMA CSR)

Figure 18. Overall survival KM curves in PRIMA and modelled OS curves

Table 22. Overall survival data comparisons

	Median (months)	Years								
		1	2	3	5	7	8	10	20	30
Routine surveillance										
PRIMA	Not reached	***	***	-	-	-	-	-	-	-
Company's base case for MA population	[redacted]	***	***	***	***	[redacted]	[redacted]	***	**	**
Company's base case for ITT population	[redacted]	***	***	***	***	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's fitted log-logistic to PRIMA KM OS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's fitted generalised gamma to PRIMA KM OS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's fitted Weibull to PRIMA KM OS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Niraparib										
PRIMA	Not reached	***	***	-	-	-	-	-	-	-
Company's base case for MA population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's base case for ITT population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's curve for ITT population (no cure assumption, based on applying a HR to the log-logistic RS curve)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Estimates provided for these studies/time points are only approximations and based on visual inspection of KM curves by the ERG
Abbreviations: ITT, intention to treat; KM, Kaplan Meier; MA, marketing authorisation; PFS, progression-free survival; OS, overall survival

Figure 19. Overall survival curves fitted to the RS KM arm of PRIMA

Finally, the ERG notes that the use of the equation: Niraparib mean OS = (RS mean OS + [Mean PFS difference x 2]) not only means that the OS benefit for niraparib is based on the PFS to OS ratio used in the model (1:2), but also based on the mean PFS difference estimated through the extrapolated PFS curves in the company's base case. Therefore, any overestimation in the relative treatment effect of PFS is doubled in the OS curves. Not surprisingly, this means that the ratio employed in the model to generate the OS curves is one of the key model drivers.

During the clarification stage, the ERG requested that the company run a scenario analysis where the mean PFS difference in the equation: Niraparib mean OS = (RS mean OS + [Mean PFS difference x 2]) was estimated as the difference in restricted means in the KM PFS curves in PRIMA, instead of the extrapolated PFS curves in the model. The restricted mean PFS from the PRIMA KM curves are [redacted] and [redacted] months for niraparib and RS, respectively. The restricted mean PFS difference between the two treatments at the data cut-off point of PRIMA is therefore [redacted] months, which compares to an estimated mean PFS gain of 39.35 months in the company's base case (and a resulting OS HR of [redacted] for niraparib vs RS).

The ERG found an error in the application of this scenario analysis in the model. As the company used the "goal seek analysis" function in Excel to estimate the HR originating from using the mean PFS difference [redacted], this generated crossing OS curves in the model (and a HR>1), where the RS OS

curve was above the niraparib OS curve. Given that niraparib mean OS = (RS mean OS + [Mean PFS difference x 2]) in this scenario equates to niraparib mean OS = 66 + (3.56 x 2), it does not make sense to have a HR>1.

The company reported that, "*truncating the PFS gain to that only observed in PRIMA [median follow-up of 13.9 months (CI 13.8, 16.0) and 13.8 months (CI 13.6, 14.1) for the niraparib and placebo groups, respectively] implies that patients treated with niraparib stop benefitting from treatment prior to treatment discontinuation. As highlighted in the CS (section B.3.3), clinical expert opinion and evidence from the SOLO-1 trial indicate that the treatment effect of a PARP inhibitor is likely to be maintained during treatment and once a patient discontinues treatment. As such it is not appropriate to truncate the benefit of niraparib at the end of the follow-up period.*"

The ERG notes that the restricted mean PFS takes into account all the data available for the trial period (latest PFS datapoint at 28 months), when more than [redacted] of patients in PRIMA had discontinued niraparib.

3.2.6.3 Time to treatment discontinuation

The PRIMA protocol indicated that patients should discontinue treatment at 3 years unless indicated by the consulting physician. Therefore, the company implemented a three-year stopping rule for treatment with niraparib in the model. The company also assumed that [redacted] of patients who had not discontinued treatment at 3 years would carry on receiving niraparib.

ITT population

The company used TTD KM data from PRIMA-1 to estimate treatment costs for niraparib in the model. The TTD KM plot for niraparib in PRIMA is provided in Figure 27 of the CS. The AIC and BIC statistics were provided in Table 30 of the CS. The company fitted the TTD KM data with a Weibull model (second best-fitting distribution) as this was considered to be more clinically accurate by the company's clinical experts than the log-logistic distribution (best-fitting curve).

After 3 years in the model, [redacted] of the patients who had not discontinued treatment ([redacted] of patients are receiving treatment at 3 years in the company's Weibull curve) were assumed to carry on treatment and thus, continue to follow the Weibull curve tail.

Patients with Stage III NVRD after primary debulking surgery

In order to derive the niraparib TTD curve for the NVRD population, the company applied the treatment effect within the NVRD effect HR of 0.340 (95% CI: 0.233 to 0.497) to the Weibull curve fitted to the ITT niraparib KM TTD data from PRIMA.

The company then weighted the ITT and the NVRD population to obtain the MA TTD curve for niraparib. The overall MA curves were then produced by weighting the ITT and the NVRD curves so that: MA TTD(t) = [redacted]% x NVRD TTD(t) + [redacted]% x ITT TTD(t).

3.2.6.3.1 ERG critique

As per

Figure 20, at around 25 months, [redacted]% of patients were still receiving treatment with niraparib in PRIMA (albeit the number of patients at risk at 25 months was [redacted] patients). The mean time on treatment with niraparib estimated with the Weibull curve in the ITT population was [redacted] months.

The proportion of patients who remained on treatment after the follow-up period in PRIMA is unknown and thus, the assumption made by the company that [redacted] of patients who had not discontinued treatment in PRIMA at 3 years carried on treatment cannot be validated. During the clarification stage, the ERG asked the company to provide a clinical rational for the assumption made. The company explained that the [redacted] assumption was based on data available from SOLO-1 and on clinical expert opinion. About [redacted] of patients carried on treatment beyond 3 years in the ITT model and all patients discontinued treatment at [redacted] years.

However, the company also noted in their clarification response that the SmPC will not specify a treatment duration of 3 years, therefore the company's scenario analysis assuming no discontinuation (see section 4.1.2) should have been considered in the base case model.

Figure 20. Niraparib TTD KM data and modelled niraparib TTD curve for the ITT population

Time (months)								
Patients								

3.2.7 Adverse events

The company modelled grade ≥3 treatment-related AEs reported in ≥5% of patients in either treatment group of the PRIMA trial in the safety population (Table 23). The impact of AEs on patients' quality of life is described in section 4.2.10 while the costs of managing AEs is described in section 4.2.11.

Table 23. AEs included in the company's base case analysis (adapted from Table 47 in the CS)

AE	Niraparib (n=484)	RS (n=244)
Anaemia	31%	2%
Thrombocytopenia	29%	0%
Platelet count decreased	13%	0%
Neutropenia	13%	1%
Hypertension	6%	1%
Neutrophil count decrease	8%	0%

Abbreviations: AE, adverse event; RS, routine surveillance

3.2.8 *Health-related quality of life*

During the PRIMA study, patients completed the EQ-5D-5L questionnaire at baseline (day 1 of treatment) and every 8 weeks (+/- 7 days) for 56 weeks, then every 12 weeks (+/- 7 days) after that, while on study treatment. During the follow-up period, if a patient discontinued treatment, assessments occurred at 4 weeks, 8 weeks, 12 weeks and 24 weeks (+/- 1 week for each time point) after the end of treatment. Using these data, EQ-5D-3L utilities were derived by mapping the 5L descriptive system data onto the 3L valuation set using the algorithm published by van Hout *et al.* 2012. The descriptive statistics for the mapped EQ-5D-3L data, at each time point of data collection, are given in Table 24.

Table 24. Descriptive mapped EQ-5D-3L statistics by time point of data collection (reproduced from Table 17 of the clarification responses)

Study visit	Mean	Median	SD	Mean age of responders	Number of responders	Compliance rate	Lower 95% CI	Upper 95% CI
SCREENING	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 3 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 5 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 7 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 9 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 11 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 13 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 15 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 18 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 21 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 24 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 27 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CYCLE 30 DAY 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
END OF TREATMENT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
POST-TREATMENT ASSESSMENT								

WEEK 1 - 4	[redacted]							
WEEK 5 - 8	[redacted]							
WEEK 9 - 12	[redacted]							
WEEK 13 - 24	[redacted]							
WEEK 25 - 36	[redacted]							
WEEK 37 - 48	[redacted]							
WEEK 49 - 60	[redacted]							
WEEK 61 - 72	[redacted]							

Abbreviations: CI, confidence interval; SD standard deviation

The company generated mapped EQ-5D-3L utilities for the PFS and PD health states and used non-treatment specific utilities to inform the base case analysis (Table 25).

Table 25. EQ-5D-3L HSUVs obtained from the PRIMA study (adapted from Table 31 of the CS)

Parameter	Observations (n)	Mean HSUV (SD)
Overall		
PFD	[redacted]	[redacted]
PD	[redacted]	[redacted]

Abbreviations: HSUV, health state utility value; PD, progressed disease; PFD, progression-free disease; RS, routine surveillance.
*Corrected during the clarification stage from 4,075 to 4,055 and 1,335 to 1,315

The company included a one-off QALY loss at the start of the model in each treatment arm to account for the impact of AEs on patients' quality of life. The company combined the incidence rates observed in PRIMA (Table 23, section 4.2.7) with the disutilities reported in Table 26 and generated a total disutility of 0.094 for niraparib and 0.004 for RS. These disutilities were assumed to last for the duration of the first model cycle (i.e. one month).

Table 26. AE disutilities included in the company's base case analysis

AE	Mean disutility	Source
Anaemia	-0.12	TA598
Thrombocytopenia	-0.09	Assumed equivalent to neutropenia
Platelet count decreased	-0.09	Assumed equivalent to neutropenia
Neutropenia	-0.09	TA598
Hypertension	-0.02	TA381
Neutrophil count decrease	-0.09	Assumed equivalent to neutropenia

Abbreviations: AE, adverse event; TA, technology appraisal

3.2.8.1 ERG critique

The ERG considers the PFS and PD related utilities derived from the PRIMA trial to be in line with the utilities identified in the company's SLR. The ERG also considers these to be similar to the mapped EQ-5D-3L HSUVs derived from SOLO-1 which were used in TA598 (

Table 27).

Table 27. Summary of HSUVs used in TA598

HSUV	Mean utility
PFS	0.819
PD1	0.771
Abbreviations: HSUV, health state utility value; PD1: first progressed disease; PFS: progression-free survival	

However, the company did not include age-related utility decrements in their analysis. Following a clarification request from the ERG, the company included age-related utility decrements as part of a sensitivity analysis. The company did not consider it appropriate to include age-related utility decrements as part of the base case for several reasons (including but not limited to):

- Utility values derived from the trial already capture how QoL changes during the observed period;
- The QoL of long-term responders is characterised by a longer life expectancy and achieving long-term remission;
- There is no evidence to suggest a patient in long-term remission should have their QoL restricted to the general population;
- Patients who achieve long-term remission are not expected to be limited by the EQ-5D domains;
- Concerns about equality for age and gender;
- Increasing the ICER (from £18,689 to £20,037 in the ITT population and from £13,456 to £14,506 in the MA population) increases the hurdle to the product being reimbursed.

The ERG disagrees with the company's rationale. Using a lifetime horizon in the model means patients can live for up to 100 years compared with the 63 years patients will have at the end of the 2-year trial. Therefore, the impact QoL data observed during the trial does not capture the impact of aging. Furthermore, there are several publications which demonstrate that HRQoL declines with age [add references]. For these reasons, the company's approach is overestimating the utility of survivors and the cost effectiveness of the more effective treatment (niraparib).

Furthermore, the company assumed that long-term survivors who are alive and progression-free at 7 years in the model carry on incurring the PFS utility of [redacted] for the rest of the model time horizon. When patients enter the model at 61 years of age, their PFS utility ([redacted]) is [redacted] than that of the general population utility (0.81) matched for age and gender. However, at the point of cure, 7 years

later, patients in the PFS state have a [redacted] utility than the general population utility (0.78), which lacks face validity.

For these reasons, the ERG applied age-related utility decrements in the model. However, the ERG also explored a scenario analysis where the general population utility values were used for patients in long-term remission.

3.2.9 Resource use and costs

3.2.9.1 Treatment costs

A confidential patient access scheme (PAS) for niraparib is in place and the results presented in this report include the PAS. Drug acquisition costs used in the model for niraparib are presented in Table 28. The company assumed no administration costs for niraparib, as niraparib is an oral treatment. The company also assumed no drug acquisition costs or administration costs for RS.

Table 28. Acquisition cost of niraparib

Pack size (number of units)	Unit size	List price per pack	PAS price per pack	PAS price per unit (per 100 mg)
56	100 mg	£4,500	[redacted]	[redacted]

Abbreviations: PAS, patient access scheme

As reported in section 4.2.3, the company updated model used the actual (weighted) niraparib dose received in PRIMA from months 1 through 18 in the PRIMA ITT (therefore, it included a combination of patients on [redacted]). The company assumed that the proportion across the different doses received in month 18 would be the same for the remainder of the treatment period with niraparib in the model..

The resulting cost per cycle (30.44 days) applied in the model is given in

Table 29. Scenario analyses were conducted by the company to explore the impact of modelling the observed dose intensity ([redacted] and a fixed daily dose of 200 mg (see section 5.1.2).

Table 29. Total acquisition costs for niraparib per cycle applied in the base case analysis (taken from the revised model)

Model cycle	Proportion of patients across dose (mg) categories			Total cost per day (per dose [mg])			Total cost per cycle
	100	200	300	100	200	300	
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]				[redacted]
3	[redacted]	[redacted]	[redacted]				[redacted]
4	[redacted]	[redacted]	[redacted]				[redacted]
5	[redacted]	[redacted]	[redacted]				[redacted]
6	[redacted]	[redacted]	[redacted]				[redacted]
7	[redacted]	[redacted]	[redacted]				[redacted]
8	[redacted]	[redacted]	[redacted]				[redacted]
9	[redacted]	[redacted]	[redacted]				[redacted]
10	[redacted]	[redacted]	[redacted]				[redacted]
11	[redacted]	[redacted]	[redacted]				[redacted]
12	[redacted]	[redacted]	[redacted]				[redacted]
13	[redacted]	[redacted]	[redacted]				[redacted]
14	[redacted]	[redacted]	[redacted]				[redacted]
15	[redacted]	[redacted]	[redacted]				[redacted]
16	[redacted]	[redacted]	[redacted]				[redacted]
17	[redacted]	[redacted]	[redacted]				[redacted]
18	[redacted]	[redacted]	[redacted]				[redacted]
18+	[redacted]	[redacted]	[redacted]				[redacted]

Abbreviations: mg, milligram

In the base case analysis, the monthly treatment costs in

Table 29 were applied in line with the TTD curve (see section 4.2.6.3). A 3-year stopping rule assumed [redacted] of patients discontinue treatment at 3 years and all patients discontinued treatment at [redacted] years in the ITT population.

Scenario analyses were conducted by the company to explore the impact of modelling no stopping rule and assuming 100% of patients discontinue treatment at 3 years (see section 5.1.2). As mentioned in section 4.2.6.3.1, the SmPC for niraparib will not specify a treatment duration of 3 years, therefore the company's scenario analysis assuming no discontinuation should be considered in the base case analysis.

3.2.9.2 Subsequent treatment costs

The cost of subsequent treatments included in the company's base case analysis is based on a weighted average calculated from the input given by three clinical experts. Clinical expert opinion provided to the company considered treatments available in the UK NHS, according to the NICE position statement of excluding products in the cancer drugs fund (CDF) from the analysis.[27] As a result, the only PARPi available through routine commissioning and included in the company's base case analysis is olaparib for 3L maintenance treatment in BRCA+ patients. The subsequent treatments included in the company's base case analysis are given in Table 30.

In response to an ERG's clarification question, the company explained that the total percentage of third-line treatments in the RS arm exceeds 100% ([redacted] as PARPi maintenance therapy (the additional [redacted] would be given after the completion of 3L chemotherapy; hence patients would receive both chemotherapy and PARPi maintenance therapy.

The company also provided a scenario analysis to reflect the cost of subsequent treatments given in PRIMA (to match the effectiveness data used in the economic analysis) (

Table 31). Another scenario considering 2L PARPis included in the CDF was also explored by the company (see Table 40 in the CS). The results of the company's scenario analyses are given in section 5.1.2.

Table 30. Subsequent treatments applied in the base case analysis (Option 1 in company's analysis - CDF rule applied) (adapted from Table 38 of the CS)

Treatment class	Second-line treatment		Third-line treatment	
	Niraparib	RS	Niraparib	RS
Carboplatin	44.4%	44.4%	30.4%	30.4%
Cisplatin	4.1%	4.1%	4.2%	4.2%
Taxane	38.1%	38.1%	44.8%	44.8%
Doxorubicin	4.6%	4.6%	9.4%	9.4%
Docetaxel	5.1%	5.1%	6.4%	6.4%
Cyclophosphamide	3.8%	3.8%	4.7%	4.7%
PARP inhibitor	0.0%	0.0%	0.0%	7.8%*
Total	100.0%	100.0%	100.0%	107.8%

Abbreviations:PARP, Poly (ADP-ribose) polymerase; RS, routine surveillance
*Assumptions proportion with a BRCA mutation (25%) multiplied by proportion platinum-sensitive after third-line chemotherapy (31%)[28]

Table 31. Subsequent treatments applied in a scenario analysis (Option 3 in company's analysis – PRIMA next anticancer therapy data) (adapted from Table 39 of the CS)

Treatment class	Second and subsequent line treatment, n/N (%)	
	Niraparib	RS
Carboplatin	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Taxane	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]
PARP inhibitor	[redacted]	[redacted]
PD(L)-1 inhibitor	[redacted]	[redacted]

Abbreviations: PARP, Poly (ADP-ribose) polymerase; PDL-1, Programmed death-ligand 1; RS, routine surveillance

The company used the BNF to calculate acquisition costs based on the available formulations, pack sizes and unit costs (see Table 41 in the CS). The company also included administration costs associated with chemotherapies using NHS Reference Costs 2018/19.[29]

As a result of the clarification stage, the company made changes to the acquisition costs of 3L olaparib and the administration cost of IV chemotherapies:

1. The unit size of olaparib in a 56 pack was amended from 100mg to 150mg;
2. The list price of 2L PARP inhibitors was amended from including the niraparib discount in the 2L setting to using the list price for olaparib and rucaparib;
3. The cost of IV chemotherapy administrations was amended from £322 (a currency code based on delivering subsequent elements of a chemotherapy cycle, SB15Z) to £241 (a currency code based on the first infusion of a cycle, SB12Z).

To calculate the total cost of a subsequent treatment regimen the company used TA528[30] to inform dosing regimens (i.e. the dose and frequency of treatment cycles) and the niraparib CDF report[31] to inform the duration of treatment with PARP inhibitors (assumed to be 6.7 months in the model) and PDL inhibitors. The dose of PARPis was taken from trial protocols (ENGOT-OV16/NOVA[32] for niraparib, SOLO-1[6] for olaparib and ARIEL-3[33] for rucaparib) and the dose of PDL inhibitors was taken from the relevant SmPCs for atezolizumab and pembrolizumab.[34, 35] These dosing regimens are summarised in Table 42 of the CS.

In the model, chemotherapy regimens (carboplatin, cisplatin and taxane) are split by platinum-sensitivity. In the company's base case analysis, 45% and 31% of patients are assumed to be platinum sensitive at 2L and 3L, respectively. According to the model these estimates were informed by the company's clinical 'Key Opinion Leader' (KoLs) Interviews, January-February 2020.

The company's scenario analysis which costs subsequent treatments based on data from PRIMA, 100% of patients are assumed to be platinum sensitive. In response to the ERG's clarification question the company explained that this is due to the treatments in PRIMA aligning with the treatments considered for platinum-sensitive patients. The total costs of treatment regimens (including acquisition costs and administration costs) according to platinum sensitivity are given in Table 32.

Table 32. Total cost per treatment regimen (taken from the revised economic model)

Subsequent treatment class	Average cost per class (Platinum-sensitive)	Average cost per class (Platinum-recurrent)
Carboplatin	£3,340	£4,878
Cisplatin	£3,157	£4,761
Taxane	£2,196	£1,801
Doxorubicin	£2,973	
Gemcitabine	£3,764	
Bevacizumab	£22,721	
Cyclophosphamide	£2,362	
PARP inhibitor	£31,072*	
PD(L) inhibitor	£45,555	

Abbreviations: PARP, Poly (ADP-ribose) polymerase; PDL-1, Programmed death-ligand 1
*£33,758 when olaparib is the only PARP inhibitor

During the clarification stage, the ERG asked the company to amend their scenario analysis using PRIMA subsequent treatment data by replacing the average cost of the three PARP inhibitors (niraparib, olaparib and rucaparib) with a cost weighted by the proportion of patients on each PARP inhibitor in PRIMA. As a result, the company amended their scenario analysis using the data in

Table 33.

Table 33. PARP inhibitors received in PRIMA

PARP inhibitor	N	Proportion of patients
Niraparib	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]
Rucaparib	[redacted]	[redacted]
Abbreviations: PARP, Poly (ADP-ribose) polymerase		

The company's initial approach to estimating the proportion of patients who receive subsequent treatments in the model was based on calculating the number of patients in the PD health state for each model cycle [PD (t+1) minus PD (t)]. Given that the company's approach did not differentiate between old and new events in the PD curve, the ERG asked the company to estimate the number of new progression events in both arms of the model in order to calculate the proportion of patients who receive subsequent treatments in every model cycle.

As a result of the clarification request, the company used the number of patients in the PFS curve [PFS (t) minus PFS (t+1)] to estimate the proportion of patients who receive subsequent treatments. Then, subsequent treatment costs are applied as a one-off treatment cost, assuming 100% of new progressions receive further treatment. The company's initial approach which used the number of patients in the PD health state for the respective cycle was still included in the model as a scenario analysis (see section 5.1.2). The ERG notes that because all PFS events were progression events according to the PRIMA CSR (except for one patient in the placebo arm of the BICR PFS analysis), the company's updated approach using the PFS curves is reasonable, as there were no deaths captured in the PFS curves.

The one-off costs applied in the model that combine the proportion of patients receiving each type of subsequent treatment (Table 30 for the base case analysis) and total cost per treatment regimen (Table 32) are given in Table 34.

Table 34. One-off cost of subsequent treatment applied in the revised base case analysis

Primary treatment	2L subsequent treatment cost	3L subsequent treatment cost	Total subsequent treatment cost
Base case analysis (Option 1 - KOL feedback CDF rule applied)			
Niraparib	[redacted]	[redacted]	£5,194
RS	[redacted]	[redacted]	£7,832
Scenario analysis (Option 3 – PRIMA next anticancer therapy data)			

Niraparib	[redacted]	[redacted]	£5,391
RS	[redacted]	[redacted]	£7,010

Abbreviations: CDF, Cancer Drugs Fund; KOL, key opinion leader; RS, routine surveillance

3.2.9.2.1 ERG critique

During the clarification stage, the ERG requested that the company provided further details on subsequent treatments received in PRIMA. The study CSR defined that "*Following the treatment discontinuation visit, all subjects were followed every 12 weeks for subsequent anticancer therapy and the assessment of survival status*. […] *Information captured for subsequent anticancer therapy was to include the name and class of the therapy(ies), start date, any dose limiting toxicities, best response on treatment* […] *and date of progression*." However, the CSR provided by the company only provided the total number of patients who received each type of therapy (shown in

Table 31) without specifying which treatments were received at each treatment line, and which treatments were given as combination regimens. In response to a clarification request from the ERG, the company stated that subsequent treatments in PRIMA were not recorded by line of therapy or by whether they were given as combination or single therapies.

The CSR only specified the number of patients who received chemotherapy at each treatment line (Table 35). The ERG cannot conciliate the information in Table 35 with that provided in

Table 31, as the latter does not specify treatment line. For example,

Table 31 shows that [redacted] patients received carboplatin as subsequent treatments, however, without knowing at which line these were received, the ERG cannot be certain that these make up the majority of patients receiving 2L chemotherapy.

In PRIMA, there were 232 progression events in the niraparib arm and 154 progression events in the RS arm. When compared to the number of patients receiving 2L chemotherapy, the proportion of patients who progressed who also received subsequent chemotherapy in PRIMA amount to 85% and 81% for niraparib and RS, respectively. The ERG notes that the number of patients receiving subsequent treatments in PRIMA is lower than what is expected in UK practice and lower than what has been reported in other trials for the same disease area. For example, the ERG in TA598 reported that the CSR for SOLO-1 suggests that 90% and 93% of the patients who progressed received subsequent chemotherapy in the olaparib and placebo arms, respectively.

The ERG acknowledges that the PRIMA data are immature and therefore data on subsequent treatments need to be interpreted with caution. Nonetheless, the ERG stresses the importance of interpreting the future results for more mature OS data together with the more mature data on subsequent treatments received in PRIMA. The ERG also notes that analysis of the time to second progression in PRIMA resulted in a non-statistically significant different HR of 0.81 (95% CI: 0.577; 1.139).

[redacted]

however it is not possible to ascertain if niraparib delays second progression events without having more mature PFS2 data.

Table 35. Summary of subsequent treatment lines in PRIMA, n (%)

Number of lines of follow-up chemotherapy*	Niraparib (N=487)	Placebo (N=246)
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]

*Treatments recorded within PRIMA included all follow-up anti-cancer therapies (e.g. PARP and PD-L1 inhibitors), except for hormonal therapy.

Finally, instead of considering the granularity of subsequent treatments from every clinical expert, the company could have elicited clinical expert opinion using the SHELF methodology to aggregate judgements on resource use.[36] In short, SHELF requires experts to come together to agree on

plausible ranges and come to a 'consensus' judgement on the true value which reduces the impact of outliers.

3.2.9.3 Disease management costs

The CS states that the resource use associated with disease management in the model was based on the British Gynaecological Cancer Society (BGCS) guidelines (used in TA598[16]); clinical expert opinion; and the draft SmPC for niraparib. The draft SmPC for niraparib anticipates that:

- A complete blood count is required weekly for the first month following treatment initiation, followed by complete blood counts monthly for the first year and;
- Heart rate and blood pressure monitoring are required weekly for the first month, followed by monthly monitoring for the first year of treatment.

The company assumed that while patients were on treatment with niraparib they have a weekly complete blood count in the first month of treatment, followed by a monthly one while on treatment. However, the company did not include the cost of heart rate and blood pressure monitoring, based on the assumption that these tests would be performed at home by patients.

The unit costs of disease management were obtained from NHS Reference Costs 2018/19.[29] The monthly frequency and cost of disease management applied in the niraparib RS arms are given in Table 36 and Table 37, respectively. The company also performed a scenario analysis where resource use was informed by UK clinical expert opinion ("UK key opinion leaders") (Table 44 in the CS). The results of the company's scenario analysis are given in section 5.1.2.

As a result of a clarification request, the company amended their base case model so that PFS state costs were not incurred beyond the point of cure in the model (i.e. 7 years).

Table 36. Cost and monthly frequency of disease management in the niraparib arm, base case analysis

	Outpatient visit Oncology, Consultant led	CT scan	Complete blood count	Total cost per cycle
Unit cost	£127	£83	£3	-
Health state				
PFD on treatment (cycle 1)	1.0	0.3	4.0	£163
PFD on treatment (cycle 2+)	1.0	0.3	1.0	£155

PFD off treatment	0.3	0.3	0.3	£64
PD	1.0	0.3	0.3	£153
Abbreviations: CT, computerised tomography; PD, progressed disease; PFD, progression-free disease				

Table 37. Cost and monthly frequency of disease management in the RS arm, base case analysis

	Outpatient visit Oncology, Consultant led	CT scan	Complete blood count	Total cost per cycle
Unit cost	£127	£83	£3	-
Health state				
PFD	0.3	0.3	0.3	£64
PD	1.0	0.3	0.3	£153
Abbreviations: CT, computerised tomography; PD, progressed disease; PFD, progression-free disease; RS, routine surveillance				

3.2.9.3.1 ERG critique

As discussed in section 4.2.3.1, the ERG disagrees with the company's long-term remission assumption in the model. However, clinical expert advice given to the ERG explained that when patients have been in remission for 10 years, they would be discharged. Therefore, the ERG conducted a scenario analysis in the model so that when the cure assumption is not assumed, the disease management costs associated with the PFS state were not incurred beyond 10 years in the analysis (see section 6.2).

The company rounded the frequency of resource use to one decimal place in the model (i.e. every three months was rounded to 0.3). The ERG considers this to be unnecessary and inaccurate. As a result, the ERG corrected the model by replacing the company's hard-coded numbers with calculations (i.e. every three months = 1/3) (see section 6.1).

Clinical expert opinion provided to the ERG suggested that disease management in UK clinical practice is variable and an alternative monitoring schedule for RS during PFD was suggested (Table 38). Clinical experts also advised that ERG that it is unreasonable to expect all patients to perform heart rate and blood pressure monitoring at home. To address these areas of uncertainty the ERG asked the company to provide one scenario using the ERG's resource use estimates for RS (Table 38) and another scenario including the cost of heart rate and blood pressure monitoring. To explore the latter, the company added a monthly outpatient visit in gynaecological oncology. The results of these scenarios are reported in section 6.2.

Table 38. Cost and monthly frequency of disease management in the RS arm, ERG scenario

	PFD	
Monitoring time	1 year	6 years
Outpatient visit Oncology, Consultant led	0.33	0.17
Complete blood count	0.33	0.17
CT scan	0.17	0.17

Abbreviations: CT: computed tomography; PFD, progression free disease; RS, routine surveillance

3.2.9.4 Adverse event costs

The company included a one-off cost in each treatment arm to account for the impact of managing AEs. Inpatient currency descriptions in NHS Reference Costs were used to inform the cost of managing anaemia, thrombocytopenia and hypertension in the base case analysis. Day case currency descriptions for those AEs were explored in a scenario analysis (see section 5.1.2). The unit costs of AE management applied in the base case analysis are summarised in Table 39. Combining these costs with the incidence rates observed in PRIMA (Table 23) the expected one-off cost to manage AEs was £494 for niraparib and £22 for RS.

Table 39. AE costs included in the company's base case analysis

AE	Unit cost	Source (currency code)
Anaemia	£669	NHS Reference Costs 2018/19 (weighted average of: SA04G, SA04H, SA40J, SA04K and SA04L)[29]
Thrombocytopenia	£715	NHS Reference Costs 2018/19 (weighted average of: SA12G, SA12H and SA12J)[29]
Platelet count decreased	£0	Assumption
Neutropoenia	£124	NHS Reference Costs* (XD25Z)
Hypertension	£595	NHS Reference Costs 2018/19 (EB04Z)
Neutrophil count decreased	£392	NHS Reference Costs* (XD25Z)

Abbreviations: AE, adverse event
* Sourced from NHS Reference Costs 2017/18[37] and inflated to a 2018/19 cost year[38]

3.2.9.5 End of life costs

End of life care costs were incurred by 51% of patients who die in the model. The company based this on the proportion of patients, reported by Gao *et al.* 2013[39], who received end of life care in a healthcare setting in England. The cost of end of life care was sourced from Guest *et al.* 2006[40] who

estimated that the cost of end of life care for patients with ovarian cancer in the UK was £4,798 according to 2000/01 prices. This was subsequently inflated to 2018/19 prices (£7, 576) by the company.[38]

4 Cost effectiveness results

In response to the ERG's clarification questions, the company submitted updated results which incorporated changes to costs and resource use. These changes are outlined in section 3.2.9. Additionally, a confidential patient access scheme (PAS) for niraparib is in place and the results presented in this report include the PAS (a simple discount of [redacted]).

4.1.1 Company's cost effectiveness results

The results of the company's updated base case analysis are presented in Table 40 for the ITT population from the PRIMA trial; and in Table 41 for the MA population, which the company defined as the ITT population from PRIMA plus patients with Stage III, NVRD after PDS. The values in Table 40 and Table 41 are discounted at 3.5% per annum, unless otherwise stated. In the company's updated base case analysis, niraparib generates a lower ICER compared with RS in the MA population (£13,456) than in the ITT population (£18,689).

Table 40. Company's base case results, ITT population

Treatment	Total Costs	Total LYG, discounted	Total LYG, undiscounted	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
RS	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,689

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance

Table 41. Company's base case results, MA population

Treatment	Total Costs	Total LYG, discounted	Total LYG, undiscounted	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
RS	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,456

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance

4.1.2 Company's sensitivity analyses

4.1.2.1 Probabilistic sensitivity analysis (PSA)

The company generated probabilistic results using 10,000 iterations. As a result of the clarification stage, the company varied the proportion of patients across niraparib dose categories in PSA using the Dirichlet distribution (previously fixed). The ERG considers the remaining parameters and respective distributions chosen for PSA, outlined in Table 48 of the company submission (CS), to be generally sound. The ERG also considers the probabilistic results to be comparable to the deterministic base-case results. The mean results generated through PSA are given in Table 42 and Table 43 for ITT and MA populations, respectively. Cost-effectiveness planes and cost-effectiveness acceptability curves (CEAC) are also given in Figure 21 to Figure 24.

Table 42. Company's PSA results, ITT population

Treatment	Total Costs	Total QALYs	Incremental costs (SD)	Incremental QALYs (SD)	ICER (£/QALY)
RS	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	£18,419

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; RS, routine surveillance; SD, standard deviation

Figure 21. Cost-effectiveness plane, ITT population (taken from Figure 25 of the company's clarification responses)

Figure 22. CEAC, ITT population (taken from Figure 26 of the company's clarification responses)

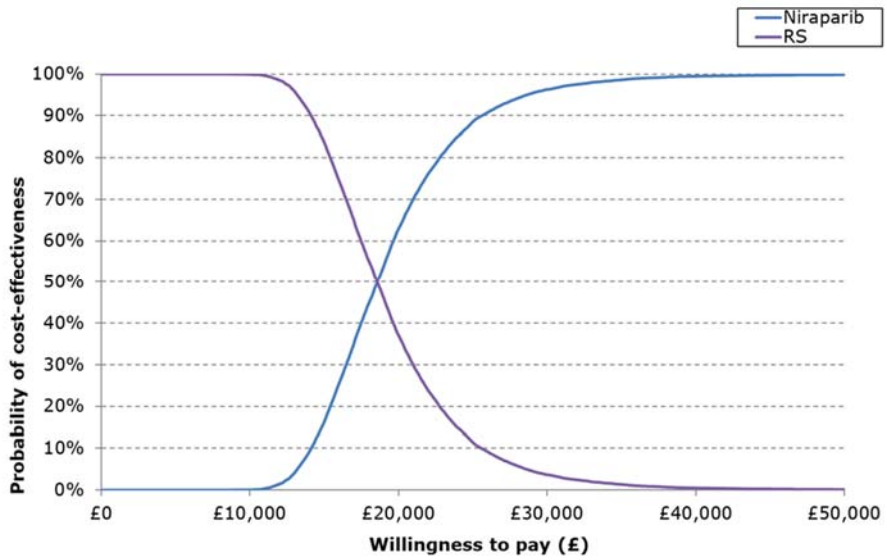


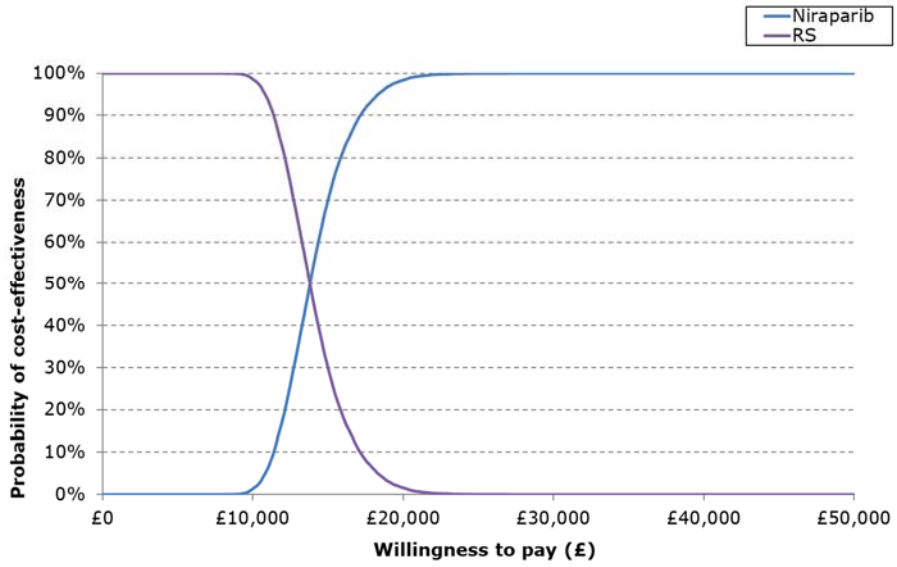
Table 43. Company's PSA results, MA population

Treatment	Total Costs	Total QALYs	Incremental costs (SD)	Incremental QALYs (SD)	ICER (£/QALY)
RS	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	£13,882

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; RS, routine surveillance; SD, standard deviation

Figure 23. Cost-effectiveness plane, MA population (taken from Figure 22 of the company's clarification responses)

Figure 24. CEAC, MA population (taken from Figure 23 of the company's clarification responses)



4.1.2.2 One-way sensitivity analysis (OWSA)

The company conducted OWSA by varying key parameters between the upper and lower 95% confidence interval (CI) of the mean value. In the absence of CI data, the mean value was varied by +/- 20%, except for hazard ratios (HRs) which were originally varied by 10%. As a result of the clarification stage, the company varied HRs within their 95% CIs (except for the OS HR for niraparib vs RS estimated from a goal seek calculation which was varied by 10% in both PSA and OWSA).

Tornado diagrams presenting the top 20 most sensitive parameters are presented in the company's reply to the ERG question in Figure 28 and Figure 29 for the MA and ITT populations, respectively.

In the ITT population, the model was most sensitive to the niraparib PFS curve, followed by the RS PFS curves. This is not surprising given that the PFS curves for niraparib and RS determine the OS curve for niraparib in the company's approach. Detailed tabular results of the company's OWSA are given in Table 35 and Table 36 of the company's clarification responses.

4.1.2.3 Scenario analysis

Scenario analysis results for the ITT population are given in Table 44 (and results for the MA population are given in Table 37 of the company's clarification response). These include scenarios requested by the ERG during the clarification stage and the company's original scenarios reported in the CS. Across both populations results were most sensitive to using the PRIMA KM PFS to determine

the PFS:OS relationship, varying the mean ΔPFS:ΔOS relationship, varying the PFS distribution for niraparib and RS, and applying a 0% or 6% discount rate.

Table 44. Scenario analyses for the ITT population for niraparib versus and RS (reproduced from Table 37 of the company's clarification responses)

Population →			ITT population			
Category	Base case	Scenario	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£)
Base case			[redacted]	[redacted]	[redacted]	18,689
Discount rate	3.5%	0.0%	[redacted]	[redacted]	[redacted]	13,191
		1.5%	[redacted]	[redacted]	[redacted]	15,432
		6.0%	[redacted]	[redacted]	[redacted]	23,127
Weight	PRIMA	UK data	[redacted]	[redacted]	[redacted]	18,689
Time horizon	39 years	35 years	[redacted]	[redacted]	[redacted]	18,745
		30 years	[redacted]	[redacted]	[redacted]	19,025
		25 years	[redacted]	[redacted]	[redacted]	19,809
PFS	G. gamma	Log-log for both niraparib and RS	[redacted]	[redacted]	[redacted]	28,143
		Weighted LLG/GG	[redacted]	[redacted]	[redacted]	22,403
Label population	PAOLA-1 approach	SOLO-1 approach	N/A	N/A	N/A	N/A
		PAOLA-1 approach with R0 effect only	N/A	N/A	N/A	N/A
		PRIMA	N/A	N/A	N/A	N/A
Long- term remission (LTR)	LTR at 7-years	No remission	[redacted]	[redacted]	[redacted]	18,087
		LTR at 10 years	[redacted]	[redacted]	[redacted]	20,755
		LTR at 5 years	[redacted]	[redacted]	[redacted]	16,415
NVRD (MA population)	[redacted]%	[redacted]%	N/A	N/A	N/A	N/A
		[redacted]%	N/A	N/A	N/A	N/A
Mean ΔPFS:ΔOS relationship	Modelled mean PFS	Restricted KM mean PFS observed in PRIMA	[redacted]	[redacted]	[redacted]	116,787
	1:2	1:1	[redacted]	[redacted]	[redacted]	34,566

Base case			[redacted]	[redacted]	[redacted]	18,689
		1:1.25	[redacted]	[redacted]	[redacted]	28,106
		1:1.5	[redacted]	[redacted]	[redacted]	23,889
		1:1.75	[redacted]	[redacted]	[redacted]	20,911
		1:2.5	[redacted]	[redacted]	[redacted]	15,584
		1:3	[redacted]	[redacted]	[redacted]	13,506
OS	Log-logistic for RS	Log-normal for RS	[redacted]	[redacted]	[redacted]	19,102
TTD	Weibull for niraparib	Log-logistic for niraparib	[redacted]	[redacted]	[redacted]	20,064
Treatment costs	Monthly dosing from PRIMA	Fixed niraparib dose	[redacted]	[redacted]	[redacted]	20,655
		Dose intensity	[redacted]	[redacted]	[redacted]	20,655
	Dose per treatment cycle (up to 18 cycles)	Dose per treatment cycle (up to 12 cycles)	[redacted]	[redacted]	[redacted]	18,667
	Apply wastage	No wastage	[redacted]	[redacted]	[redacted]	18,694
	[redacted]% discontinue at 3 years	No stopping rule	[redacted]	[redacted]	[redacted]	19,500
	[redacted]% discontinue at 3 years	[redacted]% discontinue at 3 years	[redacted]	[redacted]	[redacted]	18,546
Resource use	Literature	KOL	[redacted]	[redacted]	[redacted]	18,399
		ERG scenario for RS	[redacted]	[redacted]	[redacted]	18,877
	Blood pressure and heart rate monitoring excluded	ERG: Blood pressure and heart rate monitoring based on draft SmPC	[redacted]	[redacted]	[redacted]	18,953
	Patients in long-term remission are not monitored	Patients in long-term remission are monitored	[redacted]	[redacted]	[redacted]	19,562
Subsequent treatment	KOL with second-line and third-line chemotherapy, and third-line PARPi	PRIMA in second-line; no third-line costs applied	[redacted]	[redacted]	[redacted]	18,689
		KOL with second-line PARPi; no third-line costs applied	[redacted]	[redacted]	[redacted]	12,924
		No subsequent treatment cost	[redacted]	[redacted]	[redacted]	20,168

Base case			[redacted]	[redacted]	[redacted]	18,689
	Apply cost to patients leaving PFD	Apply cost to patients entering PD	[redacted]	[redacted]	[redacted]	19,101
	List price per PARP treatment	CDF discount	[redacted]	[redacted]	[redacted]	18,689
		Cheapest PARP list price (olaparib) applied to all PARPs	[redacted]	[redacted]	[redacted]	18,689
	100 mg olaparib tablet	150 mg olaparib tablet	[redacted]	[redacted]	[redacted]	18,689
	PARP average cost based on PRIMA	PARP simple average cost	[redacted]	[redacted]	[redacted]	18,689
	Administration HRG: SB15Z	Administration HRG: SB12Z	[redacted]	[redacted]	[redacted]	18,652
Adverse event costs	Do not apply AE 'day case' cost	Apply AE 'day case' cost	[redacted]	[redacted]	[redacted]	18,554
Quality of life	PRIMA descriptive analysis Published disutilities	Apply utility age decrement	[redacted]	[redacted]	[redacted]	20,037
		General population utilities applied to patients in long-term remission	[redacted]	[redacted]	[redacted]	19,130
		TA598 - PFD capped at general population, PD from OVA-301	[redacted]	[redacted]	[redacted]	19,879
		TA528 - EQ-5D-3L ENGOT-OV16/ NOVA	[redacted]	[redacted]	[redacted]	18,862

5 Additional economic analysis undertaken by the ERG

5.1 Model corrections

The ERG identified one minor error in the company's base case analysis (correction 1 in Table 45). Results in Table 46 and Table 47 show that all corrected base case ICERs are similar to the company's base case results, for the ITT population and the MA population.

Table 45. Corrections made to the company's model

#	Model correction	Section in ERG report
1	Replacing the hard-coded frequency of resource use in the model	4.2.9

Table 46. Company's corrected base case results, ITT population

Treatment	Total Costs	Total LYG, undiscounted	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
RS	[redacted]	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,705

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance

Table 47. Company's corrected base case results, MA population

Treatment	Total Costs	Total LYG, undiscounted	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
RS	[redacted]	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,475

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance

5.2 Exploratory and sensitivity analyses undertaken by the ERG

The ERG described the exploratory analyses undertaken throughout section 4 of this report. These are summarised in

Table 48 together with an indication of where in the report these scenarios are discussed. The ERG notes that most of the analyses in

Table 48 have been conducted by the company and were included in the model as options for running the economic analysis.

Table 48. Summary of exploratory analyses

#	Scenario	Section in ERG report
1	Use of the ITT population in the model	4.2.4.3.1
2	Removal of long-term remission approach from the model	4.2.4.3.2 and 4.2.6.1.1
3	Removal of long-term remission approach from the model and assuming PFS patients stop incurring costs at 7 years	
4	Removal of long-term remission approach from the model and assuming PFS patients stop incurring costs at 10 years	4.2.4.3.2 and 4.2.6.1.1
5	Use of a PFS to OS ratio of 1:0.66 as per TA598	4.2.4.3.3
6	Use of a PFS to OS ratio of 1:1	4.2.4.3.3 and 4.2.6.2
7	Applying age-related utility decrements in the model	4.2.8.1
8	Using the general population utility values for patients in long-term remission	4.2.8.1
9	Applying age-related utility decrements in the model and general population utility values for patients in long-term remission (#7 and #8)	4.2.8.1
10	Assuming no treatment discontinuation with niraparib as per SmPC	3.2.9.1
11	Including the cost of heart rate and blood pressure monitoring	3.2.9.3.1
12	Using alternative resource use estimates for PFS	3.2.9.3.1
13	Combining disease management assumptions (#11 and #12)	3.2.9.3.1

As explained at the beginning of section 4.2.4 the ERG has not conducted any additional analyses using the company's MA population. Results of the ERG's analysis are reported in

Table 49 for the ITT population.

The key driver of the economic results is the PFS to OS ratio used to estimate the niraparib OS curve in the model. Using the ratio proposed by the company in TA598 of 1:0.66 leads to an increase in the ITT ICER from £18,705 to £52,180 per QALY gained. When the ratio is assumed to be 1:1 the ITT ICER increases to £34,552 per QALY gained.

All the other scenarios (when run in isolation) have a modest impact on the ITT ICER.

Table 49. Results of ERG's exploratory analysis for the ITT population

#	Results per patient	Niraparib	RS	Inc. value
1	**Company's base case corrected**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			£18,705
2	**Removal of long-term remission approach from the model (including PFS costs for the entire model horizon)**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER	-	-	£18,385
3	**Removal of long-term remission approach from the model and assuming PFS patients stop incurring costs at 7 years**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			£18,088
4	**Removal of long-term remission approach from the model and assuming PFS patients stop incurring costs at 10 years**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			£18,142
5	**Use of a PFS to OS ratio of 1:0.66 as per TA598**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			£52,180
6	**Use of a PFS to OS ratio of 1:1**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			£34,552
7	**Applying age-related utility decrements in the model**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			£20,053
8	**Using the general population utility values for patients in long-term remission**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			£19,146
9	**Applying age-related utility decrements in the model and general population utility values for patients in long-term remission**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			£19,970
10	**Assuming no treatment discontinuation with niraparib as per SmPC**			

	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER	-	-	£19,514
11	**Including the cost of heart rate and blood pressure monitoring**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER	-	-	£19,578
12	**Using alternative resource use estimates for PFS**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER	-	-	£18,964
13	**Combining disease management assumptions (#11 and #12)**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER	-	-	£19,837
	Abbreviations: ICER. Incremental cost-effectiveness ratio; Inc. incremental; ITT, intention to treat; OS, overall survival; PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life year; RS, routine surveillance; TA, technology appraisal			

5.3 ERG preferred assumptions

Given the uncertainty around the survival benefit associated with niraparib, the ERG does not have a preferred base case ICER and instead has provided different exploratory analyses. These combined different scenarios. The common preferred assumptions for the economic model are listed below:

- Use of the ITT population in the model;
- Removal of long-term remission approach from the model and assuming PFS patients stop incurring costs at 10 years;
- Applying age-related utility decrements in the model;
- Assuming no treatment discontinuation with niraparib as per SmPC;
- Including the cost of heart rate and blood pressure monitoring;
- Using alternative resource use estimates for PFS.

In addition to the changes listed above, the ERG considered three different sets of combined scenarios:

1. Use of a PFS to OS ratio of 1:0.66 as per TA598;
2. Use of a PFS to OS ratio of 1:1;

3. Use of a HR between RS OS and niraparib OS of 0.70 as observed in PRIMA.

Results of these analyses are reported in Table 50. When the PFS to OS ratio of 1:0.66 is used in the model, the ICER amounts to £79,077 per QALY gained. When it is assumed that the magnitude of the improvement in PFS with niraparib is the same as the magnitude of the improvement in OS (i.e. using a PFS to OS ratio of 1:1), the ICER decreased to £45,226 per QALY gained.

The ERG notes that the OS HR for niraparib vs RS observed in PRIMA was of 0.70 (95% CI: 0.44 to 1.11), albeit not statistically significant. When a HR of 0.70 is used in the model, this leads to an ICER of £38,252 per QALY gained. This, in its turn corresponds to a PFS to OS ratio of 1:1.13 (1 month of extra PFS lead to 1.13 months of extra OS). However, given the lack of maturity and statistical significance of the HR in PRIMA, and the shape of the OS curves (see section 4.2.6.1.1), it is possible that the survival benefit with niraparib is much smaller. Given the lack of maturity of the data, it is also possible that the survival benefit of niraparib is higher than that observed in PRIMA.

When it is assumed that niraparib and RS have the same OS, the ITT ICER increases to £950,200 per QALY gained. The ERG concludes that without having more mature OS data from PRIMA it is not possible to make inferences on the survival benefits of niraparib without a paramount level of uncertainty.

For all the analyses conducted by the ERG, it was assumed that niraparib has a constant survival advantage over RS for the entire time horizon of the analysis (given the use of a HR). The ERG notes that this is unlikely to represent clinical reality, and notes that this could be surpassed with fitting an OS model to the OS KM niraparib data from PRIMA (provided survival predictions are valid).

Table 50. Results of ERG's exploratory analysis for the ITT population

		Niraparib	RS	Inc. value
1	**Use of a PFS to OS ratio of 1:0.66 as per TA598**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			£79,077
2	**Use of a PFS to OS ratio of 1:1**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER	-	-	£45,226
3	**Use of a HR between RS OS and niraparib OS of 0.70**			

	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			£38,252
	Abbreviations: ICER. Incremental cost-effectiveness ratio; Inc. incremental; ITT, intention to treat; OS, overall survival; PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life year; RS, routine surveillance; TA, technology appraisal			

5.4 Conclusions of the cost effectiveness sections

The ERG's view is that PRIMA is representative of the MA population as it includes patients with NVRD after PDS or IDS (47% of the entire ITT population in PRIMA had NVRD). Given that the company's rationale for generating an MA population is mainly based on the fact that NVRD patients have better outcomes than patients with VRD (section 3.4), the ERG considers that PRIMA does not only provide sufficient evidence to address this issue, but is also the most robust source of evidence available to estimate the cost-effectiveness of niraparib vs RS.

The ERG considers the method used by the company to estimate cure in the model unfit for decision making as PRIMA does not provide a mature enough evidence base to substantiate a cure threshold for niraparib or RS in the model; and external sources of evidence are not robust enough to suggest when a cure threshold would be reached for niraparib. However, there does seem to be some evidence to support the idea that patients receiving RS who are PF at 5 years (and therefore also at 7 years) are at low risk of recurrence.

Furthermore, the ERG does not consider that enough robust evidence exists to substantiate the use of PFS as a surrogate measure of OS in the OC setting. There is, however, some literature suggesting that if the effect of a treatment for OC extends PFS by x months, it is reasonable to estimate that the treatment will also extend OS by x months, meaning that, "*the magnitude of the improvement in PFS is the magnitude of the improvement in OS.* [Therefore], *PFS is simply a measure of a drug's effect on tumour growth while it is administered and is not a surrogate for OS*".[25, 26]

The key model driver is the method used to estimate OS for niraparib in the model. Given the company's choice to not use the OS KM data for niraparib from PRIMA to estimate survival in the model, the ERG was restricted to conducting additional analysis through the use of PFS to OS ratios and HRs to estimate the niraparib OS curve in the analysis. This assumes that niraparib has a

constant survival advantage over RS for the entire time horizon of the analysis, which is unlikely to represent clinical reality.

Given the availability of OS KM data for niraparib, the company could have presented an option in the model of using these data, instead of only using a surrogate outcome to estimate OS.

The exploratory ICERs generated by the ERG ranged from £38,252 to £950,200. The ERG concludes that without having more mature OS data from PRIMA it is not possible to make inferences on the survival benefits of niraparib without a paramount level of uncertainty.

End of Life

NICE end of life considerations apply when all the criteria below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The company have not made a case for end-of-life status and the ERG considers that this is appropriate.

References

1. National Institute for Health and Care Excellence (NICE). Final scope: Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1680], 2020. Available from: https://www.nice.org.uk/guidance/gid-ta10551/documents/final-scope. Date accessed: 26 May 2020.
2. National Institue for Health and Care Excellence. Managing advanced (stage II-IV) ovarian cancer, 2020. Available from: https://pathways.nice.org.uk/pathways/ovarian-cancer#path=view%3A/pathways/ovarian-cancer/managing-advanced-stage-ii-iv-ovarian-cancer.xml&content=view-node%3Anodes-maintenance-treatment-after-first-line-chemotherapy. Date accessed: 08 Apr 2020.
3. England N. National Cancer Drugs Fund (CDF) List, 2020. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-v1-161.pdf. Date accessed: 8 Apr 2020.
4. Tesaro/GSK. Clinical Study Report PR-5017-C: A Phase 3, randomized, double-blind, placebo-controlled, mutlicenter study of niraparib maintenance treatment in patients with advanced ovarian cancer following response on front-line platinum-based chemotherapy. 2019.
5. Ray-Coquard I, Pautier P, Pignata S, al. e. Phase III PAOLA-1/ENGOT-ov25 trial: Olaparib plus bevacizumab (bev) as maintenance therapy in patients (pts) with newly diagnosed, advanced ovarian cancer(OC) treated with platinum-based chemotherapy (PCh) plus bev. *Annals of Oncology* 2019; **30**: v851-v934.
6. Moore K, Colombo N, Scambia G, Kim B-G, Oaknin A, Friedlander M, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *New England Journal of Medicine* 2018; **379**: 2495-505.
7. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097.
8. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in healthcare, 2011. Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Date accessed: 15 Apr 2020.
9. electronic Medicines Compendium (eMC). Niraparib. Summary of Product Characteristics. 2020.
10. Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24 Suppl 6**: vi24-32.
11. Vergote I, Trope CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med* 2010; **363**: 943-53.
12. Harter P, Mouret-Reynier, M.-A. & Pignata, S. . Phase III PAOLA-1/ENGOT-ov25: maintenance olaparib with bevacizumab in patients with newly diagnosed, advanced ovarian cancer treated with platinum-based chemotherapy and bevacizumab as standard of care. 2019. p. ESGO; November 2-5, 2019; Athens, Greece.
13. Hall M, Savvatis K, Nixon K, Kyrgiou M, Hariharan K, Padwick M, et al. Maximal-Effort Cytoreductive Surgery for Ovarian Cancer Patients with a High Tumor Burden: Variations in Practice and Impact on Outcome. *Ann Surg Oncol* 2019; **26**: 2943-51.
14. Mathews CA. Maintenance olaparib after platinum-based chemotherapy in patients (pts) with newly diagnosed advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): Efficacy by surgical and tumor status in the Phase III SOLO1 trial. . *JCO* 2019. p. 5541– Poster presented at the ASCO Annual Meeting; May 31–June 4, 2019; Chicago, USA

15. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med* 2011; **365**: 2484-96.
16. National Institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy: technology appraisal guidance [TA598]. 2019.
17. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011.
18. Friedlander M, Matulonis U, Gourley C, du Bois A, Vergote I, Rustin G, et al. Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. *Br J Cancer* 2018; **119**: 1075-85.
19. Bullement A, Latimer NR, Bell Gorrod H. Survival Extrapolation in Cancer Immunotherapy: A Validation-Based Case Study. *Value Health* 2019; **22**: 276-83.
20. Othus M, Bansal A, Koepl L, Wagner S, Ramsey S. Accounting for Cured Patients in Cost-Effectiveness Analysis. *Value Health* 2017; **20**: 705-9.
21. Lambert PC, Thompson JR, Weston CL, Dickman PW. Estimating and modeling the cure fraction in population-based cancer survival analysis. *Biostatistics* 2007; **8**: 576-94.
22. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). *Cancer* 2009; **115**: 1234-44.
23. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet* 2015; **386**: 249-57.
24. David S, Tappenden P, Cantrell A. A Review of Studies Examining the Relationship between Progression-Free Survival and Overall Survival in Advanced or Metastatic Cancer, 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK425826/. Date accessed: July 2020.
25. Sundar S, Wu J, Hillaby K, Yap J, Lilford R. A systematic review evaluating the relationship between progression free survival and post progression survival in advanced ovarian cancer. *Gynecol Oncol* 2012; **125**: 493-9.
26. Wilkerson J, Fojo T. Progression-free survival is simply a measure of a drug's effect while administered and is not a surrogate for overall survival. *Cancer J* 2009; **15**: 379-85.
27. National institue for Health and Care Excellence (NICE). Position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product, 2019. Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/cancer-drugs-fund/CDF-comparator-position-statement.pdf. Date accessed: July 2020.
28. Nishio S, Katsumata N, Matsumoto K, Tanabe H, Yonemori K, Kouno T, et al. Usefulness of third-line chemotherapy for women with recurrent ovarian, fallopian tube, and primary peritoneal cancer who receive platinum/taxane regimens as first-line therapy. *J Cancer Res Clin Oncol* 2009; **135**: 551-7.
29. NHS Improvement. NHS Reference Costs 2018/19, 2019. Available from: https://improvement.nhs.uk/resources/national-cost-collection/. Date accessed: July 2020.
30. National Institute for Health and Care Excellence (NICE). Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer: technology appraisal guidance [TA528]. 2018.
31. GSK. Data on file. Niraparib CDF report. 2020.

32. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med* 2016; **375**: 2154-64.
33. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; **390**: 1949-61.
34. European Medicine Agency (EMA). Tecentriq, 2020. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/tecentriq. Date accessed: July 2020.
35. European medicine Agency (EMA). Keytruda, 2020. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda. Date accessed: July 2020.
36. O'Hagan T. The SHeffield ELicitation Framework (SHELF). Available from: http://www.tonyohagan.co.uk/shelf/. Date accessed: Oct 2019.
37. NHS Improvement. NHS Reference Costs 2017/18, 2018. Available from: https://improvement.nhs.uk/resources/reference-costs/. Date accessed: April 2020.
38. Curtis L and Burns A. Unit Costs of Health and Social Care 2019. 2019. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/. Date accessed: March 2020.
39. Gao W, Ho YK, Verne J, Glickman M, Higginson IJ. Changing Patterns in Place of Cancer Death in England: A Population-Based Study. *PLoS Medicine* 2013; **10**: e1001410.
40. Guest JF, Ruiz FJ, Greener MJ, Trotman IF. Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. *European Journal of Cancer Care* 2006; **15**: 65-73.
41. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in healthcare. *Available at https://wwwyorkacuk/media/crd/Systematic Reviewspdf (Accessed 21 March 2016)* 2011.

Appendices

5.5 Baseline characteristics PRIMA

Table 51: Baseline characteristics of the ITT patient population in the PRIMA trial, adapted from CS Table 9 and clarification response A1

Characteristic	Niraparib (N=487)	Placebo (N=246)
Median age, years (range)	62 (32-85)	62 (33-88)
Median weight, kg (range)	66.00 (38.0-137.0)	65.55 (37.8-146.5)
Race – no. (%)		
White	436 (89.5)	219 (89.0)
Black	10 (2.1)	2 (0.8)
Asian	14 (2.9)	11 (4.5)
American Indian or Alaska Native	1 (0.2)	0
Native Hawaiian or Other Pacific Islander	1 (0.2)	0
Unknown	6 (1.2)	1 (0.4)
Not reported	19 (3.9)	13 (5.3)
ECOG score - no. (%)		
0	337 (69.2)	174 (70.7)
1	150 (30.8)	72 (29.3)
International FIGO stage - no. (%)		
III	318 (65.3)	158 (64.2)
A	7 (1.4)	4 (1.6)
B	16 (3.3)	12 (4.9)
C	285 (58.5)	138 (56.1)
Not specified	10 (2.1)	4 (1.6)
IV	169 (34.7)	88 (35.8)
Primary tumour location - no. (%)		
Ovary	388 (79.7)	201 (81.7)
Fallopian tube	65 (13.3)	32 (13.0)
Peritoneum	34 (7.0)	13 (5.3)
Histologic type - no. (%)		
Serous	465 (95.5)	230 (93.5)
Endometrioid	11 (2.3)	9 (3.7)
Other	11 (2.3)	6 (2.4)
Receipt of neoadjuvant chemotherapy - no. (%)		
Yes	322 (66.1)	167 (67.9)
No	165 (33.9)	79 (32.1)
Clinical response after platinum-based chemotherapy - no. (%)		
Complete response	337 (69.2)	172 (70.0)

Partial response	150 (30.8)	74 (30.0)
Cancer antigen 125 level - no. (%)		
≤ ULN	450 (92.4)	226 (91.9)
> ULN	34 (7.0)	18 (7.3)
Missing data	3 (0.6)	2 (0.8)
No. of cycles of platinum-based chemotherapy - no. (%)		
6	333 (68.4)	170 (69.1)
7-9	124 (25.5)	62 (25.2)
Missing data	30 (6.2)	14 (5.7)
BRCA status		
BRCAmut	152 (31.2)	71 (28.9)
BRCA1	105 (21.6)	43 (17.5)
BRCA2	47 (9.7)	28 (11.4)
BRCAwt	310 (63.7)	163 (66.3)
BRCAnd	25 (5.1)	12 (4.9)
HRD status		
HRDpos	247 (50.7)	126 (51.2)
tBRCAmut	152 (31.2)	71 (28.9)
Non-tBRCAmut	95 (19.5)	55 (22.4)
HRDneg	169 (34.7)	80 (32.5)
HRDnd	71 (14.6)	40 (16.3)
Prior bevacizumab	[redacted]	[redacted]

Source: PRIMA CSR 57

Abbreviations: BRCA, breast cancer susceptibility gene; CA-125, cancer antigen 125; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRDpos, homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors; ITT, intention-to-treat; Max, maximum; Min, minimum; mut, mutation; ND, not determined; PS, performance score; PR, partial response; ULN, upper limit of normal; US, United States; wt, wild type

Table 52. Patient Demographics and Baseline Characteristics – Individualised and Fixed Dose Subgroups (ITT Population) (reproduced from clarification response, question A4)

Characteristic	Overall			
	Niraparib N (%)		Placebo N (%)	
	Fixed N=317	Individualised N=170	Fixed N=158	Individualised N=88
Age at time of screening				
Median	61.0	63.0	62.0	60.5
Min, Max	32, 83	39, 85	34, 88	33, 82
ECOG PS				
0	223 (70.3)	114 (67.1)	114 (72.2)	60 (68.2)
1	94 (29.7)	56 (32.9)	44 (27.8)	28 (31.8)
Cancer stage (FIGO) at time of diagnosis				
III, not otherwise specified	5 (1.6)	5 (2.9)	4 (2.5)	0

IIIA	3 (0.9)	4 (2.4)	4 (2.5)	0
IIIB	10 (3.2)	6 (3.5)	7 (4.4)	5 (5.7)
IIIC	186 (58.7)	99 (58.2)	88 (55.7)	50 (56.8)
IV	113 (35.6)	56 (32.9)	55 (34.8)	33 (37.5)
Primary tumor site				
Ovarian	249 (78.5)	139 (81.8)	130 (82.3)	71 (80.7)
Primary peritoneal	20 (6.3)	14 (8.2)	7 (4.4)	6 (6.8)
Fallopian tube	48 (15.1)	17 (10.0)	21 (13.3)	11 (12.5)
NACT				
Y	208 (65.6)	114 (67.1)	114 (72.2)	53 (60.2)
N	109 (34.4)	56 (32.9)	44 (27.8)	35 (39.8)
Best Response to first-line platinum-based chemotherapy				
CR	233 (73.5)	104 (61.2)	117 (74.1)	55 (62.5)
PR	84 (26.5)	66 (38.8)	41 (25.9)	33 (37.5)
HRD status				
HRDpos	160 (50.5)	87 (51.2)	83 (52.5)	43 (48.9)
tBRCAmut	99 (31.2)	53 (31.2)	45 (28.5)	26 (29.5)
non-tBRCAmut	61 (19.2)	34 (20.0)	38 (24.1)	17 (19.3)
HRDneg	108 (34.1)	61 (35.9)	54 (34.2)	26 (29.5)
HRDnd	49 (15.5)	22 (12.9)	21 (13.3)	19 (21.6)
BRCA status				
BRCAmut	99 (31.2)	53 (31.2)	45 (28.5)	26 (29.5)
BRCAwt	199 (62.8)	111 (65.3)	106 (67.1)	57 (64.8)
BRCAnd	19 (6.0)	6 (3.5)	7 (4.4)	5 (5.7)
Prior therapy				
Bevacizumab	0 (0)	6 (3.5)	0 (0)	1 (1.1)

Abbreviations: BRCA, breast cancer susceptibility gene; CA-125, cancer antigen 125; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRDpos, homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors; ITT, intention-to-treat; Max, maximum; Min, minimum; mut, mutation; ND, not determined; PS, performance score; PR, partial response; ULN, upper limit of normal; US, United States; wt, wild type

5.6 PFS sensitivity analyses PRIMA

Table 53. Sensitivity analyses of PFS results for ITT population (adapted from CS table 12)

		Niraparib (N=487)	Placebo (N=246)
Investigator assessment (ITT population)			
	Median (months)(95% CI)	13.8 (11.3,14.2)	8.2 (7.6,9.8)
	p-value	<0.0001	
	Hazard ratio (95% CI)	0.63 (0.514,0.763)	
Alternative censoring rules (ITT population)			
	Median (months)(95% CI)	[redacted]	[redacted]
	p-value	[redacted]	

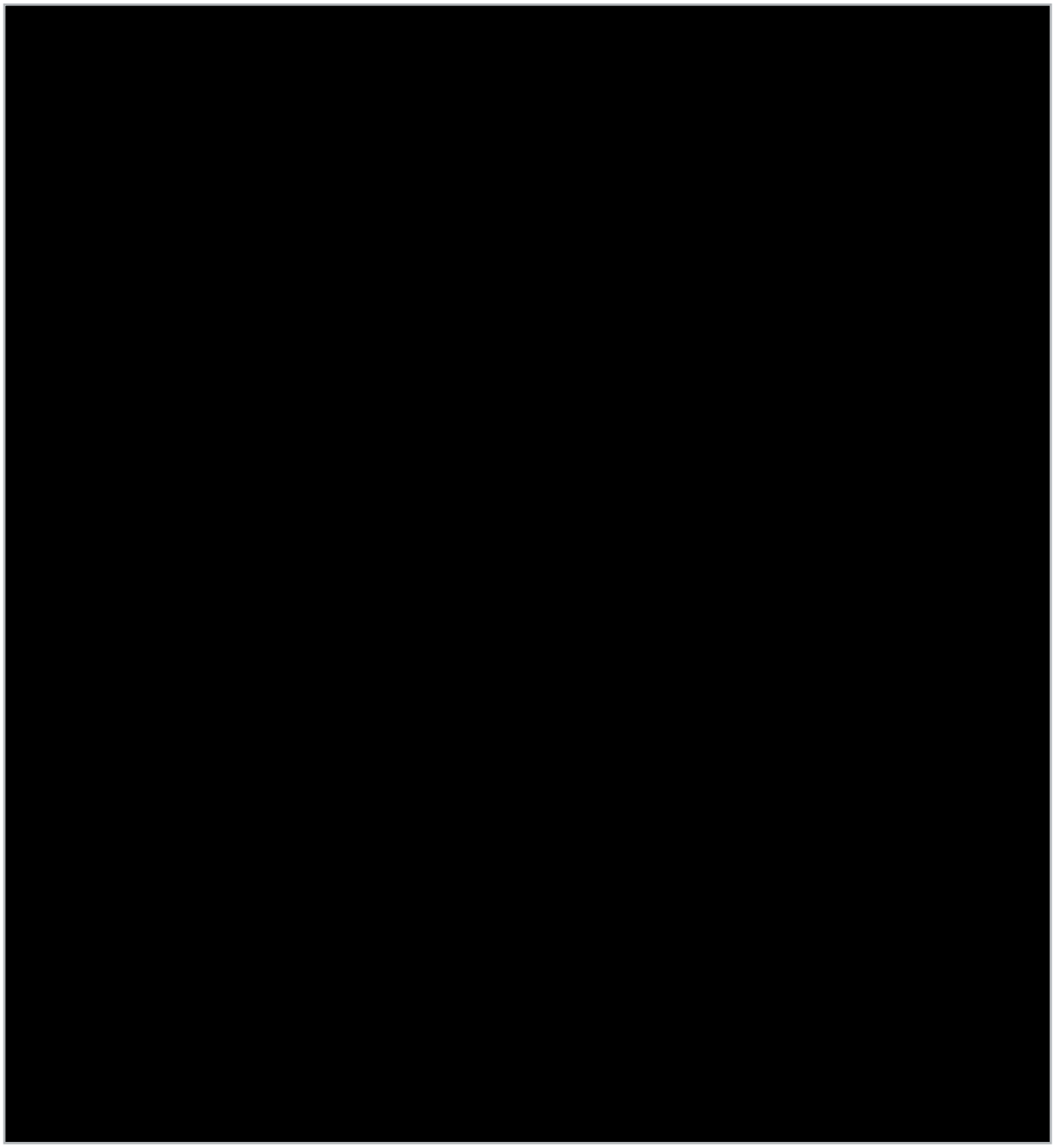
	Hazard ratio	[redacted]
Stratification values from the prior treatment eCRF (PP population)		
	Median (months)(95% CI)	[redacted]
	p-value	[redacted]
	Hazard ratio	[redacted]
Alternative event times (ITT population)		
	Median (months)(95% CI)	[redacted]
	p-value	[redacted]
	Hazard ratio	[redacted]
BICR radiology data (ITT population)		
	Median (months)(95% CI)	[redacted]
	p-value	[redacted]
	Hazard ratio	[redacted]
Stratification values from the prior treatment eCRF (PP population)		
	Median (months)(95% CI)	[redacted]
	p-value	[redacted]
	Hazard ratio	[redacted]
Subsequent anticancer therapy (ITT population)		
	Median (months)(95% CI)	[redacted]
	p-value	[redacted]
	Hazard ratio	[redacted]
Alternative Randomisation Stratification Factors (ITT population)		
	Median (months)(95% CI)	[redacted]
	p-value	[redacted]
	Hazard ratio	[redacted]

Source: CSR [57]

Abbreviations: BICR: blinded independent central review; eCRF: electronic case report form; ITT: intention-to-treat; PFS: progression-free survival

Pre-specified subgroup analyses PRIMA

Figure 25: Forest Plot of Hazard Ratios (95% CI) for PFS by Subgroup in the ITT Population



Source: CSR [57]

Abbreviations: BRCA: breast cancer susceptibility gene; BRCAmut: mutation in BRCA; tBRCAwt: BRCA wildtype; CA-125: cancer antigen 125; CI: confidence interval; CR: complete response; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; HR: hazard ratio; HRD: homologous recombination deficiency; HRDnd: homologous recombination deficiency test status not determined; HRDneg: homologous recombination deficiency test negative, referring to homologous recombination proficient (HR-proficient) tumours; HRDpos: homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumours; ITT: intent-to-treat; non-tBRCAmut: without a germline BRCA mutation; PFS: progression-free survival; PR: partial response; ULN: upper limit of normal.

5.7 Most common TEAEs PRIMA

Table 54: Most common TEAEs; ≥10% Incidence Rate in Either Treatment Subgroup (adapted from clarification response A12, Table 5)

Preferred Term	Niraparib			Placebo
	All n (%) N=484	Individualised n (%) N=169	Fixed n (%) N=315	All n (%) N=244
Nausea	278 (57.4)	90 (53.3)	188 (59.7)	67 (27.5)
Anaemia	307 (63.4)	84 (49.7)	223 (70.8)	43 (17.6)
Thrombocytopenia	222 (45.9)	57 (33.7)	165 (52.4)	9 (3.7)
Constipation	189 (39.0)	53 (31.4)	136 (43.2)	46 (18.9)
Fatigue	168 (34.7)	56 (33.1)	112 (35.6)	72 (29.5)
Vomiting	108 (22.3)	28 (16.6)	80 (25.4)	29 (11.9)
Headache	126 (26.0)	37 (21.9)	89 (28.3)	36 (14.8)
Insomnia	119 (24.6)	35 (20.7)	84 (26.7)	35 (14.3)
Platelet count decreased	133 (27.5)	38 (22.5)	95 (30.2)	3 (1.2)
Abdominal pain	106 (21.9)	30 (17.8)	76 (24.1)	75 (30.7)
Decreased appetite	92 (19.0)	32 (18.9)	60 (19.0)	20 (8.2)
Neutropenia	128 (26.4)	41 (24.3)	87 (27.6)	16 (6.6)
Diarrhoea	91 (18.8)	23 (13.6)	68 (21.6)	55 (22.5)
Hypertension	82 (16.9)	27 (16.0)	55 (17.5)	17 (7.0)
Dyspnoea	88 (18.2)	27 (16.0)	61 (19.4)	30 (12.3)
Cough	74 (15.3)	22 (13.0)	52 (16.5)	35 (14.3)
Dizziness	71 (14.7)	18 (10.7)	53 (16.8)	26 (10.7)
Asthenia	78 (16.1)	26 (15.4)	52 (16.5)	31 (12.7)
Neutrophil count decreased	82 (16.9)	21 (12.4)	61 (19.4)	5 (2.0)
Arthralgia	85 (17.6)	29 (17.2)	56 (17.8)	47 (19.3)
Back pain	64 (13.2)	17 (10.1)	47 (14.9)	24 (9.8)
Viral upper respiratory tract infection	49 (10.1)	16 (9.5)	33 (10.5)	25 (10.2)
Abdominal pain upper	41 (8.5)	10 (5.9)	31 (9.8)	22 (9.0)

5.8 Literature review of PFS and OS associated with NVRD

Table 55: Studies conducted in the US or Europe reporting overall survival or progression-free survival by residual disease status among ovarian cancer patients

Author, Year	Country	Patients	Study design	Treatment	Residual disease: definition	Residual disease: category	Overall survival (median months)	Overall survival: HR (95% CI)[a]	PFS (median months)
Delga 2020[67]	France (Nantes & Marseille cancer centers)	N=1260, stage III & IV	1985-2015	Cytoreductive surgery (PCS, ICS or FCS) with or without chemotherapy	Definition of "complete" not further defined	Complete cytoreduction	55.1 *(PCS: 59.7, ICS: 56; FCS: 48.6)*	1.0	--
						Any RD	24.6	2.1 (1.8-2.5)	--
Ghirardi 2020 (abstract)[68]	Italy	n=207, stage IIIC-IV	Retrospective, 2010-2016	PCS	Compared 1-10 mm RD at PCS vs. no gross RD at IDS	No gross RD-IDS	52.4	--	18.9
						1-10 mm-PCS	41.4	--	16.2
Liang 2019 (abstract)[69]	USA (UCLA)	N=91, advanced	n/a	NACT and IDS	No gross RD vs. visible (<1 cm)	None	38.7	--	16.3
						<1 cm	12	--	10
Babayeva 2018 (abstract)[70]	Germany (Tumor Bank Ovarian Cancer)	N=164, mostly advanced	Prospective database	PCS	Any tumor residual	None	70.0	--	--
						Any	24.7	--	--
Kobal 2018[71]	Slovenia	N=157, stage III & IV	Retrospective, 2008-2012	PCS or NACT+IDS	Complete cytoreduction (RD=0)	0 mm	PCS, NACT 54.7, 36.3	All patients: 1.0	PCS, NACT 20.7, 19.9
						1-9 mm	34.7, 25.6	1.66 (0.96-2.82)	11.2, 14.5
						>= 10 mm	31.3, 16.1	2.82 (1.79-4.46)	13.3, 8.0
Phillips 2018 (abstract)[72]	United Kingdom	N=398	Retrospective, 2007-2017	NACT and IDS (<5 cycles vs. >=5 cycles)	Complete cytoreduction = no RD	Complete (NVRD)	<5, >=5 cycles: 51.1, 53.0	--	--

						Optimal (<1cm)	36.1, 24.7	--	--
						Suboptimal (>=1)	34.3, 22.1	--	--
Torres 2018[73]	USA (Mayo clinic)	N=334, serous type, stage III-IV	Prospective database, 1994-2011	PCS	Largest residual tumor diameter	0	72.0	1.0	
						0.1-0.5 cm	39.6	1.34 (0.96-1.88)	
						0.6-1.0 cm	25.4	2.07 (1.34-3.22)	
						>1 cm	21.2	2.59 (1.74-3.86)	
Sorensen, 2018[74]	Denmark (Danish Gynecological Cancer Database)	N=2092, stage IIIB-IV	1 Jan 2005 to 30 June 2016	PCS	Extent of intra-abdominal macroscopic visible disease after PCS	0 cm	stage IIIB-C, IV 60.8, 43.4	stage IIIB-C, IV 1.0, 1.0	
						<=1 cm	29.5, 24.9	1.7 (1.5-2.0), 1.6 (1.1-2.2)	
						>1 and <=2 cm	27.8, 17.2	1.5 (1.2-1.9), 1.9 (1.2-3.1)	--
						> 2	19.8, 14.3	2.4 (2.0-2.8), 2.4 (1.8-3.2)	--
						n/a	15.2, 13.2	4.5 (2.2-9.1), 2.2 (0.8-6.2)	--
Sioulas 2018[75]	USA (Memorial Sloan Kettering)	N=496, stage IIIC	Retrospective, 2001-2010	PCS	Reported RD	None	83.4	--	26.7
						1-5 mm	54.5	--	20.7
						6-10 mm	43.8	--	16.2
						> 10 mm	38.9	--	13.6
Ataseven 2016 (abstract)[76]	Austria	N=286, stage IV	Retrospective, 2000-2014	PCS	Macroscopic resection	0	50	1.0	--
						1-10 mm	25	1.50 (1.01-2.23)	--
						> 10 mm	16	2.17 (1.43-3.70)	--
	USA					0 cm (NVRD)	76.9	--	28.9

Horowitz 2015[77]		N=2655, Stage III & IV	Patients enrolled in GOG-182 trial	PCS followed by 1 of 5 chemotherapy regimens	Complete surgical resection (microscopic, NVRD) or 0.1 to <1 cm (macroscopic)	NVRD > to <1 cm	40.6	--	15.3
Rutten 2015[38]	Netherlands	N=689, stage IIIC & IV	Observational cohort, 1998-2010	PCS or IDS	None, minimal (<1cm), gross (>=1 cm)	None	PCS, IDS[a] 59.2, 43.6	PCS, IDS[a] 1.0	PCS, IDS 23.7, 17.4
						Minimal	36.7, 26.7	2.0 (1.1-3.8), 1.8 (1.3-2.5)	16.7, 11.9
						Gross	35.6, 21.5 [a]disease specific survival (DSS)	1.8 (1.1-3.2), 3.1 (2.0-4.8)	12.5, 9.0
Vergote 2010[78]	EORTC institutions	N=632, stage IIIC or IV	RCT	PCS + platinum chemo theraphy or NACT+IDS	Optimal: no RD, suboptimal: 1-10 mm, other: > 10	Optimal	PCS, NACT: 45, 38	--	--
						Suboptimal	32, 27	--	--
						Other	26, 25	--	
Wimberger 2010[79]	Germany	N=573, stage IV	Retrospective (AGO-OVAR-3/5/7)	Chemotherapy and primary surgery	Macroscopic complete resection	0 cm	54.6	1.0	--
						0-1 cm	25.8	1.9 (1.2-2.9)	--
						>1 cm	23.9	2.1 (1.4-3.2)	--

Abbreviations: CI: confidence interval; FCS: final cytoreductive surgery; HR: hazard ratio; ICS: interval cytoreductive surgery; IDS: interval cytoreductive surgery; NACT: neoadjuvant chemotherapy; PCS: primary cytoreductive surgery; PCS: primary cytoreductive surgery; PFS: progression free survival; RD: residual disease

a. Multivariate analyses presented.

5.9 Inclusion and exclusion criteria applied to the RWE Edinburgh dataset

Table 56: Inclusion and exclusion criteria used to obtain the MA cohort and simulated-PRIMA cohort from the University of Edinburgh Ovarian Cancer Database (reproduced from CS Table 19)

MA cohort		Simulated-PRIMA cohort	
Inclusion criteria	Exclusion criteria	Inclusion criteria	Exclusion criteria
[redacted]	[redacted]	[redacted]	[redacted]

5.10 Baseline characteristics RWE Edinburgh dataset

Table 57. Patient characteristics in the MA cohort and simulated-PRIMA cohort from the University of Edinburgh Ovarian Cancer Database

Characteristic		MA cohort		Simulated-PRIMA cohort	
		n	%	n	%
	Cases	[redacted]	[redacted]	[redacted]	[redacted]
Age at diagnosis	Median years	[redacted]	[redacted]	[redacted]	[redacted]
Histological subtype	HGS	[redacted]	[redacted]	[redacted]	[redacted]
	HG endo	[redacted]	[redacted]	[redacted]	[redacted]
Documented primary site	Ovary	[redacted]	[redacted]	[redacted]	[redacted]
	Fallopian Tube	[redacted]	[redacted]	[redacted]	[redacted]
	Peritoneum	[redacted]	[redacted]	[redacted]	[redacted]
	FT/ovary	[redacted]	[redacted]	[redacted]	[redacted]
FIGO stage at diagnosis	IIIA	[redacted]	[redacted]	[redacted]	[redacted]
	IIIB	[redacted]	[redacted]	[redacted]	[redacted]
	IIIC	[redacted]	[redacted]	[redacted]	[redacted]
	III NS	[redacted]	[redacted]	[redacted]	[redacted]

	IV	[redacted]	[redacted]	[redacted]	[redacted]
Germline BRCA status	BRCAm	[redacted]	[redacted]	[redacted]	[redacted]
	BRCAwt / VUS	[redacted]	[redacted]	[redacted]	[redacted]
	untested	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS	0	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]
	NA	[redacted]	[redacted]	[redacted]	[redacted]
Chemo type	Adjuvant	[redacted]	[redacted]	[redacted]	[redacted]
	Neoadjuvant	[redacted]	[redacted]	[redacted]	[redacted]
Residual disease	Zero macroscopic	[redacted]	[redacted]	[redacted]	[redacted]
	Macroscopic	[redacted]	[redacted]	[redacted]	[redacted]
	NA	[redacted]	[redacted]	[redacted]	[redacted]
Vital status at last follow-up	Alive	[redacted]	[redacted]	[redacted]	[redacted]
	Deceased	[redacted]	[redacted]	[redacted]	[redacted]
Median follow-up	median years	[redacted]	[redacted]	[redacted]	[redacted]
Median OS	median years	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS	median years	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FIGO, International Federation of Gynaecology and Obstetrics; BRCA, BRCA1 or BRCA2; FT, fallopian tube; HG endo, high grade (grade III) endometrioid; HGS, high grade serous; NA, not available; NS, not specified; OS, overall survival; PFS, progression-free survival, RD, residual disease following cytoreductive surgery; VUS, variant of unknown clinical significance;

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1680]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by the end of **11 August**. using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Company response to draft ERG report

The Company would like to thank NICE and the ERG for the opportunity to review the draft ERG report. Issues identified by the Company are presented in the tables below. In addition to the points raised, the Company have also provided a revised economic model as a result of the comments raised by the ERG in Section 5.3 of their report. The Company request that the ERG reconsider their preferred scenario analyses in light of this updated model and the responses provided below (Issue 5), and that a preferred base case is presented in the revised ERG report.

The Company is grateful to the ERG for drawing attention to the difference between the simulated-PRIMA cohort from the University of Edinburgh Ovarian Cancer database and the PRIMA trial ITT population. The Company will seek to have the analysis from the Edinburgh database updated to exclude patients with Stage III NVRD following IDS to form a cohort more reflective of the PRIMA trial ITT population, for consideration during the technical engagement stage.

Table 1. Abbreviations

AE	Adverse event
AIC	Academic in confidence
BICR	Blinded independent central review
CEM	Cost-effectiveness model
CI	Confidence interval
CIC	Commercial in confidence
CS	Company submission
CSR	Clinical study report
ECOG	European Cooperative Oncology Group
ERG	Evidence Review Group
ESMO	European Society of Molecular Oncology
FSD	Fixed starting dose
FIGO	International Federation of Gynecology and Obstetrics
FOSI	Functional Assessment of Cancer Therapy-Ovarian Symptoms Index
HR	Hazard ratio
HRD	Homologous recombination deficiency
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ISD	Individualised starting dose
IDS	Interval debulking surgey
ITT	Intention to treat
KM	Kaplan-Meier
MA	Marketing authorisation
MCM	Mixture cure model
mg	Millgram

NACT	Neoadjuvant chemotherapy
NICE	National Institute for Health and Care Excellence
NVRD	No visbile residual disease
OC	Ovarian cancer
OS	Overall survival
PCS	Primary cytoreductive surgery
PD	Progressed disease
PDS	Primary debulking surgery
PF	Progression-free
PFS	Progression-free survival
PFS2	Progression-free survival on subsuquent treatment
RS	Routine surveillance
RWE	Real word evidence
SD	Standard deviation
SmPC	Summary of product characteristics
TA	Technology apprasial
TFST	Time to first subsequent treatment
TLR	Targeted literature review
UDS	Upfront debulking surgery
UK	United Kingdom
VBA	Visual basic for applications
VRD	Visible residual disease

Issue 1 Market authorisation population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Prognosis of stage III patients with NVRD following PDS and IDS			
Paragraph 1, page 19; "The ERG does not agree that there is a discrepancy between the expected MA for niraparib and the population in PRIMA as the trial includes a substantial proportion of patients with stage III NVRD." Paragraph 1, page 34; "The ERG does not agree that there is a discrepancy between the expected MA and the population in PRIMA." Table 1, page 35; "The ERG does not agree that there is a discrepancy between the expected MA and the population in PRIMA."	The Company asks for these statements to be reconsidered given the justification provided in the 'Justification for amendment' column. Please amend the text as follows: "The ERG considers that the ITT population in PRIMA is representative of the MA population for niraparib but notes that there is a discrepancy between the trial data and the MA population which can be corrected for. PRIMA data can be used to conduct analyses to extrapolate outcomes in order to be more representative of the MA population."	The Company does not consider the UK MA population to be fully captured by the ITT population given the exclusion of Stage III patients with NVRD following PDS; notably, this group of patients are considered by clinicians to have the most favourable prognosis, which is noted by the ERG report. The Company will explore alternative methodologies suggested by the ERG to utilise the PRIMA data to adjust for this discrepancy. Patients selected for PDS are biased towards those with lower stage, lower disease burden, and who have improved fitness and reduced co-morbidities, and therefore they are expected to have a better prognosis.[1] The exclusion of this specific group is important to the PRIMA ITT results.	Not a factual error, no change needed.

Table 15, page 79; "The ERG agrees but notes that PRIMA includes a substantial proportion of patients with stage III NVRD and thus **the population of PRIMA is representative of the full MA population**." Paragraph 3, page 87; "The ERG's view is that **PRIMA is representative of the MA population** as it includes patients with NVRD after PDS or IDS (47% of the entire ITT population in PRIMA had NVRD). Given that the company's rationale for generating an MA population is mainly based on the fact that NVRD patients have better outcomes than patients with VRD (section 3.4), the ERG considers that PRIMA does not only provide sufficient evidence to address this issue, but is also the most robust source of evidence available to estimate the cost-effectiveness of niraparib vs RS." Paragraph 1, page 141;			

"The ERG's view is that **PRIMA is representative of the MA population** as it includes patients with NVRD after PDS or IDS (47% of the entire ITT population in PRIMA had NVRD)."			
Paragraph 4, page 23; "Therefore, based on the opinion of the ERG's clinical experts, **the prognosis of patients with stage III NVRD after PDS and IDS can be considered equivalent**." Paragraph 1, page 40; "Based on the opinion of the ERG's clinical experts, **the prognosis of patients with stage III NVRD after PDS can be considered equivalent to patients with stage III NVRD after IDS** (for which data are available in PRIMA)." Paragraph 1, page 61; "As highlighted in the ESMO guidelines[10] and as shown in a study by Vergote et al., there is no significant difference in PFS and OS based on type of surgery, i.e. PDS or IDS.	The Company asks for these statements to be reconsidered and removed given the clinical evidence discussed as part of the justification. The Company respectfully disagrees that the prognosis of patients with Stage III NVRD after PDS can be considered equivalent to patients with Stage III NVRD after IDS. The company provides clinical evidence to support this. The ERG report states on page 66 "The ERG agrees that the cohort of patients excluded from PRIMA is expected to do better in terms of PFS and OS than the	The Company disagrees that the prognosis for patients undergoing PDS or IDS is the same; this theory is not supported by clinical evidence and there is no consensus agreement amongst expert clinicians. There is an inherent selection bias within the two groups; patients with a higher disease burden are often more likely to undergo NACT to minimise the tumour size before IDS, and so the cohort of patients selected for IDS is more advanced than those selected for PDS by selection. Conversely, patients with a better prognosis, for example smaller tumour size or reduced spread, are better candidates for PDS and are therefore expected to have an improved outcome after surgery. Vergote et al. studied outcomes in patients with relatively advanced disease compared to those who	Not a factual error, no change needed.

However, the ERG acknowledge that the outcomes may differ between the subgroup of patients with NVRD after IDS and PDS but notes that there is limited evidence to support this. Though, **based on the opinion of the ERG's clinical experts, the prognosis of patients with stage III NVRD after PDS can be considered equivalent to patients with stage III NVRD after IDS (for which data are available in PRIMA), and the PRIMA ITT population adequately covers the full MA population**." Paragraph 1, page 67; "Based on the opinion of the ERG's clinical experts, **it is reasonable to assume that the prognosis of patients with stage III NVRD after PDS is equivalent to patients with stage III NVRD after IDS.** " Paragraph 3, page 77; "Based on the opinion of the ERG's clinical experts, **the prognosis of patients with stage III NVRD after PDS can be considered equivalent to patients with stage III NVRD after IDS**."	PRIMA population or the patient population in UK clinical practice" and on page 67 that "the ERG acknowledge that the outcomes may differ between the subgroup of patients with NVRD after IDS and PDS with NVRD potentially being a stronger prognostic factor for patients who have PDS than for those who have IDS, but notes that there is limited evidence to support this". These statements are not in line with the statement on page 62 and highlight the confusion that may be caused by proposing that the prognosis is equivalent for patients with NVRD after PDS and IDS.	would typically, in UK clinical practice, be selected for PDS. Patients in the trial had bulky Stage IIIC or Stage IV disease, excluding Stage IIIA or stage IIIB.[2] The authors note that "**complete resection of all macroscopic disease at primary debulking surgery has been shown to be the single most important independent prognostic factor in advanced ovarian carcinoma**," thus distinguishing the prognostic impact of PDS from IDS. The authors go on to state "the importance of this prognostic factor was confirmed by the results of the multivariate analyses and the survival analyses according to the extent of residual tumor after both primary and interval debulking surgery". Vergote et al. (2010) also note that "a potential drawback of neoadjuvant chemotherapy followed by debulking surgery is that the occurrence of fibrosis after chemotherapy may make complete resection of macroscopic disease more difficult."[2], thus reducing the	

Paragraph 3, page 80; "Therefore, based on the opinion of the ERG's clinical experts, **the prognosis of patients with stage III NVRD after PDS and IDS can be considered equivalent.**"		likelihood of achieving complete macroscopic resection, which has been noted as the strongest prognostic indicator. Therefore, earlier stage patients equally suited to PDS and IDS are less likely to achieve NVRD with IDS, and consequently this group would be expected to achieve poorer long-term survival outcomes compared to patients undergoing PDS. The authors also make clear that PDS should remain the standard of care for patients with Stage IIIB OC, "The standard of care for women with Stage IIIB or earlier-stage epithelial ovarian cancer — a group with a better prognosis than the current study population — remains primary cytoreductive surgery." It is therefore expected that the ITT population in PRIMA contained only a very small minority (5%, Stage IIIA or stage IIIB) of this patient group, for whom PDS would confer the most positive prognosis. The underrepresentation of this group within PRIMA necessitates an adjustment of the ITT results to capture the improved outcomes of this cohort within the model.	

		The ESMO guidelines referenced by the ERG, authored by Lederman et al. in 2010, have been supplemented with consensus recommendations, published in 2019 by Colombo et al.[1,3] These most recent recommendations advise PDS, stating that "if resection of all macroscopic disease can be obtained based on pre-operative staging with an acceptable operative morbidity, upfront debulking surgery (UDS) [PDS] followed by carboplatin/paclitaxel is standard of care" and that as the study by Verdote et al. "contained low percentages of patients with complete UDS (<20%), the Trial on Radical Upfront Surgical Therapy (TRUST), including a qualification process for participating centres, is currently ongoing." In a recent pooled analysis of these trials, published in 2018, Verdote at al. state "for patients with FIGO Stage IIIB or lower disease, **there is no evidence to support the use of neoadjuvant chemotherapy instead of primary surgery**." [4] Additionally, PDS is recommended	

		for patients with a lower disease burden, stating “women with FIGO Stage IIIC disease with extrapelvic metastases smaller than 5 cm had a significantly better progression-free survival with upfront debulking surgery than with neoadjuvant chemotherapy, so these patients should first be considered for primary debulking surgery.” [4] Additionally, analysis presented at the Society of Gynecological Cancer in 2020 from the PAOLA-1 trial evaluated the efficacy of olaparib plus bevacizumab by timing of surgery and presence of residual tumour after surgery.[5] Unlike the trials conducted by Vergote et al and Kehoe et al. (CHORUS)[2,6], PAOLA-1 included FIGO Stage IIIA–IV (compared to only Stage IIIC – IV)[7]; this is more representative of the MA population in the CS. Patients with NVRD following PDS achieved a longer PFS compared to those with NVRD following IDS (placebo median PFS 22.1 versus 17.7 month respectively). The HRs for treatment with olaparib plus bevacizumab against placebo plus bevacizumab was 0.47 (95% CI 0.29 to 0.75) and	

		0.61 (95% CI 0.41–0.91) for NVRD after PDS compared to NVRD after IDS, respectively. This provides further clinical evidence of the improved outcomes and prognosis of patients with NVRD after PDS compared to IDS. It would, therefore, be inappropriate to equate the prognoses of both surgical interventions and outcomes when modelling the MA population for niraparib. The ESMO-ESGO recommendations and clinical evidence demonstrate the critical differences in patient characteristics and selection criteria for PDS and IDS. There is no strong evidence to support the theory that patients with Stage III NVRD after PDS achieve the same outcomes as Stage III NVRD after IDS. The Company maintains that modelling Stage III NVRD after PDS patients as a distinct cohort necessary to reflect this subgroup's improved outcomes given the subgroup's exclusion from the PRIMA ITT population.	

Paragraph 2, page 67; "As it is reasonable to assume that the prognostic benefit of NVRD between IDS and PDS is similar, the ERG recommends the company take advantage of the significant proportion of patients in PRIMA with stage III NVRD after IDS (■% of the ITT population, Table 9) to adjust the ITT results to the patient population likely to be treated in the UK. The ERG suggests the company reweight the results of patients with stage III NVRD after IDS in PRIMA to account for the patients with stage III NVRD after PDS, which were excluded from the trial."	The Company asks the ERG to reconsider and amend the text as follows: "As it is reasonable to assume that the prognostic benefit of **stage III** NVRD **after** IDS and PDS is **superior to stage III VRD**, the ERG recommends the company take advantage of the significant proportion of patients in PRIMA with stage III NVRD after IDS (■% of the ITT population, Table 9) to adjust the ITT results to the patient population likely to be treated in the UK. The ERG suggests the company reweight the results of patients with stage III NVRD after IDS in PRIMA to account for the patients with stage III NVRD after PDS, which were excluded from the trial."	The Company accepts that the prognostic benefit of Stage III NVRD following PDS may be similar to, although not the same as, the NVRD in Stage III patients after IDS. The Company thanks the ERG for their suggestions regarding the potential methods to adjust the PRIMA ITT data; the Company will explore the feasibility of these methods further before the technical engagement meeting.	
Paragraph 2, page 62;	The Company asks the ERG to reconsider and amend as follows:	The objective of the targeted literature review was to determine the OS and PFS associated with no residual disease among women with	Not a factual error, no change needed.

"The ERG also notes that, based on the identified studies *[identified through the TLR]*, the better prognosis of patients with NVRD than for patients with VRD seems to be irrespective of patients receiving PDS or IDS."	"The ERG also notes that while the evidence obtained though the targeted literature review did not point to a superior prognosis for either PDS or IDS, the review did not seek to answer this research question."	advanced (Stage III/IV) ovarian cancer receiving first-line treatment; the review did not intend to assess, or look for, differences in survival outcomes for PDS compared to IDS.	
PRIMA ITT clinical data			
Paragraph 3, page 63; "In PRIMA [redacted]% had NVRD irrespective of stage of disease and [redacted]% of patients had stage III disease and NVRD after IDS."	Please amend the text as follows: "In the PRIMA ITT population, [redacted]% had NVRD irrespective of stage of disease and [redacted]% of patients had Stage III disease and NVRD after IDS."	Transcription or calculation error	Thank you, this has been corrected.
Paragraph 1, page 66; "In addition, due to additional differences in inclusion and exclusion criteria between PRIMA and the PRIMA simulated cohort from the Edinburgh database, the PRIMA simulated cohort had more severe disease than the PRIMA population. For these	The Company asks the ERG to reconsider and remove this statement or amend the text as follows: "The survival for the PRIMA ITT population is expected to be improved compared to the PRIMA-simulated cohort."	PRIMA ITT population excludes the patient group with the most favourable survival prognoses: Stage III with NVRD after PDS. In light of the above, and considering that the Edinburgh analysis provides a conservative approach, it would be difficult to draw conclusions where	Not a factual error, no change needed.

reasons **the survival for the PRIMA population is expected to be better than the survival for the MA simulated and the PRIMA simulated cohort**."		each population's survival would lie in relation to each other.	
Estimation of proportion of stage III patients with NVRD			
Paragraph 1, page 64; "The ERG's clinical experts advise that the proportion of patients with stage III and NVRD is likely to be closer to 50-60% in the UK, but highlight that the proportion of patients with NVRD after surgery varies across UK practice and **basing this estimate on one small region in the UK may therefore not be representative of the surgical outcomes seen across the country**."	The Company asks the ERG to reconsider this assumption and amend the text to acknowledge the following: "The ERG's clinical experts advise that the proportion of patients with stage III and NVRD is likely to be closer to 50-60% in the UK, but highlight that the proportion of patients with NVRD after surgery varies across UK practice and. **The estimate of [redacted]% as base case in the CS was based upon KOL feedback alongside the PAOLA trial."**	The Company would like to highlight that the Edinburgh database analysis was only one source that was considered for this input; expert opinion was also sought which confirmed the variability of this outcome between different centres within the UK (25% - 40%).[8] Given the variability, the lower end of the range was used to make a conservative assumption when forming the base case. Sensitivity analyses up to [redacted]% are explored in the CS, which is line with the ERG's range provided. The Company agrees that surgical outcomes vary geographically and a conservative estimate of [redacted]% was made based on feedback from expert clinicians, rather than one source; a range of 25%-40% of patients with Stage III NVRD	Thank you for your comment. The ERG has added further detail to clarify that the clinical experts advising the company estimated the proportion to be 25-40%. No other changes required, the suggested amendment to the text is not addressing a factual inaccuracy.

		following PDS was given. This range was explored as a sensitivity analysis in the CS. The Company agrees that the proportion of patients with Stage III NVRD following PDS and IDS is expected to be in between 50-60%.	
Targeted literature review			
Paragraph 2, page 66; "The ERG notes that the company did not conduct a systematic, or a targeted literature review, in order to identify other relevant sources to inform the extrapolation to the MA population."	Please amend the text as follows: "The ERG notes that the company did not conduct a systematic literature review in order to identify other relevant sources to inform the extrapolation to the MA population, although a targeted literature review was conducted to determine the impact of NVRD in first-line surgery to inform the extrapolation to the MA population.	A targeted literature review was conducted to inform the extrapolation to the MA population; the objective was to determine the OS and PFS associated with patients with advanced (Stage III/IV) OC receiving first-line treatment in the US and Europe who had NVRD after PCS, and to compare these to outcomes in patients with VRD. These data were assessed to determine generalisability of the results to the MA population and the PRIMA ITT population, and to estimate a HR for 'NVRD effect' used to extrapolate the PRIMA ITT results to the wider MA population.	Not a factual error, no change needed.
Paragraph 2, page 66;	The Company requests clarification on this discrepancy to provide a response.		Not a factual error, no change needed.

“The ERG is also concerned about the discrepancy between the data reported in the clinical and economic sections of the CS, and the use of the simulated PRIMA cohort to inform the extrapolation, curve choice and cure threshold for OS in the economic model.”			
Paragraph 4, page 87; "Furthermore, the ERG notes that the company’s approach of estimating treatment effects for patents with Stage III NVRD after PDS vs the patients in PAOLA-1 who had the same characteristics as the ITT PRIMA population lacks robustness. The company’s approach effectively estimates outcomes for NVRD stage III after PDS vs the simulated PRIMA ITT in PAOLA-1 (which includes 34% of NVRD patients), therefore confounding the analysis of NVRD vs VRD outcomes."	Please include the following statement: "It should be noted, however, that the PAOLA-1 KM data population included Stage IV patients, Stage III patients with PDS and no residual disease and Stage III patients with IDS either with or without visible residual disease. This was compared with Stage III patients with PDS and NVRD (the population not included in the PRIMA trial). While patients were still included in the 'simulated-PRIMA' population who were NVRD in Stage III, the analysis still resulted in a substantial and statistically significant improvement in outcomes observed in the Stage III PDS NVRD group. The company	While the PAOLA-1 and PRIMA populations inherently differ, PAOLA-1 can give a reasonable estimation of the interactions between a population consisting of Stage III PDS patients with NVRD and all other patients with Stage III and IV ovarian cancer. The proportion of IDS patients in the PRIMA and the PAOLA-1 ‘simulated PRIMA’ populations have similar proportions of IDS, IDS with NVRD and PDS with residuals disease. It should therefore be reasonable to estimate the relative relationship between the Stage III PDS NVRD and PRIMA by using the PAOLA-1 dataset.	Not a factual error, no change needed.

	believe this to be due to the better prognosis of Stage III PDS NVRD patients, above that of Stage III IDS NVRD patients as highlighted above."		

Issue 2 Treatment effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 2, page 31; "When it is assumed that niraparib and RS have the same OS (HR of 1), the ITT ICER amounts to £950,200 per QALY gained. Given that the exploratory ICERs generated by the ERG ranged from £38,252 to £950,200; the ERG concludes that without having more mature OS data from PRIMA it is not possible to make inferences on the survival benefits of niraparib without a paramount level of uncertainty." Paragraph 3, page 140; "When it is assumed that niraparib and RS have the same OS, the ITT ICER amounts to £950,200 per	The Company ask that the scenario of no OS benefit for niraparib is either removed, or that the scenario is at a minimum identified as an extreme one and therefore the range of ICERs referenced throughout the report are updated to be reflective of clinically plausible scenarios carried out by the ERG.	Although the extent of benefit translating from PFS to OS holds some degree of uncertainty, the scenario that niraparib can be seen to hold no benefit at all to patient survival after substantial PFS gain (median PFS gain versus RS: 5.6 months in the PRIMA ITT population[9]) is an extreme and implausible scenario. In TA598[10], a trial with similar characteristics in terms of immaturity of OS, various references were made to a PFS gain having at least some indication of extending overall survival;	Not a factual error, no change needed.

QALY gained. The ERG concludes that without having more mature OS data from PRIMA it is not possible to make inferences on the survival benefits of niraparib without a paramount level of uncertainty." Paragraph 1, page 142; "The exploratory ICERs generated by the ERG ranged from £38,252 to £950,200. The ERG concludes that without having more mature OS data from PRIMA it is not possible to make inferences on the survival benefits of niraparib without a paramount level of uncertainty." Paragraph 2, page 138; "In addition to the changes listed above, the ERG considered three different sets of combined scenarios: 1. Use of a PFS to OS ratio of 1:0.66 as per TA598; 2. Use of a PFS to OS ratio of 1:1; 3. Use of a HR between RS OS and niraparib OS of 1."		• "If the effect of a new drug treatment for ovarian cancer is to extend median PFS by x months, then it is reasonable to estimate that the treatment will also extend median overall survival by x months." • "Given the magnitude of the effect on PFS, it would be reasonable to expect that olaparib will extend life, but the size of that effect is uncertain." • "The committee concluded that the extent to which the progression-free survival benefit will translate into overall-survival benefit is uncertain, but it is expected that treatment with olaparib will extend life." Additionally, in the recent NICE appraisal of niraparib (TA528[11]), the Committee accepted that the PFS benefit observed with niraparib in platinum-sensitive relapsed OC setting will translate to an OS benefit at a ratio of 1:≥1 (i.e. 1 month of mean incremental PFS translating to at least 1 month	

		of mean incremental OS benefit).[12] Clinical insight suggests that at least similar, but more likely a better relationship will be observed in the first line setting compared to the relapsed setting[13]. For reference, the table below highlights the various hazard ratios applied to the RS OS to estimate niraparib OS in the model at different applied PFS:OS ratios. Please note that the PFS:OS ratio of 1:1 corresponds to a hazard ratio of 0.74, which is less than that of the interim PRIMA results. Additionally, by applying a hazard ratio identical to that of PRIMA (0.70), the corresponding PFS:OS ratio is above 1:1 (1:1.13). The ERG's scenario 3 of a HR of 1 between RS OS and niraparib OS, is not included in the table for the previously described reasons.	

Description (LTR assumed)	**PFS:OS ratio**	**ITT - Hazard ratio applied to RS OS**

<table>
<tr>
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<table>
<tr><td>Original base-case PFS:OS ratio submitted</td><td>1:2</td><td>[redacted]</td></tr>
<tr><td>ITT - Hazard ratio from PRIMA trial</td><td>1:1.13</td><td>0.70</td></tr>
<tr><td>ERG proposed scenario 2</td><td>1:1</td><td>[redacted]</td></tr>
<tr><td>ERG proposed scenario 1</td><td>1:0.66</td><td>[redacted]</td></tr>
</table>
</td>
<td></td>
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<tr>
<td>Paragraph 2, page 138;

“In addition to the changes listed above, the ERG considered three different sets of combined scenarios:

1. Use of a PFS to OS ratio of 1:0.66 as per TA598;
2. Use of a PFS to OS ratio of 1:1;
3. Use of a HR between RS OS and niraparib OS of 1.”</td>
<td>The Company ask that the scenario of a PFS:OS relationship of 1:0.66 be removed as a plausible outcome, as it misaligns with the past evidence and research around the PFS:OS relationship.</td>
<td>The scenario in this section is based on the analysis carried out in TA598. In TA598, a surrogate outcome PFS2 was used to predict the PFS:OS relationship and the resulting relationship was described by the manufacturer as being ‘highly conservative when compared with estimates from the literature and previous NICE appraisals (1:>1)’. This relationship is only mentioned after the technical engagement phase and there is very limited detail presented around what it relates to and how it was calculated. The Company would like to ask for</td>
<td>Not a factual error, no change needed.

The rationale for the ERG’s exploratory analysis can be found in Section 3.2.4.3.2 of the ERG report.</td>
</tr>
</table>

		clarification from the ERG around the underlying assumptions and method of calculation to get to this PFS:OS relationship. Additionally, the scenario of 1:0.66 can be seen to be an unjustified scenario since a relationship of 1:1 has previously been accepted as a minimum. This is highlighted in the TA598 and TA528 submissions in the above response[10,11].	
Paragraph 3, page 141; “Furthermore, the ERG does not consider that enough robust evidence exists to substantiate the use of PFS as a surrogate measure of OS in the OC setting. There is, however, some literature suggesting that if the effect of a treatment for OC extends PFS by x months, it is reasonable to estimate that the treatment will also extend OS by x months, meaning that, “the magnitude of the improvement in PFS is the magnitude of the improvement in OS. *[Therefore],* PFS is simply a measure of a drug's effect on tumour growth while it is administered and is not a surrogate for OS”.”	The Company ask that this paragraph would be removed from the report, or evidence of PFS being used in trials for decision making in the past (TA528 and TA528[10,11]) be referenced as a precedent.	The method of using PFS as a surrogate measure OS has been previously accepted by NICE committees in HTA appraisal conducted in ovarian cancer (TA528 and TA598[10,11]). The relationships derived during this appraisal are based on long-term clinical evidence in ovarian cancer[14].	Not a factual error, no change needed.
Paragraph 4, page 25; "Most importantly, the results generated from the	The modelled HRs for the ITT and MA population are [redacted] and [redacted], respectively. The MA OS HR should not be directly compared to the PRIMA OS HR. The	The OS hazard ratio of [redacted] is associated with the MA population, however for the ITT population the hazard ratio for a 1:2 PFS:OS	The ERG thanks the company for identifying the

company's approach to estimating an OS curve for niraparib are inconsistent with the OS data observed in PRIMA. Firstly, the HR of [redacted] used by the company to generate the 1:2 ΔPFS:ΔOS relationship suggests nearly twice as much of a relative treatment effect for niraparib vs RS than that observed in PRIMA – HR of 0.70 (95% CI: 0.44 to 1.11)." Paragraph 1, page 94; "In their base case analysis, the company used a 1:2 ratio with the justification that the latter is a more conservative choice given that the 1:3 ratio was based on a different trial and different data. The company also conducted a range of scenario analyses to test different ratios (1:1, 1:1.25, 1:1.5, 1:1.75, 1:2.5, and 1:3). The hazard ratio (HR) estimated by the company between RS OS and niraparib OS to generate the ΔPFS:ΔOS relationship of 1:2 amounts to [redacted] and guarantees that: Niraparib mean OS = (RS mean OS + [Mean PFS difference x 2]) The company then applied the 0.38 HR to the RS OS fitted curve in order to estimate the niraparib OS curve in the model. " Paragraph 2, page 104; "The niraparib KM data were deemed too immature	Company request that report is updated to reflect this. Additionally, please adjust comparisons between the model ΔPFS:ΔOS hazard ratio and the PRIMA hazard ratio.	relationship was [redacted]. Throughout the report the hazard ratio of [redacted] is used when referencing the ITT population, and incorrect comparisons between the hazard ratio of [redacted] (modelled MA population) and the PRIMA hazard ratio of 0.7 are made.	error. Changes have been made in the ERG report accordingly.

to use in a fitting exercise as discussed in section 4.2.4. In order to estimate the niraparib OS curve, the company applied a HR of [redacted] to the OS RS curve as to generate the 1:2 ΔPFS:ΔOS relationship." Paragraph 4, page 105; "Most importantly, the results generated from the company's approach are inconsistent with the OS data observed in PRIMA. Firstly, the HR of [redacted] used by the company to generate the 1:2 ΔPFS:ΔOS relationship [redacted] for niraparib vs RS than that observed in PRIMA - HR of 0.70 (95% CI 0.44, 1.11)." Paragraph 2, page 109; "The restricted mean PFS difference between the two treatments at the data cut-off point of PRIMA is therefore [redacted] months, which compares to an estimated mean PFS gain of [redacted] months in the company's base case (and a resulting OS HR of [redacted] for niraparib vs RS)."			
Paragraph 2, page 140; "However, given the lack of maturity and statistical significance of the HR in PRIMA, and the shape of the OS curves (see section 4.2.6.1.1), it is possible	Please update this sentence to: "However, given the lack of maturity and statistical significance of the HR in PRIMA, and the shape of the OS curves (see	It is equally possible that the OS benefit would be much larger, and this should be included to ensure balance of the statement.	The ERG has amended the text which now reads:

that the survival benefit with niraparib is much smaller."	section 4.2.6.1.1), it is possible that the survival benefit with niraparib is either smaller **or larger**."		"However, given the lack of maturity and statistical significance of the HR in PRIMA, and the shape of the OS curves (see section 4.2.6.1.1), it is possible that the survival benefit with niraparib is much smaller. Given the lack of maturity of the data, it is also possible that the survival benefit of niraparib is higher than that observed in the PRIMA trial."
Table 21, page 103; Table 21 description of CHORUS trial data appears	Please amend Table 21 with the data as follows:	Median PFS for placebo was 10.7 months for the primary-surgery group, not 12 months, which	Thank you for your comment, this

incorrect. Median (months) is said to be **12** months for RS, while at 1 year the patients progression-free is 44%.	<table><tr><td></td><td>Median (months)</td></tr><tr><td>CHORUS*</td><td>**10.7**</td></tr></table>	explains why the proportion progression-free at 12 months was 44%.	has been amended.
Paragraph 6, page 110; "After 3 years in the model, [redacted]% of the patients who had not discontinued treatment ([redacted]% in the company's Weibull curve) were assumed to carry on treatment and thus, continue to follow the Weibull curve tail."	Please amend this sentence to: "After 3 years in the model, [redacted]% of the patients who had not discontinued treatment ([redacted] in the company's Weibull curve) were assumed to carry on treatment and thus, continue to follow the Weibull curve tail."	This sentence reads that [redacted]% of patients continue treatment after 3 years, when it should be clarified that it is [redacted]% of the [redacted]% which continue treatment.	Changes have been made to the text as requested by the company.

Issue 3 Clinical data corrections

Description of problem	Description of proposed amendment	Justification for amendment	
Paragraph 2, page 27; "In PRIMA, there were 232 progression events in the niraparib arm and 154 progression events in the RS arm. When compared to the number of patients receiving 2L chemotherapy, the proportion of patients who progressed who also received subsequent chemotherapy in PRIMA amount to [redacted]% and [redacted]% for niraparib and RS, respectively. **The ERG is**	The Company asked the ERG to reconsider this opinion and requests this statement be removed given the justification provided in the 'Justification for amendment' column.	In PRIMA, there were 232 progression events in the niraparib arm and 155 progression events in the RS arm. Data presented in Table 14.2.6.1a from the CSR, 198 and 125 patients received at least one line of follow-up anti-cancer therapy in the niraparib and placebo populations respectively. Therefore, 85% and 81% of the patients experiencing a	The ERG thanks the company for highlighting this mistake. The numbers have been amended in the report.

concerned that the number of patients receiving subsequent treatments in PRIMA is lower than what is expected in UK practice and lower than what has been reported in other trials for the same disease area."		progression event received at least one subsequent treatment in the niraparib and placebo populations respectively Furthermore, the Company would like to highlight the data on second-line treatment from PRIMA are currently very immature.	
Paragraph 1, page 45; "This was assessed by blinded independent central review (BICR), defined either by radiological assessment as per RECIST v1.1 or by clinical criteria. The ERG considers this to be appropriate. Clinical criteria were defined as follows: • CA-125 progression according to Gynecologic Cancer Intergroup (GCIG)-criteria AND additional diagnostic tests (e.g. histology/cytology, ultrasound techniques, endoscopy, positron emission tomography [PET]) which may identify new lesions or determine existing lesions qualify for unequivocal progressed disease (PD); • CA-125 progression according to GCIG criteria AND definitive	Please amend the text as follows for clarification: "defined either by radiological assessment as per RECIST v1.1 or by clinical criteria. The ERG considers this to be appropriate. Clinical criteria were defined as **either one of the following**: • CA-125 progression according to Gynecologic Cancer Intergroup (GCIG)-criteria AND additional diagnostic tests (e.g. histology/cytology, ultrasound techniques, endoscopy, positron emission tomography [PET]) which may	Additional text suggested to clarify that only one of the criteria listed must be met to be considered progressed	Thank you, this has been amended in the report.

clinical signs and symptoms of PD unrelated to non-malignant or iatrogenic causes, such as: [1] intractable cancer-related pain; [2] malignant bowel obstruction/worsening dysfunction or [3] unequivocal symptomatic worsening of ascites or pleural effusion."	identify new lesions or determine existing lesions qualify for unequivocal progressed disease (PD); • CA-125 progression according to GCIG criteria AND definitive clinical signs and symptoms of PD unrelated to non-malignant or iatrogenic causes, such as: [1] intractable cancer-related pain; [2] malignant bowel obstruction/worsening dysfunction or [3] unequivocal symptomatic worsening of ascites or pleural effusion."		
Paragraph 2, page 49; "The ERG notes that there is a slight discrepancy around the exact number of patients enrolled on fixed and individualised dose between the data provided at clarification and data from the CSR."	The Company requests this statement be removed given the justification provided.	The values referred to by the ERG relate to the SAF population, whilst the data provided at clarification concerns the randomised patient population which was taken from Table 14 of the CSR.	Thank you, this has been amended in the report.

Paragraph 1, page 56,; “Nonetheless, mean dose between fixed and individualised niraparib differed only slightly at [redacted] mg per day for fixed dosing (SD [redacted]), and [redacted] mg per day for individualised (SD [redacted]).”	Please amend the text as follows: “Nonetheless, mean dose between fixed and individualised niraparib differed only slightly at [redacted] mg per day for fixed dosing (SD [redacted]), and [redacted] mg per day for individualised (SD [redacted]).”	Typographical error. The values presented by the ERG concern the HRD positive subgroup, not the ITT population. Data taken from Table 14.3.5.13b on page 13,471 of CSR.	Thank you, this has been amended in the report.
Paragraph 2, page 57; “In the niraparib group, [redacted] patients ([redacted]) had at least one study drug interruption due to AEs versus [redacted] patients [redacted] in the placebo group, and [redacted] patients ([redacted]%) in the niraparib group and [redacted] patients ([redacted]%) in the placebo group had a dose reduction.”	Please amend the text as follows: “In the niraparib group, 385 patients (79.5%) had at least one study drug interruption due to AEs versus **44** patients (**18**.**0**%) in the placebo group and [redacted] patients ([redacted]%) in the niraparib group and [redacted] patients ([redacted]%) in the placebo group had a dose reduction.”	Typographical error. 23.8% of placebo patients had a dose interruption for any reason (not necessarily due to AE). Data taken from Table 33 of CSR and published table in PRIMA publication[9]. Dose interruption by treatment arm in ITT is not CIC and can be unmarked.	Thank you, this has been amended although the ERG notes that these data were taken from the company submission (page 63, paragraph 1).
Paragraph 2, page 57; “**Error! Reference source not found.** highlights the proportion of participants on each dose of niraparib throughout the trial, whereby [redacted] of participants were on the maximum 300mg dose by month 12, and [redacted] of participants were receiving 200mg or 100mg.“	Please amend the text as follows: “**Error! Reference source not found.** highlights the proportion of participants on each dose of niraparib throughout the trial, whereby [redacted] of participants were on the maximum 300mg	Typographical error. Alternatively, “[redacted]% of participants were receiving 100 mg.”	Thank you, this has been amended in the report.

	dose by month 12, and [redacted] of participants were receiving 200mg or 100mg."		
Paragraph 1, page 56; "The ERG notes that the difference between median time in the study between fixed and individualised dosing should be similar to the difference in median actual treatment exposure, given that this has been adjusted for dose interruptions. The implications of this discrepancy are unclear."	Please amend the text as follows: "The ERG notes that the difference between median time in the study between fixed and individualised dosing should be similar to the difference in median actual treatment exposure, given that this has been adjusted for dose interruptions. The implications of this discrepancy are unclear, **but the discrepancy observed will likely be resolved as the data matures**."	PRIMA trial originally initiated on the FSD of 300mg. Two thirds into the trial recruitment, the starting dose was adjusted to allow patients to start on an individualised starting dose (ISD), therefore the remaining one third of patients were allocated to this regimen. Due to the timings of introducing FSD versus ISD, patients have been on study for longer for the FSD than the ISD. The Company believes that the results will become similar in the two groups as the data matures.	Not a factual error, no change needed.
Paragraph 3, page 63; "In PRIMA 47.6% had NVRD irrespective of stage of disease and [redacted]% of patients had stage III disease and NVRD after IDS. In the simulated-PRIMA cohort, which only included stage IV NVRD**,** only [redacted]% had NVRD after cytoreductive surgery and in the MA simulated cohort, which included	Please amend the text as follows: "In PRIMA **46.5**% had NVRD irrespective of stage of disease and [redacted]% of patients had stage III disease and NVRD after IDS. In the simulated-PRIMA cohort, which only included stage IV NVRD**,** only [redacted]% had NVRD after cytoreductive surgery and	Typographical or calculation error.	Thank you, this has been amended in the report.

patients with stage III NVRD, only 25.4% had NVRD irrespective of stage."	in the MA simulated cohort, which included patients with stage III NVRD, only [redacted] had NVRD irrespective of stage."		
Paragraph 2, page 20 and paragraph 2, page 79; "That is, the ITT analysis may overestimate the efficacy of niraparib expected in clinical practice as the proportion of patients starting on the 300 mg dose was higher in the trial than would be expected in clinical practice, where all patients will be offered individualised dosing"	The Company requests this statement be removed given the justification provided.	Inappropriate assumption. The efficacy data collected within the PRIMA trial reflects the lower dosages of 200 mg or 100 mg that the majority of patients within the trial received. The majority of patients ([redacted]%) treated with niraparib experienced a dose reduction, often early on within treatment. By month 12 [redacted]% of patients were treated with either 200mg or 100 mg niraparib, therefore the efficacy results are reflective of the lower dosages used in practice. A post-hoc analysis showed no significant difference in PFS between the fixed dose versus the individualised dose cohorts[15].	Not a factual error, no change needed.
Paragraph 2, page 64; "However, in section B.3.3 of the CS the company indicates that long-term PFS data	Table 8 reports the survival outcomes of the MA and simulated-PRIMA cohorts from the University of Edinburgh	While definition of TFST differs from that of PFS, clinicians advised that the calculation of TFST from the Edinburgh Database closely	Thank you, this has been amended in the report.

were not available and therefore long-term data for TFST were used as a proxy to predict PFS in the economic model; at 5 and 10 years the data for the simulated PRIMA cohort show [redacted] and [redacted] of the patients are progression-free (have not started their first subsequent therapy), respectively. It is unclear if the estimates of median PFS reported in **Error! Reference source not found.** are TFST rather than PFS."	Ovarian Cancer database. Please note that TFST was used for the median PFS reported in Table 8. Additionally, please note that it was advised by clinicians that in absence of PFS data, TFST was a suitable proxy.	aligned with the PFS calculation in PRIMA.	
Paragraph 2, page 66; "The ERG is also concerned about the discrepancy between the data reported in the clinical and economic sections of the CS, and the use of the simulated PRIMA cohort to inform the extrapolation, curve choice and cure threshold for OS in the economic model."	Please amend this sentence to be more specific around the concern over discrepancies between the economic and clinical sections of the CS.	In order to address these concerns appropriately we would ask the discrepancies be made clear.	Not a factual inaccuracy at the time of writing.
Paragraph 2, page 80; "However, PHs are unlikely to hold and therefore the resulting HR with accompanying 95% CI is difficult to interpret and potentially misleading."	The Company request that this sentence is amended to state why the PH assumption is unlikely to hold.	To add balance and transparency to the statement.	Not a factual error, no change needed.

Issue 4 Interventions and comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 19, page 90; Niraparib dose received in PRIMA and included in the company's base case model. Table includes a "modelled dose" column, which includes a weighted average (mg) of the three doses of 100mg, 200mg and 300mg by the distribution of these doses across patients.	Removal of this column or updating this column to represent the average cost per patient in PRIMA.	The 'modelled dose' column inaccurately demonstrates how the proportion of doses in PRIMA were calculated in the model. In the CEM, the varying doses were not weighted, they were costed individually, and the resulting cost was weighted against the proportion of patients receiving each dose.	The column has been relabeled as suggested.

Issue 5 Modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 2, page 95; "Nonetheless, the ERG notes that PFS2 data were [redacted]% mature at data cut-off, which compares to [redacted]% maturity for the OS RS KM data from PRIMA, which the company has used to fit OS curves."	The Company asks the ERG to reconsider this opinion and requests this statement be removed given the justification provided. Please note that while the RS OS is immature, the only reason the RS OS data could be used at its current level of immaturity in the analysis is because there was long-term real-world evidence (RWE) that could be	Clarification of the chosen method of using RS OS in the analysis. RS data from PRIMA was used, although it is immature, as the curve of choice could be validated against RWE from the Edinburgh database.	Not a factual error, no change required.

Paragraph 3, page 28 and Paragraph 2, page 105; "During the clarification stage, the ERG requested that the company fitted parametric models to the niraparib OS KM data from PRIMA. The company replied that the niraparib KM data in PRIMA are too immature (10%) and therefore inappropriate to fit parametric models. However, the ERG notes that the RS KM data in PRIMA are equally immature (■%) and the company used these data to fit a log-logistic curve to estimate RS OS in the model. **The company's approach and justification are, therefore, highly inconsistent**."	used in order to validate the chosen extrapolation to estimate RS OS. With the niraparib data as well as the PFS-2 data for both niraparib and routine surveillance, there was no such long-term evidence that could be used to validate the extrapolations.		
Paragraph 5, page 28; "The ERG acknowledges that the immaturity of the OS KM data could potentially lead to modelling issues such as obtaining valid long-term survival predictions. **Nonetheless, there are options to make survival curves flexible and adjust long-term survival estimates to achieve clinically valid tails, without having to use HRs, and thus assuming a constant survival benefit between treatment arms**."	The Company asks the ERG to reconsider this opinion and requests this statement be removed given the justification provided.	The Company agrees that flexible modelling approaches can be used to achieve clinically valid tails without using a HR; however, as highlighted by the Company in response to the ERG's clarification questions the immaturity of the data precludes the reliable use of such flexible models.	Not a factual error, no change required.

Issue 6 Long-term remission

Description of problem	Description of proposed amendment	Justification for amendment	ERG approach
Paragraph 5, page 24; "The ERG considers the method used by the company to estimate cure in the model unfit for decision making." Paragraph 5, page 95; "The ERG considers that the estimation of cure in the model relies on a weak methodology, given that both the proportion of patients cured and the cure threshold were exogenously chosen by the company instead of being estimated through a robust method, such as a mixture cure model (MCM)."	The Company ask that theses passages are amended referencing that the year chosen was validated by clinicians. The year was selected to represent the period of time after which a patient which remained progression-free would have a low risk of relapse. In addition, the Company would like to highlight that the methodology employed in the economic is aligned with that adopted in TA598[10]. Furthermore, the proportion of patients in long-term remission is defined by the PFS curve within the model, which was validated by real world evidence and not set by the Company.	Incorrect conclusion. The Company would like to highlight that the methodology employed in the economics is aligned with that adopted in TA598[10]. In which the mortality of patients who were progression-free at the landmark survival time point is no longer subject to the modelled OS curves within the economic model. The TA598 ERG broadly agreed with the clinical rationale presented within the TA598 Company submission and support the chance of patients achieving long-term remission. The Committee also agreed that the use of olaparib as a first-line maintenance therapy had the potential to "cure" the disease in some patients. There is no evidence to suggest that niraparib will not be able to achieve similar long-term remission within patients who are progression free by a given threshold.	Not a factual error, no change required.

Paragraph 2, page 97; "The company did not provide any explanation as to why the proportion of patients cured for the Stage III NVRD population was not taken from the NVRD PFS curves estimated in the model, which would have been a consistent approach to that used to the ITT population. The ERG investigated this in the economic model and noted that a possible reason might be that because the Stage III NVRD population was not incorporated in the model with a robust methodology, the NVRD PFS curves cross the NVRD OS curves, therefore leading to negative numbers of patients with progressed disease in the model."	The Company ask that the report is updated to reflect the choices of using the Du Bois study.	The Du Bois study was used instead of the PFS curves for the MA population due to the inability to estimating OS for the Stage III PDS NVRD patients. Since there is no long-term evidence in PRIMA for these patients, in order to gauge the proportion of PFS to OS when NVRD patients are included, evidence outside of PRIMA was used.	Not a factual error, no change required. The ERG notes that the MA PFS curves were available for the company to estimate the proportion of cured patients.
Paragraph 3, page 97; "The company also did not provide any comparative analysis between the population in the De Bois study and the population in PAOLA-1 (from which the treatment effect for patients with Stage III NVRD after PDS was estimated), nor with the population in PRIMA. The company also did not provide any rationale for why the proportion of patients cured with niraparib and RS were assumed to be the	The Company ask that the report be updated to provide the reasoning behind the use of the Du Bois study and highlight that a conservative assumption was made that the routine surveillance and niraparib proportions were made equal.	The Du Bois study was the evidence identified by the Company which provided data sufficiently long to inform the proportion of patients progression-free and progressed at varying cure years (5, 7, and 10 years) for a population that included the NVRD patients. The MA population used evidence from a study with a similar, but somewhat different population as well as different interventions, a conservative	Not a factual error, no change required.

same in the Stage III NVRD population but were different in the ITT population. This reinforces the ERG's concerns around the company's methods to estimating the cost-effectiveness for the Stage III NVRD population, and the inconsistencies generated in the model parameters due to multiple sources being used to derive clinical parameters."		assumption was assumed that both RS and niraparib had a similar proportion of PF/PD patients.	
Paragraph 3, page 124; "However, clinical expert advice given to the ERG explained that when patients have been in remission for 10 years, they would be discharged."	The Company request this statement is removed or updated based on the justification provided.	Should the ERG decide to remove the long-term remission assumption from its base-case, then this sentence, which suggest patients who are progression-free at 10 years would be discharged, is inconsistent with other aspects of the report.	Not a factual error, no change required. The ERG notes that the fact that patients are discharged from clinical follow-up at 10 years does not imply that patients' mortality becomes the same as that of the general population from this point on.

Issue 7 Resource use and costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 3, page 122; "The ERG is concerned that the number of patients receiving subsequent treatments in PRIMA is lower than what is expected in UK practice and lower than what has been	The Company request this statement is revised to include that: " **This discrepancy is most likely due to the immaturity of the observed trial data."**	The Company assumes that this discrepancy will be resolved as the data matures.	This has been addressed in Issue 3.

reported in other trials for the same disease area. For example, the ERG in TA598 reported that the CSR for SOLO-1 suggests that 90% and 93% of the patients who progressed received subsequent chemotherapy in the olaparib and placebo arms, respectively. “			
Paragraph 1, page 91; “The ERG notes that there is a small discrepancy between the number of patients reported as being on an individual dosing regimen across the CSR and the company’s reply to the clarification questions ([redacted] patients according to the latter).”	Please note that the [redacted] patients from the PRIMA CSR is the correct number of patients on individualised dosing. Please additionally highlight the [redacted] patients with commercial in confidence mark up.	Typographical error.	Thank you, this has been amended in the report.
Paragraph 3, page 116; "The company assumed that the weighted average dose received in month 18 would be the same for the remainder of the treatment period with niraparib in the model."	Please update this sentence to: "The company assumed that the proportion across the different doses received in month 18 would be the same for the remainder of the treatment period with niraparib in the model."	The weighted dose was not used to calculate the costs, instead the cost of each dose (100 mg, 200 mg and 300 mg) at month 18 was costed and was assumed to be the same for the remainder of the treatment.	Thank you, this has been amended in the report.
Table 29, page 117;	Please amend the table to the following:	Typographical errors.	Thank you, this has been amended in the report.

The dose for month 12 is replicated in month 13. The table then cuts off the data early and month 18+ is missed out.	<table><tr><th rowspan="2">Cycles</th><th colspan="3">Proportion of patients across dose (mg) categories</th></tr><tr><th>100</th><th>200</th><th>300</th></tr><tr><td>1</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>2</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>3</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>4</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>5</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>6</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>7</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>8</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>9</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>10</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>11</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>12</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>13</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>14</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>15</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>16</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>17</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>18</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>18+</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table>		
Table 32, page 120;	Please change these table inputs to: Cisplatin, Platinum sensitive – **“£3,157”**	Typographical errors	Thank you, this has been amended in the report.

The average cost per class for Cisplatin and Taxane are different from the revised model.	Cisplatin, Platinum-recurrent – **"£4,761"** Taxane, Platinum sensitive – **"£2,196"** Taxane, Platinum recurrent – **"£1,801"**		

Issue 8 Quality of life

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 1 (bullet points), page 115; "• There is no evidence to suggest a patient in long-term remission should have their QoL restricted to the general population" "• Patients who achieve long-term remission are not expected to be limited by the EQ-5D domains;"	The Company asks that the bullet points are amended as follows: "• There is no evidence to suggest a patient in long-term remission should have their QoL capped at the mean general population QoL" "•Thinking of these women as individuals, patients who achieve long-term remission are not expected to have any defining limitations as per the EQ-5D domains; so there is no reason to believe their utility	To align statements with Company rationale presented in response to the ERG clarification questions.	Not factually incorrect, no change required.

	should be capped at the mean;"		
"• Increasing the ICER (from £18,689 to £20,037 in the ITT population and from £13,456 to £14,506 in the MA population) increases the hurdle to the product being reimbursed."	The Company request that both relative (e.g. Company base-case ICER/scenario ICER) and absolute (e.g Company base-case – scenario ICER) impact on to the ICER are presented here.	To allow inferences to be made between the differences in the manufacturer's base-case and scenario analyses of assuming age utility decrements.	Not factually incorrect, no change required.
Paragraph 3, page 115; "However, at the point of cure, 7 years later, patients in the PFS state have a higher utility than the general population utility ([redacted]), which lacks face validity."	The Company request that this sentence is removed or amended.	Within the model base-case a long-term remission assumption is applied such that patients still progression-free at 7 years would be considered in long-term remission and only subject to risk of death from all-cause mortality. As such a utility value of [redacted], notably aligned with the general population utility, does not lack face validity[16].	Not factually incorrect, no change required. The ERG notes that the company's chosen PFS utility value of [redacted] is [redacted] than that of the general population utility (0.78) matched for age and gender at 7 years in the model.

Issue 9 Disease management costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 1, page 126;	Please update this sentence to:	Typographical error	Thank you, this has been amended in the report.

"This was subsequently inflated to 2018/19 prices (£**7,567**) by the company."	"This was subsequently inflated to 2018/19 prices (£**7,576**) by the company."		

Issue 10 Technical

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 29-30; "When the long-term remission approach is removed from the economic model, the option to vary the PFS to OS ratio in the analysis does not work appropriately. The company used the equation: Niraparib mean OS = RS mean OS + [(mean PFS niraparib – mean PFS RS) x 2] To estimate a HR between the RS OS curve and the niraparib OS curve, based on the estimated niraparib	The Company have fixed this issue within the model. The revised model is submitted as part of this response. The Company request that the text is updated to reflect that the issue highlighted by the ERG has now been resolved. As a result of this update the resulting ICERs when no long-term remission is assumed are slightly different to that presented in the ERG report. The Company request that Table 49 is reviewed and updated to reflect the updated model.	Issue has now been resolved. The Company have updated the VBA in the model by replacing the "goal seek" function with the "solver" function in order to optimise the OS hazard ratio and ensure PFS:OS = 1:2. The "solver" function algorithm is known to be more accurate than the "goal seek" algorithm and as such can take longer to run. The result of using the "solver" function is that the achieved solution is more precise and leads to stable OS hazard ratio estimates.	Not factually incorrect at the time of writing the report. The ERG has updated the report with the new ICERs using the company's corrected model.

mean OS in the equation above. This HR was produced through a “goal seek analysis” function in Excel which finds the HR to satisfy the equation. When the long-term remission approach is used in the model, exploratory analyses varying the PFS to OS ratio work reasonably well in the model because the RS OS; RS PFS; and niraparib PFS curves stay relatively stable every time the ratio is varied, thus, the equation above can be used to estimate the HR (see Figure B). However, when the long-term remission assumption is not used in the model, the niraparib PFS and the OS niraparib curves cross (as the plateau in the curves imposed by the long-term remission is removed). In order to fix this problem, the company capped the PFS curve by			

the OS curve in the niraparib arm. However, capping the PFS curve by the OS curve means that every time the PFS to OS ratio is varied in the equation, the niraparib PFS curve changes because the niraparib OS curve also changed. Therefore, the equation can no longer be solved in order to estimate the niraparib OS curve that respects the new PFS to OS ratio, given the circular changes in the equation (see Figure C). The consequence of this problem is that the model does not provide stable HRs that can be used in the model to generate the niraparib OS curve and therefore, it does not produce reliable ICERs for scenarios 1 and 2 described above. Due to time constraints and given the implication of the structural changes required			

in the model, the ERG could not fix this problem. Nonetheless, the ERG considers these scenarios to be of high relevance for the Committee and so, recommends that the company fixes this problem in the model."			

Issue 11 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 2, page 32; "Additionally, based on advice from its clinical experts, the ERG considers the CS to provide an accurate description of the current treatment algorithm for the management of people with **recurrent** ovarian cancer."	Please amend the text as follows to remove "recurrent": Additionally, based on advice from its clinical experts, the ERG considers the CS to provide an accurate description of the current treatment algorithm for the management of people with ~~**recurrent**~~ ovarian cancer	Typographical error	Thank you, this has been amended in the report.
Paragraph 2, page 64;	Please amend the text as follows:	The CS contained a typographical error.	Thank you, this has been amended in the report.

"According to the data provided in the CS (Table 20), median **PFS** was [redacted] in the MA cohort ([redacted]) than the simulated PRIMA cohort ([redacted], **Error! Reference source not found.**).	"According to the data provided in the CS (Table 20) median **time to subsequent treatment** was [redacted] in the MA cohort ([redacted]) than the simulated PRIMA cohort ([redacted], **Error! Reference source not found.**).		
Paragraph 2, page 80; "The results of the primary outcome of **PAOLA-1**, PFS determined by BICR in the ITT population, showed a statistically significant benefit of niraparib treatment compared with placebo (median PFS was 13.8 and 8.2 months in the niraparib and placebo arms respectively and p<0.0001)."	Please amend the text as follows: "The results of the primary outcome of **PRIMA**, PFS determined by BICR in the ITT population, showed a statistically significant benefit of niraparib treatment compared with placebo (median PFS was 13.8 and 8.2 months in the niraparib and placebo arms respectively and p<0.0001)."	Typographical error	Thank you, this has been amended in the report.

Issue 12 CIC/AIC mark-ups

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 2, page 28;	Please amend the text as follows:	The data highlighted is unpublished and is CIC.	Thank you, this has been amended in the report.

“[redacted]; however, it is not possible to ascertain if niraparib is associated with a delay in second progression events without having more mature PFS2 data.”	[redacted] however, it is not possible to ascertain if niraparib is associated with a delay in second progression events without having more mature PFS2 data.”		
Paragraph 1, page 123; “[redacted], when the number of patients at risk was low. This might be related to the lack of data maturity, however it is not possible to ascertain if niraparib delays second progression events without having more mature PFS2 data.”	Please highlight the sentence “[redacted]” as CIC	The data highlighted is unpublished and is CIC.	Thank you, this has been amended in the report.
Table 3, Page 44;	Please amend the text as follows:	The data highlighted is unpublished and is CIC.	Thank you, this has been amended in the report (although the ERG notes this is not

“The reasons for discontinuation from study were death ((% for niraparib and % for placebo), withdrawal of consent (% for niraparib and placebo), lost to follow-up (% for niraparib and % for placebo), and other (% in niraparib and % in placebo).”	“The reasons for discontinuation from study were death (% for niraparib and % for placebo), withdrawal of consent (% for niraparib and placebo), lost to follow-up (% for niraparib and % for placebo), and other (% in niraparib and % in placebo).”		marked as CIC in table 10 of the CS).
Paragraph 3, page 47 ; “Initial analysis in HRD patients showed statistical significance for TFST (p-value<0.0001), but not for PFS2 (p-value=)”	Please amend the text as follows: “Initial analysis in HRD patients showed statistical significance for TFST (p-value<0.0001), but not for PFS2 (p-value=)”	The data highlighted is unpublished and is CIC.	Thank you, this has been amended in the report.
Paragraph 1, page 48; “in patients with HRD median PFS was 21.9 months in the niraparib arm and 10.4 months in the placebo arm (HR 0.43, 95% CI: 0.310 to 0.588, p<0.0001).”	Please amend the text as follows: “in patients with HRD median PFS was 21.9 months in the niraparib arm and 10.4 months in the placebo arm (HR 0.43, 95% CI: 0.31 to 0.59, p<0.001).”	The data highlighted is published and is not CIC.	Thank you, this has been amended in the report.

Table 5, page 50;

Table 2. Progression-Free Survival Based on BICR Assessment by Starting Dose Group (ITT Population) (adapted from clarification response, question A4)

PFS based on BICR	Fixed		Individualised	
	Nirapa rib (N = 317)	Placebo (N = 158)	Nirapari b (N = 170)	Placebo (N = 88)
Median (95% CI)				
Censored observations, n (%)				
Event rate,				

Table 3. Progression-Free Survival Based on BICR Assessment by Starting Dose Group (ITT Population) (adapted from clarification response, question A4)

PFS based on BICR	Fixed		Individualised	
	Nirapa rib (N = 317)	Placebo (N = 158)	Nirapa rib (N = 170)	Placebo (N = 88)
Median (95% CI)				
Censored observations, n (%)				
Event rate, n (%)				
p-value				
HR (95% CI)				

The data highlighted is unpublished and is CIC.

Thank you, this has been amended in the report. The ERG notes that this was not marked up as CIC in the clarification question response.

n (%) p-value HR (95% CI)			
Paragraph 2, page 51; "Median OS was [redacted] months in the niraparib arm, but not reached in the placebo arm"	Please amend as follows: "Median OS was [redacted] months in the niraparib arm, but not reached in the placebo arm""	The data highlighted is unpublished and is CIC.	Thank you, this has been amended in the report. The ERG notes that was not marked up as CIC in the CS.
Table 6, page 52; Table 4: Secondary efficacy endpoint efficacy outcomes for the ITT population, reproduced from CS, table 13 Niraparib (N = 487) Time to First Subsequent Therapy Median TFST (95% CI): 18.6 (15.8,24.7)	Please mark median OS as CIC. Niraparib (N = 487) Pla (N Time to First Subsequent Therapy Median TFST (95% CI): 18.6 (15.8,24.7); 12. (10 Censored observations, n (%): [redacted] Event rate, n (%): [redacted] p-value: 0.0001	The median OS is unpublished and CIC.	Thank you, this has been amended in the report. The ERG notes that this was not marked up as CIC in the CS.

Censored observations, n (%)		Hazard ratio (95% CI)	0.65 (0.521,0.802)
Event rate, n (%)		Progression-Free Survival 2	
p-value	0.0001	Median PFS2 (95% CI)	
Hazard ratio (95% CI)	0.65 (0.521,0.802)	Censored observations, n (%)	
Progression-Free Survival 2		Event rate, n (%)	
Median PFS2 (95% CI)		p-value	
Censored observations, n (%)		Hazard ratio (95% CI)	0.81 (0.577,1.139)
Event rate, n (%)		Overall Survival	
p-value		Median OS (95% CI)	
Hazard ratio (95% CI)	0.81 (0.577,1.139)	Censored observations, n (%)	
Overall Survival		Event rate, n (%)	
Median OS (95% CI)	NE)	NE (25.0, NE)	
Censored observations, n (%)		Hazard ratio (95% CI)	0.70 (0.442,1.106)
Event rate, n (%)			
p-value			
Hazard ratio (95% CI)	0.70 (0.442,1.106)		

<table>
<tr>
<td>Paragraph 1, page 54;

“Baseline symptoms and quality of life, as measured by FOSI, were similar between the niraparib and placebo arms in the ITT population (overall FOSI mean: niraparib [redacted] versus placebo [redacted]).”</td>
<td>Please amend as follows:

“Baseline symptoms and quality of life, as measured by FOSI, were similar between the niraparib and placebo arms in the ITT population (overall FOSI mean: niraparib [redacted] versus placebo [redacted]).”</td>
<td>The data highlighted are unpublished and CIC.</td>
<td>Thank you, this has been amended in the report.</td>
</tr>
<tr>
<td>Paragraph 2, page 57;

“In the niraparib group, 12.0% of AEs resulted in treatment discontinuation compared to 2.5% in the placebo group, and this did not differ broadly between fixed and individualised dosing ([redacted]% versus [redacted]% respectively).”</td>
<td>Please amend as follows:

“In the niraparib group, 12.0% of AEs resulted in treatment discontinuation compared to 2.5% in the placebo group, and this did not differ broadly between fixed and individualised dosing ([redacted]% versus [redacted]% respectively).”</td>
<td>The data highlighted are unpublished and CIC.</td>
<td>Thank you, this has been amended in the report.</td>
</tr>
<tr>
<td>Table 7, page 57;

Table 5. Summary of adverse events, adapted from</td>
<td>
<table>
<tr><td>Event</td><td colspan="3">Niraparib</td><td>Placebo</td></tr>
<tr><td></td><td>All
n (%)
N=484</td><td>Individua-lised
n (%)</td><td>Fixed
n (%)</td><td>All
n (%)</td></tr>
</table>
</td>
<td>The data highlighted are unpublished and CIC.</td>
<td>Thank you, this has been amended in the report. The ERG notes that this was not marked up as CIC in the</td>
</tr>
</table>

clarification response A12 and A13

Event	Niraparib			Placebo
	All n (%) N= 484	Individualised n (%) N = 169	Fixed n (%) N = 315	All n (%) N = 244)
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE with CTCA	341 (7	102 (6	239 (	46 (18.9)

		N = 169	N = 315	N = 244)
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE with CTCAE Grade ≥3	341 (70.5)	102 (60.4)	239 (75.9)	46 (18.9)
Grade ≥3 Treatment-emergent Adverse Events Reported in ≥5% of Patients in Either Treatment Subgroup				
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	139 (28.7)	25 (14.8)	114 (36.2)	1 (0.4)
Anaemia	150 (31.0)	38 (22.5)	112 (35.6)	4 (1.6)
Neutropenia	62 (12.8)	16 (9.5)	46 (14.6)	3 (1.2)
Investigations	[redacted]	[redacted]	[redacted]	[redacted]

clarification question response/CS.

E Grade ≥3	0.5)	0.4)	75.9)	
Grade ≥3 Treatment-emergent Adverse Events Reported in ≥5% of Patients in Either Treatment Subgroup				
Blood and lymphatic system disorders				
Thrombocytopenia	139 (28.7)	25 (14.8)	114 (36.2)	1 (0.4)
Anaemia	150 (31.0)	38 (22.5)	112 (35.6)	4 (1.6)

Platelet count decreased	63 (13.0)	12 (7.1)	51 (16.2)	0
Neutrophil count decreased	37 (7.6)	9 (5.3)	28 (8.9)	0
Vascular disorders				
Hypertension				
General disorders and administration site conditions				
Fatigue				

Abbreviations: CSR, clinical study report; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

	Neutropenia	62 (12.8)	16 (9.5)	46 (14.6)	3 (1.2)			
	Investigations	[redacted]	[redacted]	[redacted]	[redacted]			
	Platelet count decreased	63 (13.0)	12 (7.1)	51 (16.2)	0			
	Neutrophil count decreased	37 (7.6)	9 (5.3)	28 (8.9)	0			
	Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]			

Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CSR, clinical study report; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

<table>
<tr>
<td>Paragraph 3, page 63;

“The simulated-PRIMA population from the Edinburgh database is a more severe patient population with [redacted]% of patients having an ECOG status of 2 or 3; a population excluded from PRIMA.”</td>
<td>Please amend as follows:

“The simulated-PRIMA population from the Edinburgh database is a more severe patient population with [redacted]% of patients having an ECOG status of 2 or 3; a population excluded from PRIMA.”</td>
<td>The data highlighted are AIC.</td>
<td>Thank you, this has been amended in the report.</td>
</tr>
<tr>
<td>Table 14, Page 77;

Table 6. PFS results from PRIMA (adapted from CS Figure 13)
<table>
<tr><th>Population</th><th>Treatment arm</th><th>HR</th></tr>
<tr><td rowspan="2">Stage III patients [a]</td><td>Niraparib (n=318)</td><td rowspan="2">0.54 (95% CI: 0.42 to 0.70)</td></tr>
<tr><td>Placebo (n=158)</td></tr>
<tr><td rowspan="2">Stage IV patients</td><td>Niraparib (n=169)</td><td rowspan="2">0.79 (95% CI: 0.55 to 1.12)</td></tr>
<tr><td>Placebo (n=88)</td></tr>
</table></td>
<td>Table 7. PFS results from PRIMA (adapted from CS Figure 13)
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<tr><td>Placebo (n=88)</td></tr>
</table></td>
<td>The data highlighted are unpublished and CIC.</td>
<td>Thank you, this has been amended in the report. The ERG notes that this was not marked up as CIC in the CS (p144).</td>
</tr>
</table>

Issue 13 Stopping rule

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 5, page 111; "However, the company also noted in their clarification response that the SmPC will not specify a treatment duration of 3 years, therefore the company's scenario analysis assuming no discontinuation (see section **Error! Reference source not found.**) should have been considered in the base case model."	The Company ask that the ERG reassess their exclusion of the stopping rule in the base-case.	While the draft SmPC is not expected to include a stopping rule, the trial protocol defined completed therapy as 3 years of niraparib. The trial protocol hence states that duration of treatment will be approximately three years. Since the efficacy in the trial is based on patients receiving niraparib with a stopping rule of three years, this should be reflected and aligned with the modelled costs. Within the economic analysis, it is assumed that only [redacted]% of the [redacted]% of patients who are on treatment at 3 years would continue treatment beyond 3 years, and these patients would follow the Weibull curve. This assumption reflects the fact that if patients are still receiving benefits after 3 years, stopping or continuing treatment is at the discretion of the practitioner. In previous TAs, discrepancies between product characteristics outlined in the SmPC and those modelled were accepted where it was appropriate to do so. For example in TA431[17], stopping rules applied by the SmPC and those which NHS professionals administered	Not factually incorrect, no change required.

		in UK clinical practice differed; “We agree that the currently defined patient population is the correct one to be applied to clinical practice and have included a stopping rule that we would be happy to apply to our carefully selected patient cohorts” Clinical experts confirmed that they would follow the evidence base for continuing treatment, which defines completed therapy as three years on niraparib in the PRIMA protocol (note, patient may continue to receive treatment >3 years, if deriving clinical benefit as assessed by the Investigator). If a patient has no evidence of disease at three years clinical experts also confirmed that they would also be concerned about continuing therapy long term due to a possible risk of toxicity and secondary malignancies.	
Paragraph 2, page 40; “**The ERG notes that the duration of treatment in PRIMA may not be consistent with clinical practice**, whereby participants in PRIMA could be	The Company asks the ERG to reconsider and remove the statement given the explanation and precedence.	Although a time-limited treatment period is not expected to be defined in the SmPC, the Company considers that no more than [redacted]% of the [redacted]% of patients who are still on treatment at three years	Not factually incorrect, no change required.

treated for up to 3 years in the trial, after which time continuation of treatment was based on clinical judgement. However, it is expected that the anticipated MA for niraparib will not specify that treatment be capped at 3 years. Clinical experts advising the ERG note that decisions to continue niraparib treatment after 3 years may vary in practice and be based on individual characteristics of the patient.		will continue treatment beyond this point. The Company would like to draw the Committee's attention to TA431[17], where continuation criteria were modelled and accepted by the Committee despite no continuation/discontinuation criteria included in the SmPC.	

References

1. Colombo, N. *et al.* ESMO–ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Annals of Oncology* **30**, 672–705 (2019).
2. Vergote, I. *et al.* Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N. Engl. J. Med.* **363**, 943–953 (2010).
3. ESMO. Relapsed Epithelial Ovarian Carcinoma Treatment Recommendations. https://www.esmo.org/guidelines/gynaecological-cancers/newly-diagnosed-and-relapsed-epithelial-ovarian-carcinoma/eupdate-ovarian-cancer-treatment-recommendations.
4. Vergote, I. *et al.* Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials. *The Lancet Oncology* **19**, 1680–1687 (2018).
5. Grimm, C., Cropet, C. & Ray-Coquard, I. Maintenance olaparib plus bevacizumab (bev) after platinum-based chemotherapy plus bev in patients (pts) with newly diagnosed advanced high-grade ovarian cancer (HGOC): Efficacy by timing of surgery and residual tumor status in the Phase III PAOLA-1 trial. in (SGO, 2020).
6. Kehoe S. *et al.* Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): An open-label, randomised, controlled, non-inferiority trial. *Lancet* **386**, 249–257 (2015).

7. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer | NEJM. https://www.nejm.org/doi/full/10.1056/NEJMoa1911361.
8. Marcia Hall & Konstantinos Savvatis. Maximal-Effort Cytoreductive Surgery for Ovarian Cancer Patients with a High Tumor Burden: Variations in Practice and Impact on Outcome. *Gynecologic Oncology* (2019).
9. Gonzalez Martin A. *et al.* A randomized, double-blind, placebo-controlled multicenter phase 3 trial of niraparib maintenance treatment in patients with advanced ovarian cancer following frontline chemotherapy. *Ann. Oncol.* **28**, v351 (2017).
10. Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy.
11. NICE. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (TA598). (2018).
12. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer | Guidance and guidelines | NICE. https://www.nice.org.uk/guidance/ta528.
13. Poveda, A. *et al.* Final overall survival (OS) results from SOLO2/ENGOT-ov21: A phase III trial assessing maintenance olaparib in patients (pts) with platinum-sensitive, relapsed ovarian cancer and a BRCA mutation. *JCO* **38**, 6002–6002 (2020).

14. Friedlander, M. *et al.* Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. *British journal of cancer* **(no pagination)**, (2018).
15. Mirza, M. R. *et al.* Evaluation of an individualized starting-dose of niraparib in the PRIMA/ENGOT-OV26/GOG-3012 study. *JCO* **38**, 6050–6050 (2020).
16. Ara, R. & Brazier, J. Populating an economic model with health state utility values: moving towards better practice. *Value in Health* 37 (2010).
17. NICE. Overview | Mepolizumab for treating severe refractory eosinophilic asthma | Guidance | NICE. https://www.nice.org.uk/guidance/ta431 (2017).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy

This document is the technical report for this appraisal. It has been prepared by the NICE technical team.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1 Key issues summary

Issue	Summary	Technical Team Preliminary Judgement
Issues related to clinical effectiveness		
1. Generalisability of the PRIMA results to UK clinical practice – dose used in trial versus clinical practice	• PRIMA is a double-blind, placebo-controlled, multicentre, international phase III randomised controlled trial (RCT). The trial enrolled adults with newly diagnosed advanced (FIGO stage III to IV) high-grade serous or endometrioid tumours of the ovary, peritoneum or fallopian tube and a complete or partial response to first line platinum-based chemotherapy and compared niraparib (a PARP inhibitor) as maintenance treatment to routine surveillance. **Complete and partial response to platinum-based chemotherapy** • Approximately 69% of people in PRIMA had a complete response to first-line platinum-based chemotherapy, and 31% had a partial response. **Dosing** • Initially, participants in PRIMA were randomised to niraparib 300 mg per day or placebo. A protocol amendment to individualised dosing was introduced due to a high number of adverse events. • The anticipated marketing authorisation will use individualised dosing, with a standard starting dose of 200 mg once daily, with the dose increased to 300 mg once daily for patients with baseline bodyweight ≥77 kg and platelet count ≥150,000/µL. • On individualised dosing, participants were given a starting dose of 200 mg per day if they had a baseline body weight of less than 77 kg, a platelet count of less than 150,000/µL, or both. • Approximately two thirds (475/733) of participants enrolled in PRIMA started on the fixed 300 mg dose, and approximately one third (258/733) started on individualised dosing. Of the people enrolled on individualised dosing, [redacted]% started on 300 mg and [redacted]% started on	• It is unclear whether the proportions of people experiencing complete and partial response to platinum in PRIMA are reflective of the population who would be eligible to have niraparib in UK clinical practice after first-line platinum-based therapy. • The proportion of people starting on 300-mg dose niraparib was higher in the trial than would be expected in clinical practice. Therefore, the ITT analysis from PRIMA may overestimate the efficacy of niraparib at the dose that will be used in clinical practice. The technical team notes the ERG's point that further investigation of the lower dose of niraparib (100 mg) and its impact on clinical outcomes for ovarian cancer may be useful (ERG report 3.2.3).

	200 mg (ERG report 2.3.1). From month 7 in PRIMA, a [redacted]. The company highlights that due to shorter duration of follow up in the individualised dosing subgroup there was a smaller number of progression-free survival (PFS) events and therefore more uncertainty around the results. • Maintenance therapy with niraparib resulted in a longer median PFS (fixed [redacted] months; individualised [redacted] months) compared with placebo ([redacted] months for both groups) in both the fixed and individualised dosing groups. Hazard ratios (HRs): fixed dosing, 0.59 (95% CI: 0.457 to 0.757); individualised dosing, 0.69 (95% CI: 0.481 to 0.982). • The ERG notes that HRs should be interpreted with caution as proportional hazards are unlikely to hold for PFS in the intention to treat (ITT) population, so the assumption may not hold for these subgroups (see issue 4). • The ERG notes that the subgroup analysis should be considered exploratory as it is a *post-hoc* analysis, and PRIMA was not powered to detect a difference between the subgroups.	
2. Generalisability of the PRIMA results to UK clinical practice – exclusion of population with no visible residual disease after primary debulking surgery	• PRIMA excluded people with stage III disease with no visible residual disease (NVRD) after primary debulking surgery (PDS). It included people with stage III NVRD after interval debulking surgery (IDS) and people with stage IV NVRD after PDS or IDS. • The anticipated licensed population includes people with NVRD, irrespective of type of debulking surgery which is broader than the ITT population in PRIMA. • To account for the population excluded in PRIMA but included in the anticipated licensed population, the company generated a marketing authorisation (MA) population. This required estimating the proportion of the MA population that was not included in the PRIMA ITT population and the use of external evidence sources to estimate the clinical outcomes for this proportion of people (see issue 3). • The company used the University of Edinburgh Ovarian Cancer Database to estimate the proportion of people with stage III NVRD after PDS, that is the population included in the MA population but	• Basing the estimate of the proportion of people with stage III NVRD after PDS on one small region in the UK may not be representative of surgical outcomes across the country. • An accurate estimate of the proportion of people with stage III NVRD after PDS is important for appropriately modelling the outcomes for the whole MA population. • It is unclear whether people with NVRD after PDS will

	not the PRIMA ITT population. A systematic literature review was not done. • The Edinburgh Ovarian Cancer Database contains outcome data for patients diagnosed with ovarian cancer in the South East region of Scotland (N > 4,000). • 569 people in the Edinburgh dataset matched the MA population, of which [redacted] were stage III with NVRD. The PAOLA-1 trial also includes 25% of patients with stage III NVRD after PDS. • There were some differences in the patient characteristics between the Edinburgh database and the PRIMA trial. The Edinburgh database population: o has more severe disease: 30% of patients having an ECOG status of 2 or 3 (this population was excluded from PRIMA) o has a smaller proportion (24%) that received neoadjuvant chemotherapy than the placebo arm in PRIMA (67.9%). • The ERG note that the population estimated from the Edinburgh dataset by the company was not representative of the population that was excluded from the PRIMA ITT population as it included people with stage III NVRD irrespective of surgery type and not specifically after PDS. • The ERG's clinical experts advised that the proportion of patients with NVRD after surgery varies across UK practice. They estimated the proportion of patients with stage III NVRD following PDS to be between 25 to 40% in UK clinical practice.	receive similar relative benefits as the ITT population.

3. Sources of evidence for estimating progression-free survival for people with stage III no visible residual disease after primary debulking surgery	• Through a targeted literature review the company identified 2 studies (PAOLA-1 and SOLO-1) that reported the effect of PARP inhibitors on PFS outcomes for people with advanced ovarian cancer and NVRD after PDS receiving first-line treatment. The company used data from PAOLA-1, SOLO-1 and PRIMA as sources of evidence for estimating PFS for people with stage III disease and NVRD after PDS. **PAOLA-1** • Data from PAOLA-1 were used in the company's base case analysis as an external source of evidence for estimating PFS for people with stage III disease and NVRD after PDS. • PAOLA-1 compared olaparib (a PARP inhibitor) and bevacizumab with placebo and bevacizumab as first-line treatment of advanced ovarian cancer and included people with stage III disease with NVRD after PDS. Therefore, this analysis assumes a class effect between olaparib and niraparib and may be confounded by the use of bevacizumab in both treatment arms. • In the company's analysis, people in the PAOLA-1 ITT population were compared with those in PAOLA-1 who had stage III disease and NVRD after PDS. HRs quantifying the 'NVRD effect' (the difference between the 2 placebo arms of these cohorts) and the 'treatment effect' (the difference between the 2 treatment arms of these cohorts) were generated and applied to the RS and niraparib PFS curves for the ITT population in PRIMA, respectively (ERG report 2.4.4). • The HRs derived from PAOLA-1 and applied to the PRIMA ITT curves were: 'NVRD effect', 0.49 (95% CI: 0.329 to 0.723); 'treatment effect', 0.34 (95% CI: 0.233 to 0.497). **SOLO-1** • Data from SOLO-1 were used in the company's scenario analysis as an external source of evidence for estimating PFS for people with stage III disease and NVRD after PDS.	• The technical team agrees with the ERG that data from PRIMA stage III NVRD after IDS is likely to provide the most robust estimate of treatment effect in people with stage III NVRD after PDS. This method relies on fewer assumptions such as class effect and avoids issues around comparability between trials. It is acknowledged that this approach relies on the assumption that there is similar prognosis for people with stage III NVRD after PDS and IDS. The technical team welcomes comments on the validity of this assumption. • The technical team agrees with the ERG that it may not be appropriate to apply HRs estimated from one trial directly to curves in PRIMA, particularly when proportional hazards have been demonstrated not to hold for PFS in PRIMA (see issue 4).

	• SOLO-1 compared olaparib with placebo as first-line treatment of advanced ovarian cancer in people with a BRCA mutation and included people with stage III disease with NVRD after PDS. Therefore, this analysis also assumes a class effect between olaparib and niraparib and does not represent both BRCA positive and negative patients. • This scenario analysis used the same method used with the PAOLA-1 data (see above) using data from SOLO-1 to estimate 'NVRD effect' and 'treatment effect' HRs and applying these to the PFS curves for the ITT population in PRIMA. • The HRs derived from SOLO-1 and applied to the PRIMA ITT curve were: 'NVRD effect', 0.753 (95% CI: 0.521 to 1.327); 'treatment effect', 0.718 (95% CI: 0.491 to 1.393). **PRIMA stage III subgroup** • The company conducted subgroup analyses of people in the PRIMA trial with stage III and stage IV disease. This analysis indicated that niraparib was more effective for stage III disease than for stage IV. The PRIMA stage III subgroup included people with VRD and NVRD after IDS but did not include people with NVRD after PDS. • The company stated that it could be assumed that the efficacy of niraparib observed in the stage III subgroup would be at least as good as in patients with stage III NVRD after PDS. • This scenario analysis applied the 'NVRD effect' HR derived from PAOLA-1 (see above) to the RS PFS curve for the ITT population in PRIMA and applied the HR observed in the stage III PRIMA subgroup to the niraparib PFS curve for the ITT population in PRIMA. • The HR derived from the stage III PRIMA subgroup was: 0.54 (95% CI 0.42 to 0.80). *[Factual inaccuracy identified after appraisal committee meeting 1. Correct information is 0.54 (95% CI 0.42 to 0.70)]* • The company justified using data from the PAOLA-1 trial in its base case, over data from SOLO-1 or PRIMA because:	

	o The non-NVRD and NVRD subgroups were mutually exclusive in PAOLA-1, however in SOLO-1, 44% of the ITT population was stage III patients with NVRD. This overlap between the NVRD subgroup and the ITT population in SOLO-1 means the prognostic effect of having NVRD is potentially underestimated. o PAOLA-1 included both BRCA positive and negative patients, whereas SOLO-1 only included BRCA positive patients. The expected licensed population for niraparib includes both BRCA positive and negative patients. o The HRs obtained from PRIMA included people with stage III VRD, which is likely to be an underestimate of the survival for stage III patients with NVRD. • The ERG noted the following limitations with the company's approach: a. PAOLA-1 and SOLO-1 are not directly comparable to PRIMA due to confounding caused by differences in study design and patient characteristics, and no adjustments have been made for any differences between the trials (ERG report 2.4.4.1). b. The estimated treatment effect relies on the assumption of a class effect, which has not been shown (ERG report 2.4.5). c. It may not be a valid approach to apply HRs directly to the PFS curve in PRIMA when proportional hazards have been shown not to hold for PFS in PRIMA (see issue 4; ERG report 2.4.4.1 to 2.4.4.3). • The ERG's preferred approach is to use the subgroup of patients in PRIMA with stage III disease and NVRD after IDS to estimate the treatment effect of niraparib in people with stage III disease and NVRD following PDS. This allows for the ITT population from the PRIMA trial to be used to estimate clinical and cost-effectiveness for the full population covered by the anticipated marketing authorisation. • The ERG's approach relies on the assumption that there is no difference in PFS and OS based on PDS or IDS. ESMO guidelines	

	state and a study by Vergote *et al.* shows that there is no significant difference in PFS and OS based on PDS or IDS. • The ERG suggested that the company explore the impact on results of re-weighting the proportion of patients with stage III disease and NVRD after IDS in PRIMA to be reflective of the proportion of patients with stage III NVRD (irrespective of type of surgery) in clinical practice. There are several methods available for this approach, including corrected group prognosis, the average covariate method, and inverse probability of treatment weighting (ERG report 2.4.3).	
4. Maturity of clinical trial results and proportional hazards	• At the point of primary analysis overall survival (OS) data are immature with 9.9% and 12.6% of people having died in the niraparib and placebo arms, respectively. Median OS was [redacted] months in the niraparib arm but not yet reached in the placebo arm. There was no statistically significant difference between treatment arms (hazard ratio [HR] 0.70, 95% confidence interval [CI]: 0.442 to 1.106). • Progression free survival on subsequent treatment (PFS2) data are also immature with [redacted]% and [redacted]% of people experiencing a second progression in the niraparib and placebo arm, respectively. There was no statistically significant difference between treatment arms (HR 0.81, 95% CI: 0.577 to 1.139). • The company presented an assessment of the proportional hazards assumption for PFS in the ITT population based on an inspection of plots of the log cumulative hazards and Schoenfeld residual. The company concluded that the relative hazards are likely to vary over time and the assumptions of proportional hazards is unlikely to hold for PFS for the ITT population. • The ERG state that the PFS HR and 95% CI is therefore difficult to interpret and potentially misleading (ERG report 2.3.1).	• No significant differences in overall survival have been observed between the niraparib and placebo arms in PRIMA, therefore the extent to which niraparib might be expected to extend life is uncertain. The lack of mature data for the long-term outcomes introduces uncertainty into the clinical and cost effectiveness evidence. • The technical team agrees with the ERG that as the relative hazards are likely to vary over time, the HR for PFS in the ITT population should be interpreted with caution.
5. Estimation of overall survival using a Δ progression-free survival: Δ overall survival ratio	• The company considered that the niraparib OS data from PRIMA were too immature to fit OS curves through standard parametric modelling (see issue 4). Therefore, the company adopted an alternative method to estimate OS, using PFS data.	• The PFS to OS ratio used to estimate OS for niraparib in the model is a key driver of the results.

	• Submissions in previous appraisals (TA528 and TA620) have used a relationship between PFS and OS to estimate OS curves. TA528 and TA620 used data from Study 19 to obtain this estimate. The company claim that Study 19 provides the only available long-term OS data on PARP inhibitors. • Study 19 compared olaparib monotherapy with RS in BRCA+ patients for second-line maintenance treatment, with a 7-year follow-up. The company used Study 19 to derive a ΔPFS:ΔOS ratio. For the ITT population in PRIMA, the company used a ΔPFS:ΔOS ratio of 1:2 to generate a HR between RS OS and niraparib OS. The HR was then applied to the RS OS fitted curve (fitted by a standard parametric model to Kaplan-Meier data in PRIMA) to estimate the niraparib OS curve in the model (ERG report 3.2.4.1). • The company used Spearman's rank correlation to show the statistical association between PFS and OS outcomes observed in Study 19 up to 12 months. However, the ERG noted that this does not provide any indication of the magnitude of this relationship beyond 12 months or how the relationship should be quantified. • The use of HRs to estimate the niraparib OS curve assumes that niraparib has a constant survival advantage over RS for the entire time horizon of the analysis (39 years). • The ERG raised concerns with the methods used to model overall survival. It noted that the OS HR of [redacted] used by the company in the ITT model to generate the 1:2 ΔPFS:ΔOS relationship is not reflective of the treatment effect for niraparib vs RS observed in PRIMA (OS HR 0.70, 95% CI: 0.44 to 1.11). • In previous appraisals the committee concluded that using a ΔPFS:ΔOS ratio of either 1:2 or 1:1.5 was unreliable and not adequately supported by the trial evidence available at the time (TA620) or provided uncertain estimates due to the uncertainty around the PFS results (TA528). • The ERG for TA528 noted that the OS and PFS relationship appears not to be stable between different populations. • The ERG noted that the application of a HR to a log-logistic model is methodologically inappropriate and using a Weibull or generalised	• It is unclear if it is appropriate to extrapolate data from Study 19 to this population in order to derive the ΔPFS:ΔOS. • Clinical input is required to determine if it is appropriate to assume that niraparib has a constant survival advantage over routine surveillance over the entire time horizon of the model. • OS Kaplan-Meier data from PRIMA is available for niraparib and could be used to fit a curve to estimate niraparib OS in the model. It is acknowledged that these data are immature and that any estimations of a survival benefit with niraparib should be interpreted with caution. • Clinical input is required to determine if it is plausible for 1% of people to be alive at age 100 after treatment with niraparib.

	gamma curve to fit the RS KM OS data would resolve this issue; however the Weibull curve is likely to considerably underestimate long-term survival and the generalised gamma is likely to overestimate it (ERG report 3.2.6.2.1). • The ERG also noted that based on the equation used to calculate niraparib OS by the company, any over estimation in the relative treatment effect of PFS is doubled in the OS curves (ERG report 3.2.6.2.1). • Concerns over OS modelling are further substantiated as at 39 years (the time horizon used in the model) 100% of people in the RS arm are dead, but 1% of people in the niraparib arm remain alive (at age 100) (ERG report 3.2.5). • The ERG considered 3 different sets of scenarios to investigate changes in OS modelling. These were: a) PFS to OS ratio of 1:0.66 as per TA598 b) PFS to OS ratio of 1:1 c) HR between RS OS and niraparib OS of 0.7 as observed in PRIMA. • The ERG concluded that without having more mature OS data from PRIMA it is not possible to make inferences on the survival benefits of niraparib without a paramount level of uncertainty. • For these analyses conducted by the ERG, it was assumed that niraparib has a constant survival advantage over RS for the entire time horizon of the analysis (given the use of a HR). The ERG notes that this is unlikely to represent clinical reality, and notes that this could be surpassed with fitting an OS model to the OS KM niraparib data from PRIMA (provided survival predictions are valid).	
Issues related to cost-effectiveness		
6. Company's model structure	• The company model uses a partitioned survival approach with 3 health states: progression-free survival, disease progression and death. • PRIMA collected data on second progression events (PFS2), defined in PRIMA as time to progression on the next anti-cancer therapy.	• It is acknowledged that the data for PFS2 are immature, however, this is not considered to be a valid reason for not including it in the economic model. The technical team prefer that

	• Data on PFS2 events could have been used to capture second progression-related costs and the impact of secondary events on quality of life (ERG report section 3.2.4.3). At clarification the company reported that PFS2 data from PRIMA were too immature to be included in the model. • The ERG notes that that at data cut-off PFS2 data were [redacted] mature and more immature data has been included in the company model.	the PFS2 data from PRIMA is used to inform a second progression health state within the company's model.
7. Estimation of long-term remission	• Based on evidence from the University of Edinburgh Ovarian Cancer database and expert opinion, the company assumed that people who are disease free at 7 years in the model do not relapse again and start incurring the general population mortality (long-term remission). • For the PRIMA ITT population, the proportion of people assumed to be in long-term remission at 7 years was estimated from the PFS and OS curves used in the model. For the stage III with NVRD after PDS population included in the company's MA population, the proportion of people assumed to be in long-term remission at 7 years was taken from a study by Du Bois *et al.,* 2009, which evaluated the outcomes in patients with advanced ovarian cancer receiving platinum-based chemotherapy. • The ERG states that the company's estimation of long-term remission in the model relies on a weak methodology as is relies on external sources of evidence. However, it also notes that PRIMA does not provide robust evidence to substantiate a cure threshold for niraparib. • Clinical expert advice given to the ERG was that when patients have been in remission for 10 years, they would be discharged. • The ERG's preferred assumptions included removing the long-term remission approach from the model. It also conducted a scenario analysis assuming PFS patients stop incurring costs at 10 years, based on clinical advice. • Scenario analysis performed by the company indicates there is a minimal effect on the ICER when long-term remission is removed from the model.	• There are no sufficiently mature data to substantiate that niraparib leads to long term remission in a higher proportion of patients than RS at 7 years.

8. Modelling of progression-free survival	• The company presented three alternative options to model PFS: o the company's base case for the ITT population (including a 7-year cure assumption) o the company's base case for the MA population (applying HRs for the stage III NVRD population to the base case ITT curves and including a 7-year cure assumption; see issue 2) o the ITT population excluding the cure assumption (ERG report 3.2.6.1.1). • Time to first subsequent treatment data from the University of Edinburgh Ovarian Cancer Database was used as a proxy for PFS data and used for comparative analysis with the parametric model by the company. • The ERG considers CHORUS to be an appropriate study to consider when validating the long-term estimates of PFS from the model. • The ERG preferred assumptions included using the ITT population curves excluding the cure assumption for niraparib and RS PFS estimates in the model.	• The University of Edinburgh data uses time to first subsequent therapy (TFST) as a proxy for PFS. It is likely that TFST is an overestimate of PFS as subsequent treatment may not be started immediately following progression.
9. Time to treatment discontinuation	• The PRIMA protocol indicated that people should discontinue treatment at 3 years unless continuation was deemed appropriate by the consulting physician. • Therefore, the company included a 3-year stopping rule in its model but assumed that [redacted] of participants who had not discontinued treatment at 3 years would carry on receiving niraparib. • The ERG noted that as the proportion of patients who remained on treatment after the follow-up period in PRIMA is unknown, this assumption cannot be validated (ERG report, 3.2.6.3). • It is unclear what niraparib dose is assumed for the participants who continue treatment following the 3-year stopping rule in the company model. • The proposed summary of product characteristics does not specify a treatment duration of 3 years and recommends that treatment with niraparib should be continued until disease progression or toxicity.	• The clinical evidence from PRIMA will incorporate the treatment benefit for people who continued to receive niraparib after 3 years of treatment but this proportion is unknown. • It is unclear if the proportion of people who continue receiving niraparib in PRIMA is the same as in the modelled population. This has consequences for the clinical and cost-effectiveness as the

	• The ERG's preferred assumptions included assuming no treatment discontinuation with niraparib.	proportion included for the costs may not be equal to the proportion included for the effects. • Clinical input is needed to determine if the proportion of participants assumed to continue receiving niraparib after 3 years in the company's model is likely to reflect clinical practice. • It is important to understand the dose of niraparib given to people who continue in the model following the 3-year stopping rule as this will have an impact on the cost-effectiveness estimate.
10. Utility values	**Capturing age in utility values** • The company did not include age-related utility decrements in its base-case analysis. The average age of participants in PRIMA is 62, however, the lifetime time horizon in the model means patients can live up to 100 years. • The company included age-utility decrements in a scenario analysis but does not deem it appropriate. • At clarification, the company stated that there is a concern about equality for age and gender should age-related utility decrements be included in the analysis. • The ERG's preferred assumptions included applying age-related utility decrements in the model. **Company's utility values for PFS** • The company assume that the PFS utility value ([redacted]) is appropriate throughout the full model time horizon. When people enter the model at 61 years of age, their PFS utility is [redacted] than that of the general population utility (0.81). However, at 7 years (the point of	• Age-related utility decrements should be included in the base-case analysis. • The company's approach may overestimate the utility of people who survive long term which will impact the cost-effectiveness estimate.

	cure in the company model), patients in the PFS state have a [redacted] utility than the general population utility (0.78).	
11. Subsequent treatments	• Subsequent treatments in PRIMA were not recorded by line of therapy, or by whether they were given as combination or single therapies. • A small proportion of patients in PRIMA [redacted] (less than [redacted]). These treatments are recommended within the Cancer Drugs Fund (CDF) for second-line use and are therefore not established in routine clinical practice in the UK. • The company's base case did not include treatments recommended within the CDF, in line with NICE's position statement on CDF products. • In PRIMA, there were 232 progression events in the niraparib arm and 154 progression events in the RS arm. The proportion of patients who also received subsequent chemotherapy in PRIMA amount to 85% and 81% for niraparib and RS, respectively (ERG report 3.2.9.2.1). The ERG notes that the number of people receiving subsequent treatments in PRIMA is lower that what is expected in UK practice.	• The proportion of people receiving subsequent treatment in PRIMA may not be representative of UK clinical practice. This may have implications on more mature OS data from PRIMA and its generalisability to UK clinical practice.
12. Cancer Drugs Fund	• Company proposes that niraparib be included in the CDF to allow time for the data in PRIMA to mature. OS data are immature (11%). The PRIMA trial is ongoing and will continue to collect data on OS, which is expected to reach maturity in [redacted] • The committee may consider a recommendation for use within the CDF if the following criteria are met: o the ICERs presented have the plausible potential for satisfying the criteria for routine use, o it is possible that the clinical uncertainty can be addressed through collection of outcome data from patients having treatment in the NHS, o it is possible that the data collected (including from research already underway) will be able to inform a subsequent update of the guideline (normally within 24 months).	• The technical team note that the current clinical trial data are very immature and that further data collection is planned which may reduce important uncertainties in clinical outcome data.

2 Questions for engagement

Generalisability of the PRIMA results to UK clinical practice – dose used in trial versus clinical practice

1. Based on the complete and partial response rates observed in the PRIMA trial after platinum-based chemotherapy, is the patient population of the trial reflective of the population that would be eligible for niraparib after response to first-line platinum-based chemotherapy in UK clinical practice?

2. Is the niraparib dose used in PRIMA reflective of likely dosing in clinical practice?

3. The company assumed that the weighted average dose of niraparib received in month 18 of treatment would be the same for the duration of the treatment period with niraparib in the model. Is it reasonable to assume that the dose tolerated by month 18 would be expected to continue to be tolerated?

4. Is the company's post-hoc subgroup analysis of fixed versus individualised dosing robust enough to make a judgement on the issue around changing the dosing procedure?

Generalisability of the PRIMA results to UK clinical practice – exclusion of population with no visible residual disease after primary debulking surgery

5. There are a range of estimates for the proportion of people with stage III disease with NVRD. In clinical practice, what is the estimated proportion of people with stage III disease with NVRD: irrespective of type of debulking surgery; after IDS and after PDS? Is evidence available to support these estimates?

6. Can the company provide further justification for the choice of the proportion of patients with stage III disease with NVRD after PDS?

Sources of evidence for estimating progression-free survival for people with stage III no visible residual disease after primary debulking surgery

7. The company has used data from various sources in its base case and scenario analyses for estimating PFS for people with stage III disease and NVRD after PDS and the ERG have suggested an alternative approach. What is the most appropriate method for estimating the outcomes in the population excluded in PRIMA but included in the expected licensed population (people with stage III disease with NVRD after PDS)?

8. Is it appropriate to apply hazard ratios derived from data in PAOLA-1, SOLO-1 and the PRIMA stage III subgroup to the PRIMA ITT curves?

9. How are the confounding factors, such as bevacizumab use in PAOLA-1 and BRCA mutation status in SOLO-1 likely to affect the 'NVRD effect' and 'treatment effect'?

10. Is it reasonable to assume a class effect between olaparib and niraparib in order to estimate the 'NVRD effect' and 'treatment effect'?

11. Is the assumption that patients with stage III disease and NVRD after IDS have similar prognosis to patients with stage III disease and NVRD after PDS in line with what is seen in clinical practice?

Estimation of overall survival using a ∆ progression-free survival: ∆ overall survival ratio

12. The company used Study 19 (which evaluated olaparib as second line treatment in BRCA+ patients with 7-year follow-up) to estimate a PFS:OS ratio and therefore assumed a class effect between olaparib and niraparib. Is it appropriate to assume this class effect as a basis for estimating the PFS:OS ratio?

13. Is it appropriate to assume that niraparib has a constant survival advantage over routine surveillance over the entire time horizon of the model?

14. The company provided a scenario analysis with PFS:OS ratios ranging from 1:1 up to 1:3. What is likely to be the most appropriate ratio to use when estimating OS from PFS in this population?

15. The company's MA base case OS curve predicts that [redacted] of patients would be alive at 30 years in the niraparib arm of the model, when they would be 91 years old. This estimate compares with [redacted] in the company's curve for the ITT population (and [redacted] with no cure assumption). Is it clinically plausible that this proportion of people would be alive at this stage?

16. The ERG noted that the HR used by the company to generate the 1:2 ΔPFS:ΔOS relationship is not reflective of the treatment effect for niraparib compared with routine surveillance observed in PRIMA. The hazard ratio of [redacted] used by the company to generate the 1:2 ΔPFS:ΔOS relationship suggests [redacted] relative treatment effect for niraparib compared with routine surveillance than that observed in PRIMA (HR of 0.70 [95% CI 0.44 to 1.11]). Can this discrepancy in treatment effect between the hazard ratio generated from the ΔPFS:ΔOS ratio and the data in PRIMA be explained?

17. In the company's model, at 39 years (the time horizon used in the model) 100% of people in the routine surveillance arm are dead, but 1% of people in the niraparib arm remain alive (at age 100). How clinically plausible is this estimate?

Company's model structure

18. Given that patients can experience multiple disease progressions, would a 4-state model (progression-free, progression-free 2, progressed disease and death) be more suitable for decision making, as data are available from PRIMA for progression-free and 2nd progression-free survival?

Estimation of long-term remission

The ERG agrees with company that the appropriate use of mixture cure models relies on the existence of mature data from studies with long follow-up times that exceed anticipated point of cure time, as well as sufficient numbers of patients at risk at the end of follow-up in order to robustly estimate a cure fraction.

19. What is the most appropriate method for estimating the point of long-term remission, given the immature data available from PRIMA?

20. The company have assumed long-term remission is achieved in people who have had progression-free disease for 7 years. Does this align with what is seen in clinical practice?

The company justified using data from Du Bois *et al.,* 2009 to estimate the proportion of people in long-term remission in the stage III NVRD after PDS population because it included a large sample size, assessment of a range of surgical outcomes and long follow-up (144 months) allowing for PFS and OS data to be extracted at 5, 7 and 10 years. The ERG suggest that this data could also be taken from the NVRD PFS curves estimated in the model, which would be consistent with the approach used in the ITT population.

No comparative analysis has been provided between the De Bois *et al.,* study and the population in PAOLA-1 (where treatment effect for patients with stage III disease and NVRD after PDS was estimated), nor with the population in PRIMA.

21. Is the approach to estimating the proportion of people in long-term remission in the stage III disease and NVRD after PDS population using external data from Du Bois *et al.,* 2009 appropriate?

22. Is the ERGs assumption of removing long-term remission from the model appropriate?

23. In UK clinical practice, is it correct that after 10 years in progression free disease, patients in this population are discharged?

Modelling of progression-free survival

24. The company uses data from the University of Edinburgh Ovarian Cancer database on TFST as a proxy for data on PFS, which it uses to validate long-term model estimates. Is TFST a reasonable alternative for PFS in this population?

Time to treatment discontinuation

25. Can it be assumed that all people who have no radiological evidence of residual disease after 3 years will stop treatment?

26. Based on clinical expert opinion and evidence from SOLO-1, the company assumed that [redacted] of participants who had not discontinued treatment at 3 years would carry on receiving niraparib. Based on clinical experience with similar treatments, what is the expected proportion of patients who would continue to receive niraparib at the end of the 3-year treatment period?

27. What length of time is it reasonable to assume niraparib would continue to be given to people who did not discontinue treatment at 3 years?

28. What dose of niraparib was included in the model for people who continued to receive treatment after 3 years?

Utility values

29. Are the utility values that the company have used clinically plausible?

Subsequent treatments

30. Are the proportions of people receiving subsequent treatment in PRIMA representative of UK clinical practice?

Cancer Drugs Fund

31. Is there further data being collected that could reduce uncertainty surrounding longer-term effectiveness and health outcomes in the relevant population(s)?

32. When will these additional data become available?

33. How suitable is the technology for use in the Cancer Drugs Fund (CDF)?

NICE National Institute for Health and Care Excellence

Technical engagement response form

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1680]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **9 October 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

1. Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
2. Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
3. Do not include medical information about yourself or another person that could identify you or the other person.
4. Do not use abbreviations.
5. Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
6. If you provide journal articles to support your comments, you must have copyright clearance for these articles.
7. Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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8. Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.21 to 3.1.30) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	Nikki Roebuck, Zsofia Kiss
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	GSK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Submitting company

Company cover statement

The Company would like to thank NICE and the Evidence Review Group (ERG) for the opportunity to review and respond to the technical questions for engagement. The Company's responses are presented in the table below. In addition to the response the Company has presented a revised base-case (Appendix 1) which includes revised data from the University of Edinburgh database Ovarian Cancer study and the removal of the long-term remission modelling assumption. Deterministic, probabilistic and key scenario analyses accompany the revised base-case.

With a simple discount of [redacted]%, across all analyses ran niraparib remained within a cost-effective range versus routine surveillance. At a willingness to pay threshold of £30,000 or more niraparib was a 100% and 98% cost-effectiveness in the marketing authorisation (MA) and intention-to-treat (ITT) population, respectively. Niraparib can therefore be considered a cost-effective treatment option within the marketing authorisation population, following response to first-line platinum-based chemotherapy.

Questions for engagement

Issue 1: Generalisability of the PRIMA results to UK clinical practice – dose used in trial versus clinical practice	
1. Based on the complete and partial response rates observed in the PRIMA trial after platinum-based chemotherapy, is the patient population of the trial reflective of the population that would be eligible for niraparib after response to first-line platinum-based chemotherapy in UK clinical practice?	Complete and partial response after platinum-based chemotherapy have been reached in 69.2% and 30.8% of the eligible population in the niraparib arm of the PRIMA trial, respectively. Clinical insight, obtained through an advisory board and through 1:1 discussions with the clinical community, suggests that this is reflective of the United Kingdom (UK) clinical practice. Furthermore, these estimates included 21 patients recruited from 9 UK sites.
2. Is the niraparib dose used in PRIMA reflective of likely dosing in clinical practice?	The PRIMA trial included two cohorts of patients (those initiating treatment on a fixed dose and those initiating on individualised dosing). The marketing authorisation reflects the dose schedule administered in the individualised dosing population. Details have been provided on the maturity, baseline patient characteristics and outcomes of the individualised dose cohort in the Company's response to ERG clarification A4 and A12. These data have also been reviewed and accepted by European Medicines Association (EMA). UK clinical insight, obtained through

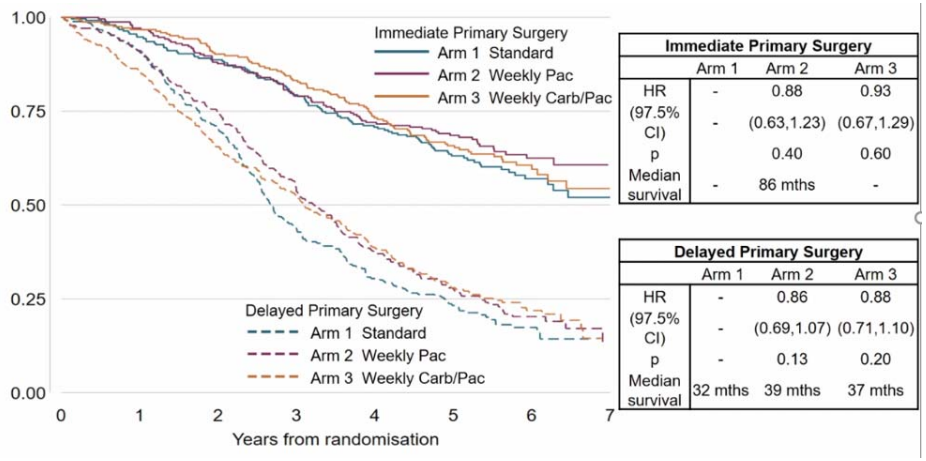
	a clinical advisory board and through 1:1 discussions with the clinical community, confirm that the preference will be to use the individualised dosing schedule in clinical practice. Their experience has found that this supports toxicity management and reduces dose delays. Please note that according to the recently conducted dosing analysis, [redacted] patients have started on individualised dosing in the ITT population of the PRIMA trial. Of these [redacted] and [redacted] patients started on 200mg on the niraparib and placebo arms, respectively and [redacted] and [redacted] patients started on 300mg on the niraparib and placebo arms, respectively. A total of [redacted] and [redacted] patients were mis-dosed in the two arms, respectively. Therefore, [redacted]% of the patients in the individualised patient group started on 200mg and [redacted]% started on 300g ([redacted]% of the individualised dose patients received an incorrect dose).
3. The company assumed that the weighted average dose of niraparib received in month 18 of treatment would be the same for the duration of the treatment period with niraparib in the model. Is it reasonable to assume that the dose tolerated by month 18 would be expected to continue to be tolerated?	As presented in response to the ERG clarification question B17, it can be observed that the dose distribution (300 mg, 200 mg and 100mg) is relatively stable from [redacted] to [redacted] within the PRIMA trial. Clinical insight suggests that this trend would continue and that they would not expect the dose distribution or tolerability to change significantly between [redacted] and treatment discontinuation in clinical practice. Long-term safety data from the NOVA trial supports the tolerability of niraparib for the treatment of ovarian cancer. It was observed that dose reductions due to treatment emergent adverse events were highest in Month 1 of trial and declined every month thereafter.[1]
4. Is the company's post-hoc subgroup analysis of fixed versus individualised dosing robust enough to make a judgement on the issue around changing the dosing procedure?	A detailed dosing analysis package was submitted to EMA. This formed the basis of the decision to include the individualised dosing regimen as the recommended starting dose in the Committee for Medicinal Products for Human Use (CHMP) opinion.[2] UK clinical insight, obtained through an advisory board and 1:1 discussions with the clinical community, has also confirmed that this flexibility in starting dose is appropriate and will be applied in UK clinical practice.
Issue 2: Generalisability of the PRIMA results to UK clinical practice – exclusion of population with no visible residual disease after primary debulking surgery	
5. There are a range of estimates for the proportion of people with stage III disease with NVRD. In clinical practice, what is the estimated proportion of people with stage III disease with NVRD: irrespective of type	In the UK there are no centralised guidelines for reporting of surgical outcomes, nor are there robust data collection mechanisms to appropriately report the proportion of patients who are classified as stage III no visible residual disease (NVRD) after primary debulking surgery (PDS) in standard practice. This therefore results in inconsistencies in the terminology used to describe

of debulking surgery; after IDS and after PDS? Is evidence available to support these estimates?	the surgical outcome. Discordance of up to 48% between a surgeon's operative assessment and pre-treatment imaging has been reported, including in surgeries deemed to be complete cytoreduction.[3,4] Furthermore, assessment of surgical outcomes can be complicated by the difficulty in differentiating between the disease and tissue changes due to surgical dissection.[3] Most patients do not undergo imaging after PDS to identify areas of residual disease in clinical practice. Therefore, accuracy in determining the presence or absence of visible residual disease (VRD) remains dependent on the individual surgeon and the extent of their experience in treating advanced ovarian cancer. In light of the above, the Company agree with the clinicians' and the ERG's assumption that the proportion of patients who are stage III NVRD after PDS is in the range of 25%-40%, however, please note that as part of the revised Edinburgh database analysis a more conservative lower bound was identified from the available real world evidence (see response to question 6 below).
6. Can the company provide further justification for the choice of the proportion of patients with stage III disease with NVRD after PDS?	To address the proportion of patients' ineligible for the PRIMA trial, the Company chose to work with a robust dataset (the Edinburgh Ovarian Cancer Database), that has been used previously in a NICE submission in ovarian cancer (TA598 [olaparib 1L])[5], to identify the number of patients in a real-world setting. Since the ERG report, an updated analysis was run with the Edinburgh Ovarian Cancer Database, focusing on a simulated MA-population and a PRIMA-like population, which now only exclude patients with stage III disease with NVRD after PDS. This new analysis revealed that [redacted]% of the MA-like population are classified as stage III NVRD after PDS. Restricting to a more contemporary cohort of patients diagnosed between 2010 and 2015, to understand if practice has changed over time, showed a similar proportion; [redacted]% of the population met the required surgical criteria. This contemporary cohort value has been used for our analysis presented in the appendix. This figure is lower than what has been anticipated by clinical experts and the ERG (25-40%). Furthermore, this demonstrates a large variability across treatment centres. The economic model has been updated to reflect the revised data from the contemporary cohort (Appendix 1), to provide a more conservative estimate of the MA population outcomes. Details of this revised database analysis are available in Appendix 2.

Issue 3: Sources of evidence for estimating progression-free survival for people with stage III no visible residual disease after primary debulking surgery	

7. The company has used data from various sources in its base case and scenario analyses for estimating PFS for people with stage III disease and NVRD after PDS and the ERG have suggested an alternative approach. What is the most appropriate method for estimating the outcomes in the population excluded in PRIMA but included in the expected licensed population (people with stage III disease with NVRD after PDS)?	The Company thanks the ERG for their suggestion of utilising the PRIMA data to inform the survival of stage III patients with NVRD after PDS (patient group excluded from PRIMA but expected to be included in the licensed population[2]). The ERG's approach assumes that the unobserved prognosis and treatment effect in stage III patients with NVRD after PDS is equivalent to that of the observed stage III patients with NVRD after interval debulking surgery (IDS) within the trial.
	
	The Company have discussed this alternative approach, which is understood to be a reweighting of the patient population –to increase the relative contributions of those who have NVRD after IDS– and have concluded that is it not appropriate to assume that the real-world prognosis and treatment effect in stage III patients with NVRD after IDS and PDS are equivalent for the trial patients for the following reasons:
	
	• ***<u>The prognosis of stage III NVRD patients after PDS is expected to be different (referred to as the 'NVRD effect' in the MA adjustment)</u>***
	  • ***Patients selected for PDS are biased towards those who are expected to have a better prognosis***
	  o Those selected for PDS are more likely to have lower staging, reduced disease burden, better fitness levels and less comorbidities.[7]
	  o Clinical data from the UK-led ICON-8 trial highlights this bias and shows a large difference in survival between the patients who had immediate surgery and those who had delayed surgery. This is most likely driven by differences in disease characteristics between patients who were selected for primary and patients selected for interval surgery (Figure 1).[8]

Figure 1: ICON-8 OS, by timing of surgery. Presented at ESMO Virtual 2020 congress[8]



Immediate Primary Surgery	Arm 1	Arm 2	Arm 3
HR	-	0.88	0.93
(97.5% CI)	-	(0.63,1.23)	(0.67,1.29)
p		0.40	0.60
Median survival	-	86 mths	-

Delayed Primary Surgery	Arm 1	Arm 2	Arm 3
HR	-	0.86	0.88
(97.5% CI)	-	(0.69,1.07)	(0.71,1.10)
p	-	0.13	0.20
Median survival	32 mths	39 mths	37 mths

Abbreviations: Carb, carboplatin; CI, confidence interval; ESMO, European Society for Medical Oncology; HR, hazard ratio; OS, overall survival; Pac, paclitaxel

- ***Stage III patients with NVRD after PDS are considered by clinicians to have the most favourable prognosis***
    - Clinical insight, obtained through an advisory board and 1:1 discussions with the clinical community, confirms an expected prognostic advantage for stage III patients achieving NVRD after PDS compared to IDS. Please refer to response to question 11 for further details.

- ***<u>The Treatment effect is expected to be different between patient groups (referred to as the 'treatment effect' in the MA adjustment:</u>***
    - A recent oral presentation presented at International Gynecologic Cancer Society (IGCS) in September 2020 confirmed a previously reported finding from 2019 that higher and lower risk groups have different treatment effects. All patients within the low-risk subgroup were stage III patients, underwent PDS and achieved complete tumour resection (i.e. NVRD), whereas in the high-risk subgroup the majority of patients underwent IDS (>56%), and of these patients between 68%

(bevacizumab) and 71% (olaparib plus bevacizumab) achieved complete tumour resection. Within a broad patient population (patients with and without a BRCA mutation) olaparib plus bevacizumab combination treatment resulted in a 40% and 54% reduction in the risk of progression in the high and low risk populations, respectively (Table 1). As such it is appropriate to expect that the treatment effect will be different between patients who underwent PDS and IDS.

Table 1: PFS in high and low risk PAOLA-1 patient populations

Subgroup	Median PFS (months)		HR (95% CI)
	Olaparib + bevacizumab	Bevacizumab	
High risk	20.3 (n=399)	14.7 (n=196)	0.60 (0.49 – 0.74)
Low risk	39.3 (n=138)	22.9 (n=73)	0.46 (0.30 – 0.72)

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

Therefore, the Company believe that assuming that the prognosis of stage III NVRD after PDS is equivalent to the prognosis after IDS would not characterise the survival or outcomes of the subgroup of patients excluded from PRIMA correctly. Furthermore, through the use of external data sources, the Company's approach takes into account the expected prognostic and treatment effect for stage III patients with NVRD after PDS (as highlighted above).

Despite this, the Company acknowledges the concerns raised by the ERG and the NICE technical team on the data sources used to inform the MA extrapolation. The Company originally considered three data sources (PAOLA-1, SOLO-1, PRIMA), all of which are presented and included as scenarios within the CS. Furthermore, the Company believes that some of this uncertainty could be addressed through data collection – through inclusion of the MA population in the data collection arrangement, were this product to go into the Cancer Drugs Fund (CDF).

Scenario analyses indicated that the cost-effectiveness results for the MA population were consistent regardless of the data source used and support the findings based on the PRIMA ITT population. To select the most appropriate source for the base case analysis, the Company consulted UK clinical and economic experts at an advisory board (April 2020). The consensus was that PAOLA-1 was the most appropriate data source for the following reasons:

	• Distinct subgroups and no overlap between VRD and NVRD patient groups • Broad patient population including patients with and without a *BRCA* mutation The Company acknowledge that the PAOLA-1 data set has its limitations; for example the concomitant bevacizumab use across treatment arms (please refer to response to question 9). Overall, the Company believe that their approach, which allows survival for patients with stage III NVRD after PDS to be modelled, is appropriate. In an attempt to alleviate the concerns of the ERG and the NICE Technical Team, the Company have reduced the proportion of patients who are stage III NVRD after PDS within the base case analysis (please refer to question 6 and Appendix 1) and have conducted a scenario analyses where the 'NVRD effect' is modelled as opposed to the 'NVRD effect and treatment effect' for the niraparib treatment arm (Appendix 1).
8. Is it appropriate to apply hazard ratios derived from data in PAOLA-1, SOLO-1 and the PRIMA stage III subgroup to the PRIMA ITT curves?	In response to the ERG clarification questions (question A5) the Company assessed the proportional hazards assumption for the following progression-free survival (PFS) datasets: • PAOLA-1[9] o NVRD versus VRD placebo plus bevacizumab treatment arms o NVRD versus VRD olaparib plus bevacizumab treatment arms • SOLO-1 (BRCAmut patients only) [10] o NVRD versus ITT placebo treatment arms o NVRD versus ITT olaparib treatment arms It was concluded that the proportional hazards assumption between the NVRD and VRD PFS arms (or ITT for SOLO-1) cannot be rejected. Therefore, it was considered appropriate to assume that the PFS hazards for the NVRD and VRD patient groups are proportional. The Company's model base case applies hazard ratios (HR) obtained from PAOLA-1 to the PRIMA ITT curves to predict the curves for the anticipated MA population. This approach assumes that the PFS hazards for the NVRD and VRD patient groups are proportional. This assumption is in line with the conclusions drawn from the assessment provided by the Company in response to ERG clarification question A5. On this basis, the Company believe it is appropriate

	to apply HRs to achieve the PFS curves for the NVRD patient group in order to estimate PFS for the MA population. It is worth mentioning that the Company's model does not assume proportional hazards between niraparib and routine surveillance for PFS.
9. How are the confounding factors, such as bevacizumab use in PAOLA-1 and BRCA mutation status in SOLO-1 likely to affect the 'NVRD effect' and 'treatment effect'?	The Company's response to question A7 and A8 of the ERG clarifications discussed the potential impact of bevacizumab treatment (PAOLA-1) and the presence of a *BRCA* mutation (SOLO-1) on the estimation of the 'NVRD effect' and the 'treatment effect' within the economic model. ***Impact of bevacizumab treatment*** • As highlighted in the Company's response to ERG question A7, the "NVRD effect" derived from PAOLA-1 may be underestimated due to bevacizumab monotherapy treatment within the NVRD and VRD PAOLA-1 subgroups. Furthermore, the Company acknowledge that the "treatment effect" may also be confounded by bevacizumab treatment within the NVRD and VRD PAOLA-1 subgroups. • Both the "NVRD effect" and the "treatment effect" were calculated by comparing patients receiving the same baseline treatment (olaparib plus bevacizumab or bevacizumab monotherapy) to estimate the difference in PFS on NVRD patients relative to VRD patients. The Company expects that the impact of confounding will be minor as the relative difference between subgroups were analysed. Furthermore, the Company would like to reiterate that the decision to use the PAOLA-1 data within the base-case analysis was driven by clinical and economic expert opinion. ***Impact of a BRCA mutation*** • Both the presence of a *BRCA* mutation and the achievement of NVRD following PDS impact the prognosis of a patients with ovarian cancer: o The presence of a *BRCA* mutation significantly increases the lifetime risk of developing ovarian cancer, but patients without a *BRCA* mutation are associated with worse survival than those who carry the mutation.[11–13] This improvement is evident from the PRIMA and PAOLA-1 trial, where the risk of progression was observed to be lower in patients with a *BRCA* mutation compared to those without.[9,14]

	○ Patients with stage III NVRD following PDS have a better prognosis than patients with stage III/IV VRD, irrespective of treatment received (Section B.2.14 of the CS). • Despite the evidence on how these factors individually affect patients' prognosis, the Company is unaware of explicit evidence on how these two factors interact. The analysis conducted by the Company considered the relative difference between the SOLO-1 ITT and NVRD patient populations. As such the *BRCA* mutation factor is included in both arms of the analysis and is not expected to have a large impact on the magnitude of the "NVRD effect" or the "treatment effect" derived from the SOLO-1 data.
10. Is it reasonable to assume a class effect between olaparib and niraparib in order to estimate the 'NVRD effect' and 'treatment effect'?	The Company sought further UK clinical opinion on the assumption of a class effect between niraparib and olaparib. Feedback was obtained from three UK clinicians, and was consistent across responses. All three clinicians agreed that similar benefits are expected across all PARP inhibitors. Feedback included: • They did not expect to see significant differences between PFS and overall survival (OS) benefit across PARP inhibitors. • They would expect all PARP inhibitors to behave similarly. • They would expect to see a class effect across PARP inhibitors and expect to see the SOLO-1 data reflected in PRIMA. In addition, the similarities across PARP inhibitor treatment is reflected within the second-line setting (NOVA, SOLO-2 and ARIEL-3).[15–17] The Company believe that there is no reason to why PARP inhibitors would behave differently within the first-line setting. Given the second-line evidence and the feedback from UK clinicians, the Company believe it is reasonable to assume a class effect between niraparib and olaparib in order to estimate the "NVRD effect" and the "treatment effect".
11. Is the assumption that patients with stage III disease and NVRD after IDS have similar prognosis to patients with stage III disease and NVRD after PDS in line with what is seen in clinical practice?	The overarching aim of debulking surgery in newly diagnosed advanced ovarian cancer is to achieve NVRD, providing the patient with the best opportunity for long-term relapse free survival. Often the surgeon will not attempt surgery until they are confident of removing all disease and

	therefore the practice of pre-surgical NACT is becoming more common, to shrink disease burden and increase the chance of achieving NVRD. A number of trials, including those by Vergote et al (2010) and Kehoe et al (2015) have tried to address the equivalence of long-term outcomes following PDS compared to IDS.[18,19] However, both studies have been open to criticism, particularly due to the poor survival rates. In the European Organisation for Research and Treatment of Cancer (EORTC) study by Vergote et al, only 61 out of 310 (19.4%) enrolled patients underwent PDS and had NVRD. In comparison 151 out of 322 (51.2%) enrolled patients underwent IDS and achieved NVRD. Despite that smaller proportion of patients having achieved NVRD in the PDS treatment arm, the survival outcomes were comparable between the PDS and IDS populations (Vergote 2010 supplementary materials, Figure 1 and 2).[18] This therefore suggests an improved prognosis for patients who achieve NVRD after PDS compared to after IDS. If the balance of NVRD after PDS and IDS was similar between treatment arms, then the patients within the PDS group should have been expected to have performed better. In the second study by Kehoe et al, only 17% of patients who underwent PDS had NVRD. In comparison, 39% of patients in the primary chemotherapy treatment arm were classified as NVRD. As with Vergote, the survival outcomes across the two treatment arms are similar (Kehoe 2015, Figure 2), even though the PDS treatment arm contained a smaller proportion of NVRD patients. Therefore, if the treatment arms had been balanced, it should have been expected that the PDS treatment arm would have performed better.[19] Notably, both of these studies were conducted in European and Canadian patients, and the regional differences in the surgical practices again highlight the subjectivity of the residual disease assessment. The ongoing TRUST trial hopes to definitively address this question,[20] however recruiting centres need to fulfil specific quality assurance criteria (e.g. ≥50% complete resection rate in upfront surgery for International Federation of Gynecology and Obstetrics (FIGO) IIIB-IVB patients, ≥36 debulking-surgeries/year) and agree to independent audits by TRUST quality committee delegates to participate. Again, this will leave a bias as not all UK National Health Service (NHS) centres can meet these standards. Clinical insight has also confirmed this prognostic advantage for stage III patients achieving NVRD following PDS compared to IDS, especially in a real life setting or clinical trials that have

	a different study objective. Patients are self-selected for appropriate surgery based not only on their disease burden, but also on their age, fitness and comorbidities. Subset analysis of the most recent first-line trials; SOLO-1[10] and PAOLA-1[21] trials, both demonstrated more favourable outcomes for patients in the control arms who were stage III NVRD after PDS. Therefore, the assumption of similar outcomes following PDS and IDS is not clinically appropriate.
Issue 5: Estimation of overall survival using a ∆ progression-free survival: ∆ overall survival ratio	
12. The company used Study 19 (which evaluated olaparib as second line treatment in BRCA+ patients with 7-year follow-up) to estimate a PFS:OS ratio and therefore assumed a class effect between olaparib and niraparib. Is it appropriate to assume this class effect as a basis for estimating the PFS:OS ratio?	The Company believe that Study 19 provides the best evidence to inform long-term OS predictions for PARP inhibitors in the absence of mature first-line OS data. The Company's rationale is described in detail in Section B.3.3 of the Company Submission (CS) and in response to ERG clarification question B3. As presented in the Company's response to question 10, feedback from UK clinicians was that a class effect between PARP inhibitors is expected. Clinical experts agree that PARP inhibitor benefit in terms of PFS and OS are expected to be similar and that the SOLO-1 data is expected to be reflected within the PRIMA trial. Previous ovarian cancer technology appraisals have utilised the ∆PFS:∆OS methodology to inform their modelled OS in the absence of mature trial data (TA528 [niraparib 2L][22], TA598 [olaparib 1L][5] and TA611 [rucaparib 2L][23]). In TA528 (niraparib 2L) the Committee accepted that Study 19 was the best available evidence source to inform the ∆PFS:∆OS relationship and that a minimum of ∆PFS:∆OS=1:1 was to be expected. The NICE Decision Support Unit review (Davis et al.[24]) published in 2012 and based on literature identified between 2001 and 2011 concluded that the level of evidence supporting a relationship between PFS and OS varies considerably by cancer type and that it is not always consistent even within one specific cancer type. This review was not specific to ovarian cancer nor did it capture the evolving treatment landscape in ovarian cancer in recent years. Hence the Company believe that Davis et al should not be relied upon for decision making for the following reasons: • The review covered advanced and metastatic cancers and did not include any data from ovarian cancer trials.

	• The study period was 2001-2011 and pre-dated the extended use of PARP inhibitors • The review was not systematic and only identified n=266 references. The authors note that over 3,000 references would have been identified if a full systematic search had been conducted. • The review was conducted prior to the emergence of PARP inhibitors with the primary publication for Study 19 (olaparib) being published in the same year (2012). Given the evidence available from Study 19, past precedent from previous oncology submissions in ovarian cancer and UK clinical expert opinion, the Company believe that: • It is appropriate to model a ΔPFS:ΔOS relationship within this analysis. • Study 19 provides the best available evidence to inform this relationship and it is appropriate to assume a class effect as a basis for estimating the ΔPFS:ΔOS ratio. ***Note:*** *Study 19 included patients with and without a BRCA mutation, and the full ITT dataset were used to inform the ΔPFS:ΔOS relationship for this submission and not just the subgroup of patients with a BRCA mutation as suggested in this question.*
13. Is it appropriate to assume that niraparib has a constant survival advantage over routine surveillance over the entire time horizon of the model?	In order to model OS with niraparib a HR derived through the application of ΔPFS:ΔOS relationship is applied to the OS curve for routine surveillance. While the application of a HR usually leads to the assumption that the treatment maintains a constant survival advantage relative to its comparator, this is not strictly true within the economic model. OS for both treatments is restricted by the risk of death from all-cause mortality. Within the Company's base case analysis this restriction impacts the OS curve for niraparib to a greater extent (i.e. comes into effect earlier on in the model time horizon) than the OS curve for routine surveillance, and therefore a constant survival advantage over the model time horizon is not assumed for niraparib. Furthermore, assuming proportional hazards (i.e. a constant survival advantage) may be appropriate between niraparib and routine surveillance OS. Figure 2 and Figure 3 demonstrate that the proportional hazards assumption cannot be rejected for the observed trial period for two reasons: • The log-cumulative hazards for niraparib and routine surveillance do not cross and remain relatively parallel overtime

	• The Schoenfeld residuals plot shows an approximate zero slope and the p-value is >0.05 ([redacted]) thus not rejecting the hypothesis of time independent residuals.

	Figure 2: [redacted]  **Figure 3:** [redacted]

	
14. The company provided a scenario analysis with PFS:OS ratios ranging from 1:1 up to 1:3. What is likely to be the most appropriate ratio to use when estimating OS from PFS in this population?	The Company believe that a ΔPFS:ΔOS relationship of 1:2, as presented in the base-case analysis, is the most appropriate ratio when estimating OS change from PFS change in this population, and that the ratio of 1:1.13 should be considered as the lower bound, for the following reasons: • ***Chemotherapy alone increases OS on at least a 1:1 ratio in patients with ovarian cancer. Treatment with a PARP inhibitor should improve this relationship further*** o A systematic literature review conducted by Sundar et al. (2012) to assess the relationship between PFS and post-progression survival in ovarian cancer concluded "*If the effect of a new drug treatment for ovarian cancer is to extend median PFS by x months, then it is reasonable to estimate that the treatment will*

also extend median overall survival by x months." The review sourced evidence from n=37 clinical trials which evaluated alternative chemotherapy regimens in patients (n=15,850) with advanced ovarian cancer.[24]

- ***Independent published analyses support a greater than 1:2 relationship***
    - In a cost-effectiveness analysis of niraparib versus routine surveillance in the first-line maintenance setting by Barrington et al. 2020 a 1:3 ΔPFS:ΔOS relationship is modelled in the base-case analysis.[26] The magnitude of this ΔPFS:ΔOS relationship was based on data from five clinical trials in ovarian cancer (Vergote 2010, Kehoe 2015, Tewari 2019, Bristow 2007 and Armstrong 2006[18,19,27–29]). The authors acknowledge that the ratio ranged between 1:2 and 1:4.
- ***Clinical trial data indicates that treatment effect is maintained as data maturity increases***
    - Observed data from PRIMA demonstrates that treatment with niraparib results in an OS HR of 0.70 (95% CI 0.44 to 1.11) relative to routine surveillance. Whilst this data is still immature, a HR of 0.70 translates into an ΔPFS:ΔOS of approximately 1:1.13. Therefore, any relationship lower than 1:1.13 would imply that the OS benefit of niraparib observed in the PRIMA trial would be lost as more mature OS data becomes available from PRIMA. Long-term evidence available from Study 19 and SOLO-2 demonstrates that the OS treatment effect of olaparib has improved relative to routine surveillance over time (Table 2). As highlighted in response to question 10, UK clinical opinion is that a class effect is expected between niraparib and olaparib, and as such it is anticipated that the niraparib OS treatment effect will likely improve as the data matures.

Table 2: Olaparib treatment effect (OS) over time

Trial	1st datacut	2nd datacut	3rd datacut	4th datacut
Study 19	Ledermann 2012[30]	Ledermann 2014[31]:	Ledermann 2016[32]	Friedlander 2018[33]

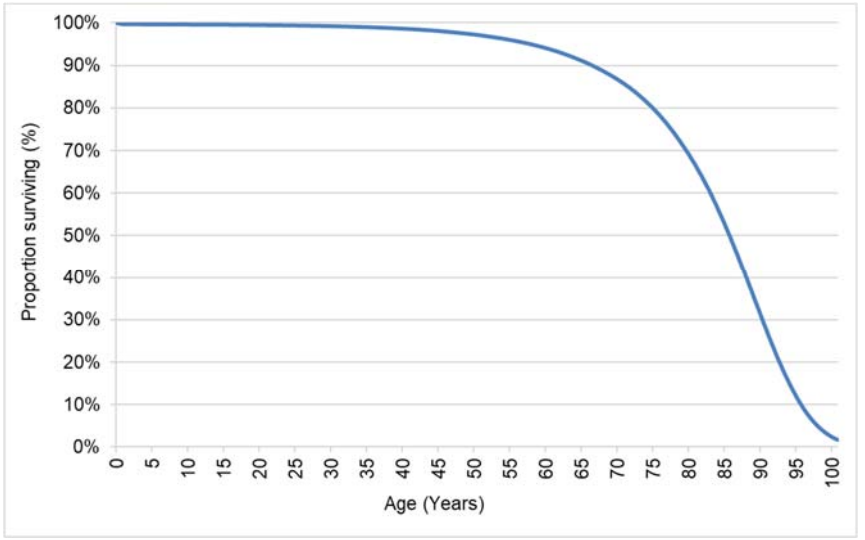
	HR 0.94 (95% CI, 0.63 to 1.39; P=0.75)	HR 0·88 (95% CI 0·64–1·21; p=0·44)	HR 0·73 (95% CI 0·55–0·0.96; p=0.025)	HR 0.73 (95% CI 0.55–0.95, p=0.0214)
SOLO-2	Pujade-Lauraine 2017[16] HR 0·80 (95% CI 0·50–1·31; p=0·43)	Poveda 2020 (ASCO)[34] HR 0·74 (95% CI 0·54–1.00; p=0·0537)	-	-

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival

- ***Clinical expert opinion supports at least a 1:1 relationship***
    - Following further discussions with UK clinical experts the Company disagrees with the ERG's assumption that the ΔPFS:ΔOS relationship could be less than 1:1, in particular with the assumption that ΔPFS:ΔOS=1:0.66. Feedback from UK clinical experts was that:
        - They expect to see at least a 1:1 ΔPFS:ΔOS relationship and that it is plausible to expect a greater than 1:1 relationship.
        - They believe outcomes should be better in the first-line setting compared to the relapsed setting, where a minimum of a 1:1 relationship was accepted by the TA528 (niraparib 2L) committee:
            - TA528 Final Appraisal Document, page 7[22]: *"The committee concluded that there is no reason to suppose that the overall survival benefit will be less than the progression-free survival benefit, but it is uncertain whether the overall survival benefit will be equal to or exceed the progression-free survival benefit."*

- During the NICE Technical Engagement TC (24th September 2020), the ERG confirmed that the ΔPFS:ΔOS = 1:0.66 assumption was an exploratory analysis. The Company strongly disagree with this estimate and do not believe it reflects the ratio

	between PFS and OS in the first-line maintenance setting. Furthermore, the Company has twice requested more clarity from the ERG on the underlying methodology of this analysis, as it is only mentioned briefly in the Technical Engagement response from AstraZeneca. The Company understands that this estimate was based on PFS-2 data (not OS) from the SOLO-1 trial and as such is not directly comparable to the PFS:OS methodology applied within this appraisal. Further, this estimate was referred to as "highly conservative" in the Company's (AstraZeneca) response to the NICE Technical Engagement questions. As such, the Company do not believe that this estimate provides clinically plausible OS predictions and recommend that ΔPFS:ΔOS = 1:1.13 is considered as the lower bound.
15. The company's MA base case OS curve predicts that [redacted] of patients would be alive at 30 years in the niraparib arm of the model, when they would be 91 years old. This estimate compares with [redacted] in the company's curve for the ITT population (and [redacted] with no cure assumption). Is it clinically plausible that this proportion of people would be alive at this stage?	Figure 4 presents all-cause survival by age for women (sourced from UK Office for National Statistics lifetables[35]). This data is used within the economic model to restrict the OS curves to ensure the risk of death per cycle is always greater or equal to the all-cause risk of death per cycle. According to these data, an individual aged 91 would have a 27% chance of remaining alive. This figure is larger than the modelled survival for niraparib for both the MA and the ITT population (with and without the long-term remission assumption). Given that first-line treatment for patients with advanced ovarian cancer is of curative intent, the Company believe that it is

	clinically plausible for [redacted]% and [redacted]% of niraparib patients in the MA and ITT population, respectively, to be alive at aged 91. **Figure 4: All-cause survival by age** 
16. The ERG noted that the HR used by the company to generate the 1:2 ΔPFS:ΔOS relationship is not reflective of the treatment effect for niraparib compared with routine surveillance observed in PRIMA. The hazard ratio of [redacted] used by the company to generate the 1:2 ΔPFS:ΔOS relationship suggests [redacted] relative treatment effect for niraparib compared with routine surveillance than that observed in PRIMA (HR of 0.70 [95% CI 0.44 to 1.11]). Can this discrepancy in treatment effect between the hazard ratio generated from the	PRIMA OS data is highly immature with only [redacted] ([redacted]%) and [redacted] ([redacted]%) of patients experiencing an event by the time of datacut off (May 17, 2019). As a result of this data immaturity, survival analyses techniques to extrapolate the observed Kaplan-Meier (KM) data did not yield clinically valid survival predictions for niraparib. Long-term real-world evidence from the University of Edinburgh Ovarian Cancer database allowed the Company to successfully extrapolate the PRIMA routine surveillance OS KM. By comparing the survival predictions to the real-world evidence, the Company were able to select a clinical plausible OS curve for routine surveillance (log-logistic, which was also found to be of good statistical fit). There is currently no real-world evidence to inform the selection of survival curves for niraparib, and given the immaturity of the data, survival analysis techniques cannot predict the OS results.

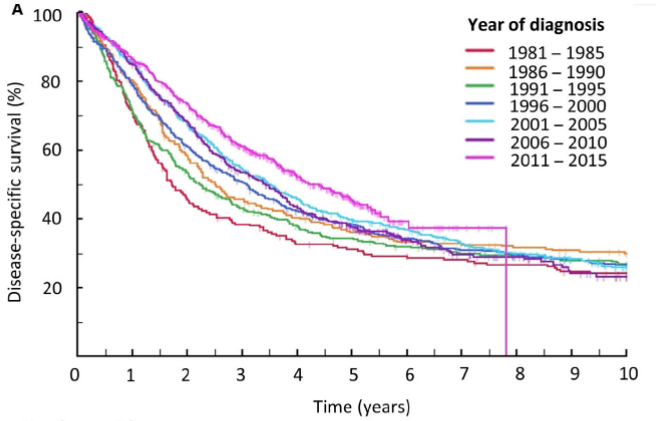
ΔPFS:ΔOS ratio and the data in PRIMA be explained?	Therefore, as described in Section B.3.3 of the CS and in response to ERG question B3, the Company opted to model a mean ΔPFS:ΔOS relationship to inform the niraparib OS curve. This method has been adopted in previous technology appraisal (TA528 [niraparib 2L][22], TA598 [olaparib 1L][5], TA611 [rucaparib 2L][23]) and existing published literature (Guy et al[36]; Barrington). The method is flexible as it allows the user to select an appropriate ΔPFS:ΔOS relationship in order to produce clinically plausible long-term survival predictions for niraparib relative to routine surveillance. The observed OS HR from PRIMA (0.70 [95% CI 0.44 to 1.11]) predicts a numerical but not significant OS benefit for niraparib relative to placebo, however the data is still very immature ([redacted]%). Clinical experts support a class effect across PARP inhibitors (please see response to questions 10 and 12). Long-term data from SOLO-2 and Study 19 demonstrate that as the data matures the treatment effect on OS improves relative to routine surveillance (please see response to questions 12 and 14). Therefore, the OS treatment effect for niraparib should be expected to improve as the PRIMA data matures. The modelled OS HR of [redacted] (derived from assuming a ΔPFS:ΔOS = 1:2 in the ITT population) represents the OS treatment effect for niraparib relative to routine surveillance over a lifetime horizon and not for the observed trial period. Assuming a lower ΔPFS:ΔOS ratio would result in a greater modelled OS HR. The base case ratio of 1:2 was selected based on long-term survival data for chemotherapies and PARP inhibitors, clinical opinion and past precedent set in NICE appraisals (please see response to question 14). As highlighted above, it is reasonable to assume that the treatment effect may improve as the data matures, in line with PARP inhibitor trials in ovarian cancer. In addition, the modelled HR= [redacted] lies within the 95% confidence interval of the observed data. As such, the Company believe that this estimate appropriately reflects the potential niraparib OS treatment effect over a lifetime horizon.
17. In the company's model, at 39 years (the time horizon used in the model) 100% of people in the routine surveillance arm are dead, but [redacted]% of people in the niraparib arm remain alive (at age 100). How clinically plausible is this estimate?	Figure 4 presents all-cause survival by age for women (sourced from UK Office for National Statistics lifetables[35]). According to these data, an individual aged 100 would have a 2% chance of remaining alive. This figure is larger than the modelled survival for niraparib ([redacted]%). Given that first-line treatment for patients with advanced ovarian cancer is of curative intent and that there is clinical evidence to support patients achieving long-term remission (please refer to question

	23), the Company believe that it is clinically plausible for [redacted]% of patients treated with niraparib to remain alive at aged 100 years. Study 19[33] and SOLO-2[34] have demonstrated that PARP inhibitors extend life relative to routine surveillance, and as such it is plausible that patients treated with niraparib will remain alive for longer than patients in the routine surveillance treatment arm.
Issue 6: Company's model structure	
18. Given that patients can experience multiple disease progressions, would a 4-state model (progression-free, progression-free 2, progressed disease and death) be more suitable for decision making, as data are available from PRIMA for progression-free and 2nd progression-free survival?	The Company disagree that the addition of a fourth health state into the model structure would be more suitable for decision making, given the current data package. The Company believe that extending the model structure into a more complex one will not in this case alleviate any of the current uncertainty. The Company's rationale is as follows: • Subsequent treatments across treatment arms are relatively similar and are captured sufficiently as one-off cost upon progression. • Quality of life has been demonstrated to remain stable during second-line treatment, and as such the incremental impact of decrements in utility due to relapse will be negligible (please refer to response to ERG clarification question B9 – part c). • PFS-2 data from PRIMA is immature ([redacted]%), hence including this endpoint would lead to additional uncertainty and increased assumptions about the timings of subsequent treatment. • The addition of the fourth health state would not alleviate any uncertainty surrounding the OS estimates within this appraisal. During the NICE Technical Engagement TC (24th September 2020), the NICE Technical Team made it clear to the Company that the reason behind requesting a four health state model was to allow the same model structure to be used for niraparib during any future CDF resubmissions (if niraparib was to be accepted into the CDF). The Company is open to including mature PFS-2 data within a future model structure for use in a potential CDF resubmission. However, at this stage the Company finds it more appropriate to maintain the current three health state model structure.

Issue 7: Estimation of long-term remission	
19. The ERG agrees with the company that the appropriate use of mixture cure models relies on the existence of mature data from studies with long follow-up times that exceed anticipated point of cure time, as well as sufficient numbers of patients at risk at the end of follow-up in order to robustly estimate a cure fraction. What is the most appropriate method for estimating the point of long-term remission, given the immature data available from PRIMA?	Please refer to response to question 22. The Company acknowledge the ERG's concern surrounding the modelling of long-term remission and as such have removed this assumption from the analyses. The Company would like to highlight that despite the ERG's criticism of the long-term remission modelling approach, the potential for patients to achieve long-term remission is still valid to this decision problem (please see response to question 20, 22 and 23). As such, the Company agrees with the ERG's decision to explore scenario analyses in which patients who are progression-free at 7 and 10 years stop incurring disease management costs.
20. The company have assumed long-term remission is achieved in people who have had progression-free disease for 7 years. Does this align with what is seen in clinical practice?	Please refer to response to question 22. From a clinical perspective, the Company believes that a long-term remission timepoint of 7 years is a clinically reasonable assumption which reflects clinical practice for the following reasons: • ***Clinical feedback supports discharging patients who remain progression-free from routine follow-up at 5 years*** o Feedback obtained by the Company from two UK clinicians confirmed that after 5 years patients would be discharged from regular follow-up and would only be offered the option of an annual review. One clinician stated that patients were also given the option to visit their general practitioner on the emergence of symptoms as opposed to a secondary care annual review with rapid access to oncology if needed. • ***Long-term evidence from the Edinburgh Cancer Centre demonstrates a reduction in risk of progression at approximately 6 years reviewing a wider OC population*** o o

	o Figure ***5*** and o o o **Figure *6***, obtained from a recent publication by the Edinburgh Cancer Centre, demonstrate a plateau in disease-specific survival and PFS from approximately 6 years, respectively. Please note that the population of this study captured a wider OC patient population than the PRIMA trial including patients from all stages.[6]

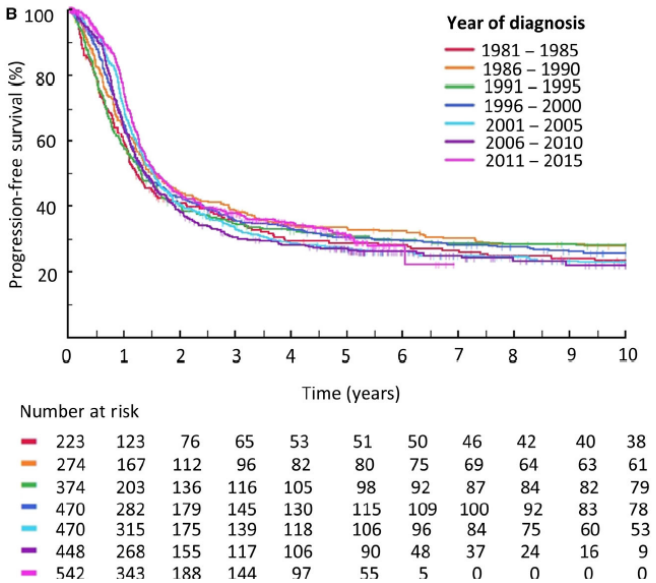
Figure 5: Disease-specific survival rate by year of diagnosis[6]



Number at risk

223	155	97	81	67	63	59	56	52	47	44
275	215	154	120	104	92	84	81	76	72	68
374	261	193	152	131	117	107	99	96	89	84
470	363	273	224	181	158	140	122	111	102	91
470	393	306	240	195	164	143	120	99	82	67
448	365	282	210	167	128	75	57	44	27	17
541	424	337	243	154	90	22	6	0	0	0

Figure 6: Progression-free survival rate by year of diagnosis[6]



- ***Evidence presented in TA598 (olaparib 1L) supports a 5-year long-term remission time point***[5]
    - Page 65 of CS: "*Expert advice that patients free of progression 5 years after completing 2 years of olaparib therapy are expected to be 'exceptional' responders and considered for discharge to primary care*"
    - Page 65 of CS: "*Relapse after 5 years of disease-free survival is rare in ovarian cancer*"

	o Page 65 of CS: "*Data from the Edinburgh Ovarian Cancer Database suggest that the rate of relapse following diagnosis of ovarian cancer reduces to zero at approximately 7-8 years*" o Page 62 of TA598 ERG report: *"the ERG's clinical advisors broadly agreed with the company's experts [… expert clinical input stating that people who do not progress within five years are exceptional responders who are highly unlikely to experience a relapse event ..]. However, they could not rule out the possibility that receiving a PARP inhibitor, such as olaparib, could delay future recurrences. Consequently, the point at which patients in the olaparib arm were at a very low risk of recurrence could be after the 5-year time point assumed in the model."* o Page 1 of TA598 Final Appraisal Determination (FAD) document: "*Using olaparib earlier in the treatment pathway would be an important development because earlier use can achieve the greatest benefit and may have the potential to cure the disease."* o Page 5 of TA598 FAD: *"The availability of olaparib as a first-line maintenance treatment is an important development in the management of BRCA mutation-positive advanced ovarian cancer because it is expected to have the greatest benefit when used early, and is considered to have the potential to cure the disease in some people if given before the first recurrence."* • ***ERG (BMJ-TAG within this appraisal) clinical experts support the likelihood of long-term remission between 5 and 10 years*** o NICE ID1680 ERG report page 99: *"Clinical expert opinion provided to the ERG, and clinical expert opinion reported in TA598, is somewhat consistent in reporting that if RS patients are PF at 5 years they are less likely to relapse."* o NICE ID1680 ERG report page 125: *"However, clinical expert advice given to the ERG explained that when patients have been in remission for 10 years, they would be discharged."* Given the evidence presented above, it is clear that the point at which patients are deemed to have achieved long-term remission is variable, with the consensus supporting a time point

	between 5 and 10 years. As such, the Company believe that the mid-point of 7 years is consistent with the available evidence and is aligned with what is seen in UK clinical practice.
The company justified using data from Du Bois *et al.,* 2009 to estimate the proportion of people in long-term remission in the stage III NVRD after PDS population because it included a large sample size, assessment of a range of surgical outcomes and long follow-up (144 months) allowing for PFS and OS data to be extracted at 5, 7 and 10 years. The ERG suggest that this data could also be taken from the NVRD PFS curves estimated in the model, which would be consistent with the approach used in the ITT population. No comparative analysis has been provided between the De Bois *et al.,* study and the population in PAOLA-1 (where treatment effect for patients with stage III disease and NVRD after PDS was estimated), nor with the population in PRIMA. 21. Is the approach to estimating the proportion of people in long-term remission in the stage III disease and NVRD after PDS population using external data from Du Bois *et al.,* 2009 appropriate?	Please see response to question 22. The Company acknowledge the ERG's concern surrounding the modelling of long-term remission and as such have removed this assumption from the analyses. The Company would like to highlight that despite the ERG's criticism of the long-term remission modelling approach, the potential for patients to achieve long-term remission is still valid to this decision problem (please see response to question 20, 22 and 23). As such, the Company agree with the ERG's decision to explore scenario analyses in which patients who are progression-free at 7 and 10 years stop incurring disease management costs (approximately [redacted]% of the ITT patient population are on treatment at 7 years within the company's base-case).
22. Is the ERGs assumption of removing long-term remission from the model appropriate?	The Company agrees with the NICE Technical Team that PRIMA does not yet provide sufficiently mature data to demonstrate long-term remission within the economic evaluation, however real-world evidence and UK clinical expert opinion does support the opportunity of long-term remission through successful first-line maintenance therapy (please refer to response to ERG clarification question B5 – part d and response to questions 20 and 23). The Company also agrees with the ERG that there is insufficient data to inform a mixture cure model, which could have served as an alternative to the Company's modelling approach. In order to alleviate the concern of the of the ERG, the Company has removed the long-term remission assumption from modelling.

	However, whilst the ERG has criticised the methodological application of the long-term remission assumption within the Company's model, it is important to note that from a clinical perspective, the potential for a patient to achieve long-term remission remains valid to this decision problem. As such the Company agrees with the ERG's decision to consider patients who are progression-free at specific time points as discharged (Section 5.2 and 5.3 of the ERG report). This assumption means that patients will stop incurring disease management costs and can be considered as discharged from routine follow-up (approximately [redacted]% of the ITT patient population are on treatment at 7 years within the company's base-case).
23. In UK clinical practice, is it correct that after 10 years in progression free disease, patients in this population are discharged?	As highlighted in the CS, in the response to the ERG clarification questions (B5 - part d) and in response to question 20 the Company believe that there is evidence to support long-term remission in patients following successful first-line treatment. The BMJ-TAG ERG clinical experts also agree that it is possible for patients to achieve long-term remission as a result of first-line treatment: • NICE ID1680 ERG report page 99: *"Clinical expert opinion provided to the ERG, and clinical expert opinion reported in TA598, is somewhat consistent in reporting that if RS patients are PF at 5 years they are less likely to relapse."* • NICR ID1680 ERG report page 125: *"However, clinical expert advice given to the ERG explained that when patients have been in remission for 10 years, they would be discharged."* Furthermore, in the ERG's preferred assumptions, patients who remain progression-free at 10 years are assumed to incur no further disease management costs (Section 5.3 of NICE ID1680 ERG report). The ERG also considered scenario analyses where patients who remained progression-free at 7 years stopped incurring disease management costs (Section 5.2 of NICE ID1680 ERG report). In order to elicit further evidence surrounding the opportunity of long-term remission the Company sought feedback from further UK clinical experts. Two clinicians provided feedback on the question *"Would you discharge patients at 10 years or continue to monitor?".* Responses were consistent between the clinicians and both confirmed that after 5 years patients would be discharged from regular follow-up and would return annually for a review. One clinician

	stated that patients were also given the option to visit their general practitioner on the emergence of symptoms as opposed to regular annual review. The Company, the ERG, and clinical experts (ERG and Company) all support the opportunity of achieving long-term remission from successful first-line maintenance treatment. The point of long-term remission remains under consideration with clinical experts suggesting this point could be between 5 and 10 years. It is therefore highly likely that patients who are progression-free at 10 years will be discharged from regular follow-up in UK clinical practice.
Issue 8: Modelling of progression-free survival	
24. The company uses data from the University of Edinburgh Ovarian Cancer database on TFST as a proxy for data on PFS, which it uses to validate long-term model estimates. Is TFST a reasonable alternative for PFS in this population?	The Edinburgh Ovarian Cancer Database analysis has been re-run to capture the correct population in the PRIMA-like population and to obtain the PFS data instead of the time to first subsequent treatment (TFST) data. PFS in the database is defined as the time to first progression as measured by radiology, tumour marker (CA125) or the treating physician where other investigations were not evaluable. Based on this revised analysis, the outcomes have been re-evaluated and the conclusions compared to the initial CS have not been changed, estimates of PFS in the PRIMA-like population from the Edinburgh Ovarian Cancer Database were [redacted]% and [redacted]% at 5 and 10 years, respectively after the index date.
Issue 9: Time to treatment discontinuation	
25. Can it be assumed that all people who have no radiological evidence of residual disease after 3 years will stop treatment?	The PRIMA protocol specified treatment duration for approximately 3 years or 36 months. However, patients could continue to receive treatment for longer than 3 years if they were deemed to still be deriving clinical benefit as assessed by the Investigator (i.e. if disease was still present at the point of randomisation but had not grown or progressed during the time of maintenance treatment). Clinical insights confirmed that the treatment duration of niraparib in UK clinical practice would be aligned with the PRIMA trial design. This is supported by the updated results of the SOLO-1 trial, which showed that the benefit of a PARP inhibitor continues long-term despite a 2 year treatment stopping rule for olaparib maintenance therapy.[37]

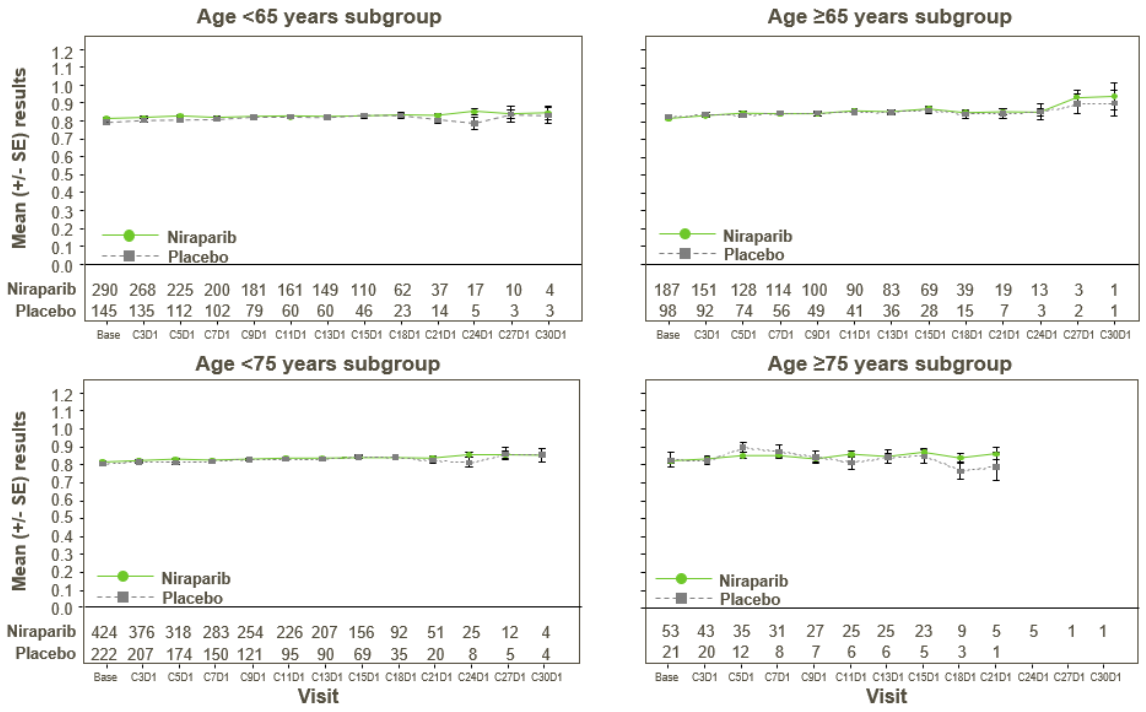
26. Based on clinical expert opinion and evidence from SOLO-1, the company assumed that [redacted] of participants who had not discontinued treatment at 3 years would carry on receiving niraparib. Based on clinical experience with similar treatments, what is the expected proportion of patients who would continue to receive niraparib at the end of the 3-year treatment period?	The input of [redacted]% was an informed estimate for patients who would continue treatment beyond 3 years in clinical practice. Observed KM data from PRIMA indicates that approximately [redacted]% of all patients in the ITT population have discontinued niraparib by 2 years (Figure 7). Assuming [redacted]% of patients remaining on treatment at 3 years would continue, translates into [redacted]% and [redacted]% of the MA and ITT population continuing treatment beyond 3 years within the economic model, respectively, with the remainder discontinuing at 3 years. IThese inputs will be confirmed by the final data cut of the PRIMA trial, however insights from the recently published PARP trial data suggest that these figures are consistent with those observed for olaparib discontinuation in SOLO-1; n=27 (10%) of olaparib patients remained on treatment past the 2-year trial stopping rule.[38]

	Figure 7: [redacted]  Abbreviations: ITT, intention to treatment; TTD, time to treatment discontinuation
27. What length of time is it reasonable to assume niraparib would continue to be given to people who did not discontinue treatment at 3 years?	The TA528 (niraparib 2L) Committee stated that *"Time to treatment discontinuation, as measured in the NOVA trial, is a better indicator of treatment length in clinical practice than progression-free survival"*.[39] Therefore, within the economic model it was deemed appropriate for patients who do not discontinue at 3 years to continue on treatment as per the tail of the extrapolated time to treatment discontinuation (TTD) curve (Figure 8).

	UK clinical insight suggests that they would look to optimise the benefits of niraparib maintenance treatment with the possible risk of toxicity and secondary malignancies that would have to be considered with continuing therapy long term. **Figure 8:** [redacted]  Abbreviations: ITT. intention-to-treat; KM, Kaplan-Meier; TTD, time to treatment discontinuation
28. What dose of niraparib was included in the model for people who continued to receive treatment after 3 years?	As presented in the Company's response to the ERG clarification question B17, the observed dose recorded in PRIMA for the first 18 months is modelled within the cost-effectiveness analysis. For Month 18 and onwards a last observation carried forward (LOCF) assumption is applied. This

	means that for the remainder of the time on treatment, patients are assumed to receive the niraparib dose observed in Month 18 (100 mg – [redacted]%; 200 mg – [redacted]%; 300 mg – [redacted]%).
Issue 10: Utility values	
29. Are the utility values that the company have used clinically plausible?	The Company believe that the utility values applied in the economic model (PFD=[redacted] and PD=[redacted]) are clinically plausible for the following reasons: 1. The utility values are reflective of the patient population of this appraisal as they were derived directly from EQ-5D patient reported outcomes collected during the PRIMA trial. 2. The utility values are consistent with published data sources across first-line and second-line PARP maintenance therapies. PFD and PD utility values identified within the Company's SLR for PARP maintenance therapy studies ranged from 0.769-0.872 and 0.649-0.828, respectively. 3. Quality of life within the PRIMA trial has been demonstrated to be consistent across age groups. Data presented at ESMO 2020 highlights that in subgroups of patients over the age of 65 and 75, the mean EQ-5D-5L score remained at approximately 0.8 (Figure 9).[40] This demonstrates that the patient's quality of life is not negatively impacted by age, which is assumed to be case when age-adjusted utility values are modelled.

Figure 9: EQ-5D-5L index by age group (PRIMA ITT population)[40]



Abbreviations: SE, standard error; ITT, intention-to-treat

Issue 11: Subsequent treatments	
30. Are the proportions of people receiving subsequent treatment in PRIMA representative of UK clinical practice?	The CS noted that the subsequent treatments recorded in the PRIMA trial are immature (Section B.3.5), however clinical insight suggested that they are representative of UK clinical practice with the exception of the PARP and immunotherapy use in the niraparib arm ([redacted]% and [redacted]% respectively). Please note that the company base case did not include second-line subsequent active maintenance option, due to the NICE position statement on comparators within the CDF.[41]A recent study from Hall et al. (2020) observed real-world treatment patterns in patients

	with advanced ovarian cancer in the UK.[42] Although that study structured their results differently and showed subsequent treatment options per line and also in combinations, which cannot be observed from PRIMA, the overall results were in line with the observed information from the PRIMA study.
Issue 12: Cancer Drugs Fund	
31. Is there further data being collected that could reduce uncertainty surrounding longer-term effectiveness and health outcomes in the relevant population(s)?	The data collection of the PRIMA trial is ongoing, and the Company are committed to continue the follow up of all randomised patients. The projected final OS analysis for PRIMA is in [redacted] with [redacted]% data maturity. Currently there are no other planned data cuts until the final analysis. The Company believe that niraparib would be suitable for use in the CDF, as it would allow the PRIMA trial data to mature and to provide more insight around the uncertainty of OS. In addition, access to the CDF and therefore the opportunity to collect real world evidence from the systemic anti-cancer therapy (SACT) dataset would also decrease uncertainty around the overall outcomes of the full marketing authorisation population.
32. When will these additional data become available?	
33. How suitable is the technology for use in the Cancer Drugs Fund (CDF)?	

Appendix 1. Cost-effectiveness analyses

The revised base case includes the addition of updated data from the University of Edinburgh Ovarian Cancer database and the removal of the long-term remission assumption from a survival perspective. The revised base-case settings are as follows:

- **MA population:**
  1. MA population with PAOLA-1 derived 'NVRD effect' and 'treatment effect'
     a. [redacted]% of stage III patients with NVRD after PDS
  2. Removal of the long-term remission assumption in terms of survival and assuming progression-free patients stop incurring disease management costs at 7 years
  3. ΔPFS:ΔOS = 1:2
  4. Age related utility decrements not applied
  5. Assuming [redacted]% of patients **who remain on treatment** at 3 years discontinue treatment as per the PRIMA trial design
     a. MA – [redacted]% of patients remain on treatment at 3 years, hence [redacted]% ([redacted]% x [redacted]%) of all patients discontinue at 3 years
  6. Including the cost of heart rate and blood pressure monitoring for niraparib as per the draft Summary of Product Characteristics (SmPC)
  7. Using alternative resource estimates for PFS (routine surveillance only)
- **ITT population:**
  1. ITT PRIMA data
  2. Removal of the long-term remission assumption in terms of survival and assuming progression-free patients stop incurring disease management costs at 7 years
  3. ΔPFS:ΔOS = 1:2
  4. Age related utility decrements not applied
  5. Assuming [redacted]% of patients **who remain on treatment** at 3 years discontinue treatment as per the PRIMA trial design
     a. ITT – [redacted]% of patients remain on treatment at 3 years, hence [redacted]% ([redacted]% x [redacted]%) of all patients discontinue at 3 years
  6. Including the cost of heart rate and blood pressure monitoring for niraparib as per the draft SmPC
  7. Using alternative resource estimates for PFS (routine surveillance only)

Base case analyses

Base case results with a simple list price discount of [redacted]% for the MA and ITT population are presented in Table 3 and Table 4, respectively. For the MA population niraparib generates [redacted] incremental quality adjusted life years (QALYs) and £[redacted] incremental costs over a lifetime horizon compared with routine surveillance, resulting in an incremental cost-effectiveness ratio (ICER) of £14,184 per QALY gained. For the ITT population niraparib generates [redacted] incremental QALYs and £[redacted] incremental costs over a lifetime horizon compared to routine surveillance, resulting in an ICER of £19,178 per QALY gained.

Table 3: Revised base case analyses - MA population

Treatment arm	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER versus baseline (£/QALY)
RS	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,184

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; MA, marketing authorisation; QALYs, quality-adjusted life years; RS, routine surveillance.

Table 4: Revised base case analyses - ITT population

Treatment arm	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER versus baseline (£/QALY)
RS	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,178

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance.

Probabilistic sensitivity analyses

Probabilistic results for the MA and ITT population over n=10,000 iterations are presented in Table 5 and Table 6, respectively. Accompanying incremental cost-effectiveness planes (ICEP), cost-effectiveness acceptability curves (CEACs) and cost-effectiveness acceptability frontiers (CEAFs) are presented in Figure 10 to Figure 15.

For the MA population niraparib generates [redacted] incremental QALYs and £[redacted] incremental costs over a lifetime horizon compared with routine surveillance, resulting in an ICER of £14,383 per QALY gained. For the ITT population niraparib generates [redacted] incremental QALYs and £[redacted] incremental costs over a lifetime horizon compared to routine surveillance, resulting in an ICER of £18,910 per QALY gained. Mean probabilistic results lay close to the deterministic base-case results, and niraparib was 100% and 98% cost-effective at a willingness to pay of £30,000 per QALY or more for the MA and ITT population, respectively.

Table 5: Probabilistic analyses - MA population (n=10,000)

Treatment arm	Total costs (£)	Total QALYs	Incremental costs (£) (SD)	Incremental QALYs (SD)	ICER versus baseline (£/QALY)
RS	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	14,383

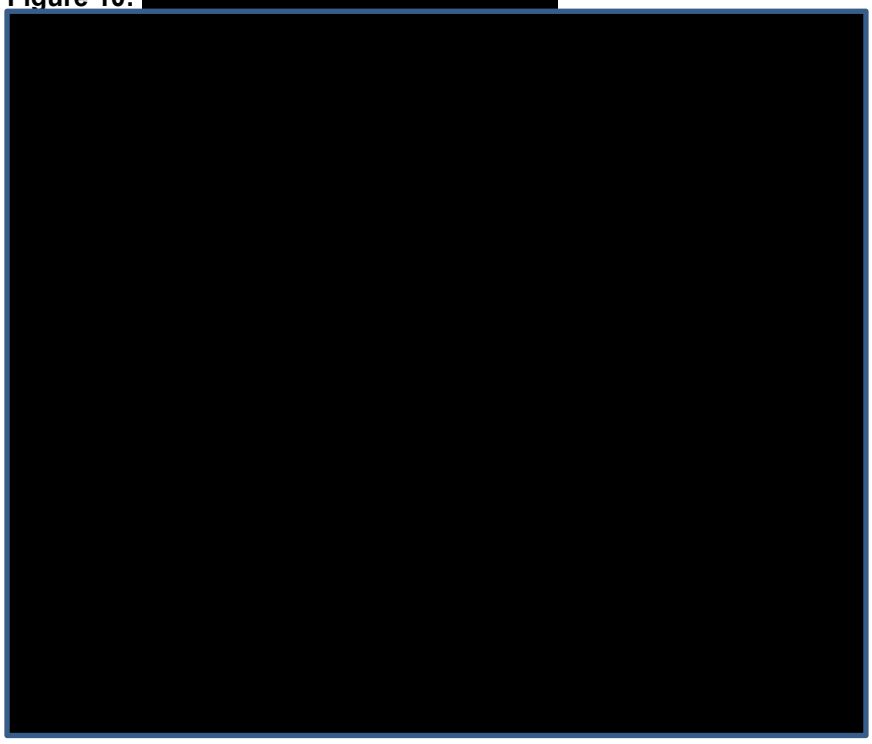
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; MA, marketing authorisation; QALYs, quality-adjusted life years; RS, routine surveillance; SD, standard deviation

Table 6: Probabilistic analyses - ITT population (n=10,000)

Treatment arm	Total costs (£)	Total QALYs	Incremental costs (£) (SD)	Incremental QALYs (SD)	ICER versus baseline (£/QALY)
RS	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	18,910

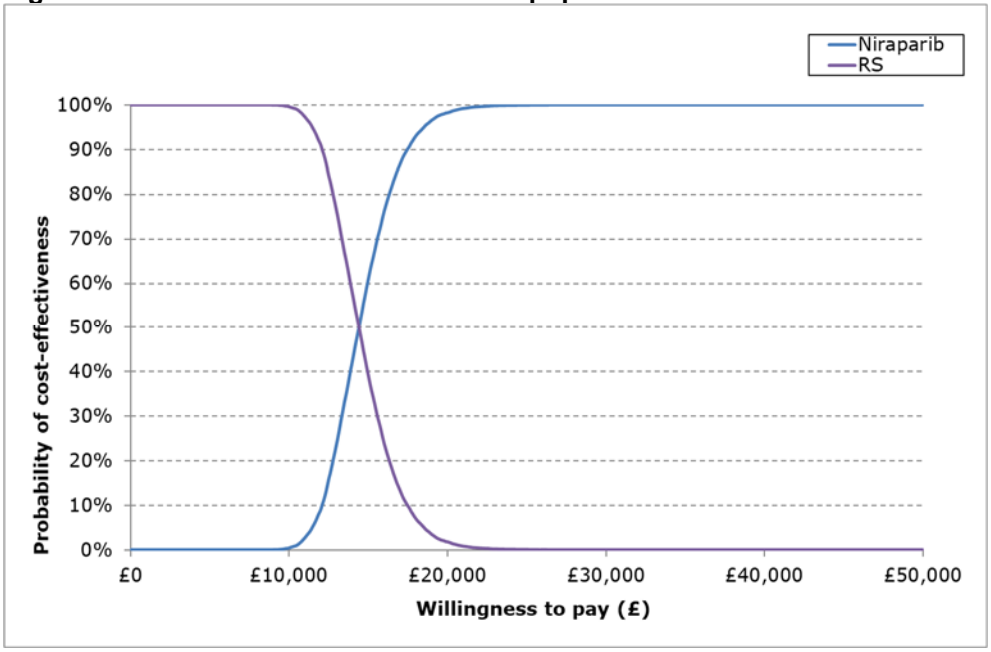
Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance; SD, standard deviation

Figure 10: [redacted]



Abbreviations: ICEP, incremental cost-effectiveness plane; MA, marketing authorisation; PSA, probabilistic sensitivity analysis; WTP, willingness to pay; RS, routine surveillance

Figure 11: Probabilistic CEAC for the MA population

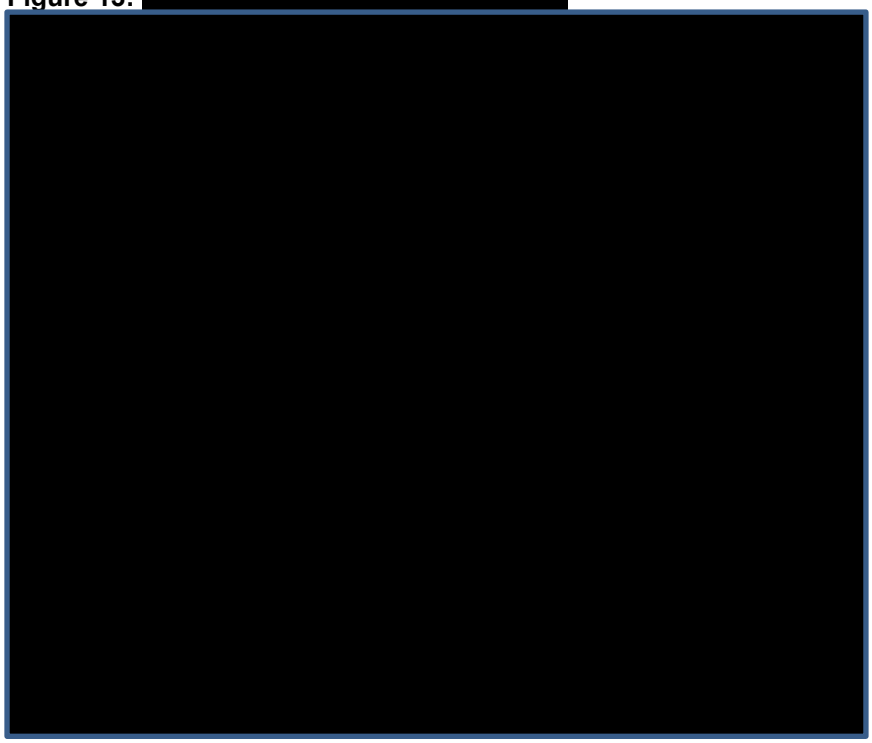


Abbreviations: CEAC, cost-effectiveness acceptability curve; MA, marketing authorisation; PSA, probabilistic sensitivity analysis; WTP, willingness to pay; RS, routine surveillance

Figure 12: Probabilistic CEAF for the MA population

Abbreviations: CEAF, cost-effectiveness acceptability frontier; MA, marketing authorisation; PSA, probabilistic sensitivity analysis; WTP, willingness to pay; RS, routine surveillance

Figure 13: [redacted]



Abbreviations: ICEP, incremental cost-effectiveness plane; ITT, intention-to-treat; PSA, probabilistic sensitivity analysis; WTP, willingness to pay; RS, routine surveillance

Figure 14: Probabilistic CEAC for the ITT population

Abbreviations: CEAC, cost-effectiveness acceptability curve; ITT, intention-to treat; WTP, willingness to pay; RS, routine surveillance

Figure 15: Probabilistic CEAF for the ITT population

Abbreviations: CEAF, cost-effectiveness acceptability frontier; ITT, intention-to treat; PSA, probabilistic sensitivity analysis; WTP, willingness to pay; RS, routine surveillance

Deterministic sensitivity analyses

One-way sensitivity analyses (OWSA) tornado diagrams for the MA and ITT populations are presented in Figure 16 and Figure 17, respectively. Accompanying tabulated results are presented in Table 7 and Table 8.

For the MA population the results were most sensitive to the scale and shape of the niraparib PFS distribution, the 'NVRD effect' HR, the proportion of stage III patients with NVRD after PDS, and routine surveillance subsequent treatment costs. For the ITT population the results were most sensitive to the scale and shape of the niraparib PFS distribution, the routine surveillance PFS distribution, and the routine surveillance OS distribution. The ICERs remained below £22,000 across all parameters varied for the MA and ITT populations, respectively, with the exception of when the upper bound of the niraparib PFS shale and scale parameters were modelled.

Figure 16: OWSA tornado diagram for the MA population

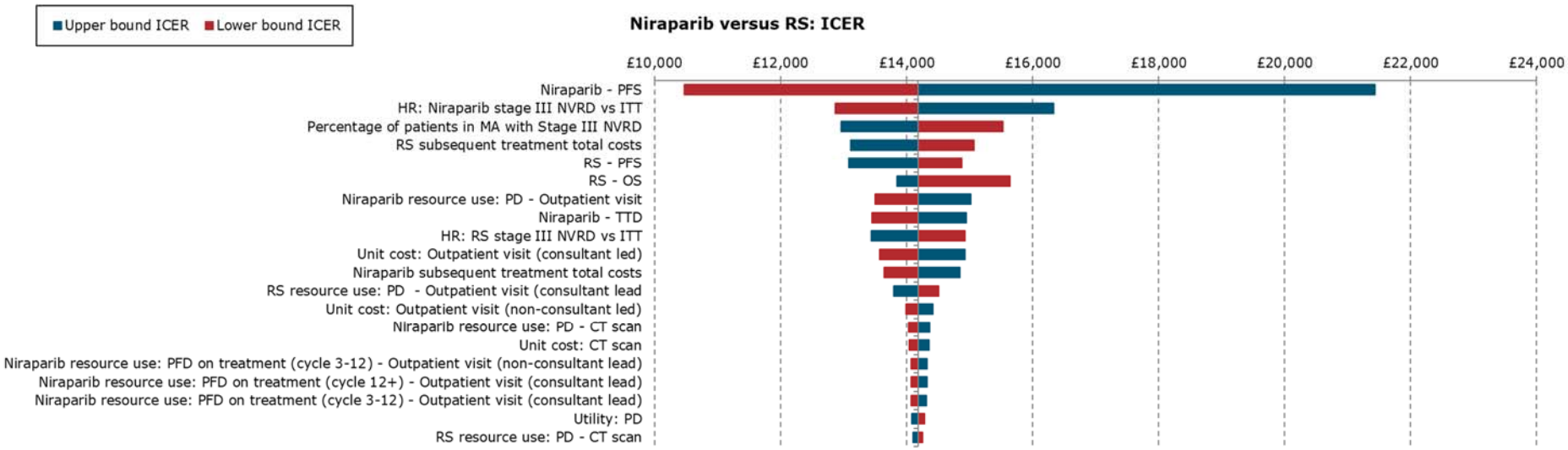


Table 7: Tabulated OWSA results for the MA population

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Niraparib - PFS	[redacted]	[redacted]	[redacted]	10,474	21,435	10,961
HR: Niraparib stage III NVRD vs ITT	0.34	0.23	0.50	12,870	16,334	3,464
Percentage of patients in MA with Stage III NVRD	0.13	0.08	0.18	15,535	12,957	2,578
RS subsequent treatment total costs	7,831.83	5,068.35	11,187.01	15,069	13,110	1,959
RS - PFS	[redacted]	[redacted]	[redacted]	14,881	13,082	1,799
RS - OS	[redacted]	[redacted]	[redacted]	15,645	13,847	1,798
Niraparib resource use: PD - Outpatient visit	1.00	0.65	1.43	13,496	15,020	1,524
Niraparib - TTD	[redacted]	[redacted]	[redacted]	13,451	14,947	1,496
HR: RS stage III NVRD vs ITT	0.49	0.33	0.73	14,929	13,440	1,489
Unit cost: Outpatient visit (consultant led)	126.91	82.13	181.28	13,575	14,923	1,348
Niraparib subsequent treatment total costs	5,194.49	3,361.60	7419.83	13,638	14,847	1,209
RS resource use: PD - Outpatient visit (consultant lead	1.00	0.65	1.43	14,508	13,792	716
Unit cost: Outpatient visit (non-consultant led)	131.01	84.78	187.14	13,990	14,420	430
Niraparib resource use: PD - CT scan	0.33	0.22	0.48	14,034	14,367	333
Unit cost: CT scan	83.23	53.87	118.89	14,042	14,357	316
Niraparib resource use: PFD on treatment (cycle 3-12) -	1.00	0.65	1.43	14,069	14,324	254

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Outpatient visit (non-consultant lead)						
Niraparib resource use: PFD on treatment (cycle 12+) - Outpatient visit (consultant lead)	1.00	0.65	1.43	14,071	14,321	250
Niraparib resource use: PFD on treatment (cycle 3-12) - Outpatient visit (consultant lead)	1.00	0.65	1.43	14,073	14,319	246
Utility: PD	0.74	0.73	0.75	14,288	14,083	206
RS resource use: PD - CT scan	0.33	0.22	0.48	14,255	14,098	157

Figure 17: OWSA tornado diagram for the ITT population

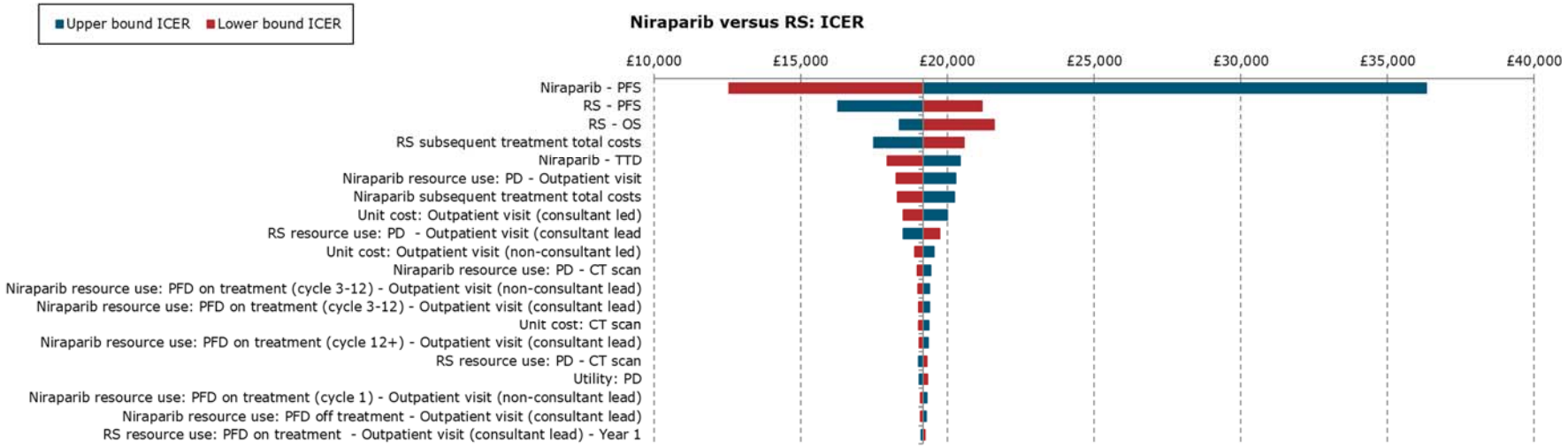


Table 8: Tabulated OWSA results for the ITT population

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Niraparib - PFS	[redacted]	[redacted]	[redacted]	12,566	36,339	23,774
RS - PFS	[redacted]	[redacted]	[redacted]	21,176	16,276	4,900
RS - OS	[redacted]	[redacted]	[redacted]	21,585	18,373	3,212
RS subsequent treatment total costs	7,831.83	5,068.35	11,187.01	20,566	17,494	3,071
Niraparib - TTD	[redacted]	[redacted]	[redacted]	17,955	20,439	2,484
Niraparib resource use: PD - Outpatient visit	1.00	0.65	1.43	18,259	20,294	2,035
Niraparib subsequent treatment total costs	5,194.49	3,361.60	7,419.83	18,301	20,244	1,943

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Unit cost: Outpatient visit (consultant led)	126.91	82.13	181.28	18,496	20,006	1,510
RS resource use: PD - Outpatient visit (consultant lead	1.00	0.65	1.43	19,748	18,487	1,261
Unit cost: Outpatient visit (non-consultant led)	131.01	84.78	187.14	18,882	19,538	657
Niraparib resource use: PD - CT scan	0.33	0.22	0.48	18,977	19,422	445
Niraparib resource use: PFD on treatment (cycle 3-12) - Outpatient visit (non-consultant lead)	1.00	0.65	1.43	19,005	19,389	383
Niraparib resource use: PFD on treatment (cycle 3-12) - Outpatient visit (consultant lead)	1.00	0.65	1.43	19,011	19,382	371
Unit cost: CT scan	83.23	53.87	118.89	19,015	19,377	361
Niraparib resource use: PFD on treatment (cycle 12+) - Outpatient visit (consultant lead)	1.00	0.65	1.43	19,043	19,342	299
RS resource use: PD - CT scan	0.33	0.22	0.48	19,303	19,027	276
Utility: PD	0.74	0.73	0.75	19,313	19,047	266
Niraparib resource use: PFD on treatment (cycle 1) - Outpatient visit (non-consultant lead)	4.00	2.59	5.71	19,079	19,299	220
Niraparib resource use: PFD off treatment - Outpatient visit (consultant lead)	0.33	0.22	0.48	19,090	19,286	196

Parameter	Base case value	Upper bound value	Lower bound value	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
RS resource use: PFD on treatment - Outpatient visit (consultant lead) - Year 1	0.33	0.22	0.48	19,245	19,098	147

Key scenario analyses

Results of key scenario analyses, relevant to this technical engagement, are presented in Table 9. Across all scenarios ran, the ICER remained below £30,000 for both the MA and ITT populations; with the exception of scenarios 4, 10 and 11.

Table 9: Key scenario analyses

Scenario number	Scenario	Treatment arm	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
MA population							
1	Base case	RS	[redacted]	[redacted]	-	-	-
		Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	14,184
2	NVRD effect only	RS	[redacted]	[redacted]	--	-	
		Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	16,241
3	Assume patients PF at 10 years stopping incurring costs	RS	[redacted]	[redacted]	-	-	-
		Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	14,267
4	ΔPFS:ΔOS = 1:1	RS	[redacted]	[redacted]	-	-	-
		Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	34,696
5	ΔPFS:ΔOS = 1:1.13	RS	[redacted]	[redacted]			
		Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	27,669
5	ΔPFS:ΔOS = 1:1.5	RS	[redacted]	[redacted]			
		Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	18,634
6	ΔPFS:ΔOS = 1:2.5	RS	[redacted]	[redacted]	-	-	-
		Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	11,728
ITT population							
7	Base case	RS	[redacted]	[redacted]	-	-	-
		Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	19,178
9	Assume patients PF at 10 years stopping incurring costs	RS	[redacted]	[redacted]	-	-	-
		Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	19,266
10	ΔPFS:ΔOS = 1:1	RS	[redacted]	[redacted]	-	-	-
		Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	40,649
11	ΔPFS:ΔOS = 1:1.13	RS	[redacted]	[redacted]			
		Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	34,470
12	ΔPFS:ΔOS = 1:1.5	RS	[redacted]	[redacted]	-	-	-

Scenario number	Scenario	Treatment arm	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
		Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	25,080
13	ΔPFS:ΔOS = 1:2.5	RS	[redacted]	[redacted]	-	-	-
		Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	15,787

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; MA, marketing authorisation; NVRD, no visible residual disease; PF, progression-free; PFS, progression-free survival; OS, overall survival; QALYs, quality-adjusted life years; RS, routine surveillance; SD, standard deviation

Appendix 2. University of Edinburgh database analysis

Retrospective real-world evidence study

To better understand the long-term outcomes of the patient population in the PRIMA study and quantify the difference between this population and the MA population, a retrospective database analysis was conducted with the help of a team at the University of Edinburgh, using the University of Edinburgh Ovarian Cancer Database.

The database contains outcome data for patients diagnosed with ovarian cancer in the South East region of Scotland ([redacted]). In order to obtain reliable follow-up data, patient identification was restricted to patients with newly diagnosed ovarian cancer who had not received any active maintenance therapy, diagnosed between the 1st January 2000 and the 21st December 2015 and followed up until last patient record or until January 2019.

Due to its historic nature, and the absence of alternative treatments at the time, the data were also assumed to be reflective of the routine surveillance arm within the economic analysis. The research study aimed to capture the following cohorts:

- The anticipated MA population for niraparib
- Then disaggregated into:
    - A simulated-PRIMA ITT population (stage III/IV patients excluding Stage III patients with NVRD after PDS)
    - A stage III population with NVRD after PDS (i.e. patients included in the MA population but not in the simulated-PRIMA cohort).

The MA cohort and simulated-PRIMA cohort were obtained by applying the inclusion and exclusion criteria set out in Table 10.

Table 10: [redacted]

MA cohort		Simulated-PRIMA cohort	
Inclusion criteria	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**
• Patient must have histologically confirmed, advanced (stage III or IV) high-grade serous or endometrioid ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who have completed first line platinum-based chemotherapy	• Patient has mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer. • Patient has undergone more than two cytoreductive surgeries. • Patient is to receive bevacizumab. • Patient has had treatment with a	• Patient must have histologically confirmed, advanced (Stage III or IV) high-grade predominantly serous or endometrioid ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who have completed first line platinum-based chemotherapy (neoadjuvant or adjuvant).	• Patient has mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer. • Patient has undergone more than two cytoreductive surgeries. • Patient is to receive bevacizumab. • Patient has had treatment with a

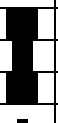
MA cohort		Simulated-PRIMA cohort	
Inclusion criteria	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**
(neoadjuvant or adjuvant). • Patient must have clinical complete response or partial response following completion of chemotherapy course. • All stage III and IV patients are eligible, irrespective of VRD, after primary or interval cytoreductive surgery or inoperable disease.	known PARP inhibitor. • Demonstrate stable or progressive disease in response to first line chemotherapy.	• Patient must have clinical complete response or partial response following completion of chemotherapy course. • All Stage IV patients are eligible, irrespective of residual disease, after primary or interval cytoreductive surgery. Stage III patients are required to have VRD after primary surgery. Stage III patients after interval debulking surgery are eligible irrespective of surgery outcome. Patients with inoperable Stage III and IV disease are eligible.	known PARP inhibitor. • Demonstrate stable or progressive disease in response to first line chemotherapy. • Patients diagnosed at Stage III with NVRD after PDS

Abbreviations: MA, marketing authorisation; NVRD, no visible residual disease; PDS, primary debulking surgery; VRD, visible residual disease

The data extracted included patient characteristics and survival estimates. Baseline characteristics from the cohorts were similar to those observed in PRIMA. However, the simulated-PRIMA population from the University of Edinburgh data set were a slightly more severe patient population (as assessed by their European Cooperative Oncology Group [ECOG] score and proportion of patients achieving NVRD status after interval cytoreductive surgery) compared to those included in the RS arm of PRIMA. [redacted]. Thus, [redacted] of the MA population was classified as stage III NVRD after PDS if evaluable outcomes were taken into account, but [redacted] if non evaluable outcomes were included.

Table 11: [redacted]

Characteristic		MA cohort		Simulated-PRIMA cohort	
		n	%	n	%
-	Cases	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic		MA cohort		Simulated-PRIMA cohort	
		n	%	n	%
Age at diagnosis	Median years				
Histological subtype	HGS				
	HG endo				
Documented primary site	Ovary				
	Fallopian Tube				
	Peritoneum				
	FT/ovary				
FIGO stage at diagnosis	IIIA				
	IIIB				
	IIIC				
	III NS				
	IV				
Germline BRCA status	BRCAm				
	BRCAwt / VUS				
	untested				
ECOG PS	0				
	1				
	2				
	3				
	NA				
Chemo type	Adjuvant				
	Neoadjuvant				
Residual disease	Zero macroscopic				
	Macroscopic				
	NA				
Vital status at last follow-up	Alive				
	Deceased				
Median follow-up from simulated randomisation	median years				
Median OS from simulated randomisation	median years				
Median PFS* from simulated randomisation	median years				

Abbreviations: FIGO, International Federation of Gynaecology and Obstetrics; BRCA, BRCA1 or BRCA2; FT, fallopian tube; HG endo, high grade (grade III) endometrioid; HGS, high grade serous; NA, not available; NS, not specified; OS, overall survival; PFS, progression-free survival, RD, residual disease following cytoreductive surgery; VUS, variant of unknown clinical significance; *Time to first progression as defined by radiology, tumour marker (CA125) or the treating physician where other investigations were not evaluable

The median OS was approximately [redacted] in the simulated-PRIMA group, compared with [redacted] in the stage III NVRD cohort. By combining the two cohorts to estimate the median OS for the MA population, it can be demonstrated that the MA curve lies above the simulated-PRIMA curve with a median OS of approximately [redacted] (Figure 18).

Figure 18: [redacted]

Abbreviations: MA, marketing authorisation; NVRD, no visible residual disease; OS, overall survival; PDS, primary debulking surgery

The estimated OS of the MA population presented in Figure 18 is consistent with the findings of the targeted literature review described in the company submission; patients with stage III NVRD have improved OS compared to those in the simulated-PRIMA and MA cohorts, but are still at high risk of death over their lifetime. Figure 18 also shows that there is a small group of patients who will continue to live beyond 7 years, and who are described in this submission as being in long-term remission.

The results from this analysis were also used to aid the selection of the appropriate OS distributions of the RS arm within the economic analysis. As, the patients studied as part of the Edinburgh database had more advanced disease than the trial population, the survival data obtained from the Edinburgh Ovarian Cancer database should be used as a minimum benchmark for the validation of the RS survival curve. The landmark survival rates for OS within the PRIMA like population of the Edinburgh dataset is [redacted] for 1, 5, 10 and 15 years respectively.

References

1. Mirza, M. R. *et al.* Long-term safety in patients with recurrent ovarian cancer treated with niraparib versus placebo: Results from the phase III ENGOT-OV16/NOVA trial. *Gynecologic Oncology* (2020) doi:10.1016/j.ygyno.2020.09.006.
2. FRANCISCO, E. M. Meeting highlights from the Committee for Medicinal Products Human Use (CHMP) 14-17 September 2020. *European Medicines Agency* https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-14-17-september-2020 (2020).
3. Eskander, R. N. *et al.* Correlation between Surgeon's assessment and radiographic evaluation of residual disease in women with advanced stage ovarian cancer reported to have undergone optimal surgical cytoreduction: An NRG Oncology/Gynecologic Oncology Group study. *Gynecol. Oncol.* **149**, 525–530 (2018).
4. Chi, D. S. *et al.* Prospective Study of the Correlation Between Postoperative Computed Tomography Scan and Primary Surgeon Assessment in Patients With Advanced Ovarian, Tubal, and Peritoneal Carcinoma Reported to Have Undergone Primary Surgical Cytoreduction to Residual Disease 1 cm or Less. *JCO* **25**, 4946–4951 (2007).
5. Overview | Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy | Guidance | NICE. https://www.nice.org.uk/guidance/ta598.
6. Anushka, I., Rye, T. & Churchman, M. Patterns of clinicopathological features and outcome in epithelial ovarian cancer patients: 35 years of prospectively collected data. *International Journal of Obstretics and Gynaecology* (2020).
7. Colombo, N. *et al.* ESMO–ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Annals of Oncology* **30**, 672–705 (2019).

8. Andrew Clamp. ICON8: Overall survival results in a GCIG phase III randomised controlled trial of weekly dose-dense chemotherapy in first line epithelial ovarian, fallopian tube or primary peritoneal carcinoma treatment. Annals of Oncology (2020) 31 (suppl_4): S551-S589. 10.1016/annonc/annonc276. (2020).
9. Harter, P., Mouret-Reynier, M.-A. & Pignata, S. Phase III PAOLA-1/ENGOT-ov25: maintenance olaparib with bevacizumab in patients with newly diagnosed, advanced ovarian cancer treated with platinum-based chemotherapy and bevacizumab as standard of care. (2019).
10. Mathews, C. A. *et al.* Maintenance olaparib after platinum-based chemotherapy in patients (pts) with newly diagnosed advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): Efficacy by surgical and tumor status in the Phase III SOLO1 trial. Poster presented at the ASCO Annual Meeting, Chicago, USA on May 31–June 4, 2019. *JCO* **37**, 5541–5541 (2019).
11. Janavičius, R. Founder BRCA1/2 mutations in the Europe: implications for hereditary breast-ovarian cancer prevention and control. *EPMA J* **1**, 397–412 (2010).
12. Chetrit, A. *et al.* Effect of BRCA1/2 Mutations on Long-Term Survival of Patients With Invasive Ovarian Cancer: The National Israeli Study of Ovarian Cancer. *JCO* **26**, 20–25 (2008).
13. Moschetta, M., George, A., Kaye, S. B. & Banerjee, S. BRCA somatic mutations and epigenetic BRCA modifications in serous ovarian cancer. *Ann. Oncol.* **27**, 1449–1455 (2016).
14. González-Martín, A. *et al.* Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *New England Journal of Medicine* **0**, null (2019).
15. Mirza, M. R. A randomized, double-blind phase 3 trial of maintenance therapy with niraparib vs placebo in patients with platinum-sensitive reucurrent ovarian can... ESMO 2016 Congress | OncologyPRO. (2016).

16. Pujade-Lauraine, E. *et al.* Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* **18**, 1274–1284 (2017).

17. Coleman, R. L. *et al.* Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet* **390**, 1949–1961 (2017).

18. Vergote, I. *et al.* Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N. Engl. J. Med.* **363**, 943–953 (2010).

19. Kehoe, S. *et al.* Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *The Lancet* **386**, 249–257 (2015).

20. Reuss, A. *et al.* TRUST: Trial of Radical Upfront Surgical Therapy in advanced ovarian cancer (ENGOT ov33/AGO-OVAR OP7). *Int. J. Gynecol. Cancer* **29**, 1327–1331 (2019).

21. Phillip Harter. Efficacy of maintenance olaparib plus bevacizumab by biomarker status in clinical higher- and lower-risk patients with newly diagnosed, advanced ovarian cancer in the PAOLA-1 trial. Plenary V. (2020).

22. Overview | Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer | Guidance | NICE. https://www.nice.org.uk/guidance/ta528/.

23. NICE. Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer | Guidance | NICE. https://www.nice.org.uk/guidance/ta611 (2019).

24. Davis, S., Tappenden, P. & Cantrell, A. *A Review of Studies Examining the Relationship between Progression-Free Survival and Overall Survival in Advanced or Metastatic Cancer*. (National Institute for Health and Care Excellence (NICE), 2012).

25. Sundar, S., Wu, J., Hillaby, K., Yap, J. & Lilford, R. A systematic review evaluating the relationship between progression free survival and post progression survival in advanced ovarian cancer. *Gynecol. Oncol.* **125**, 493–499 (2012).

26. Barrington, D. A. *et al.* Niraparib maintenance in frontline management of ovarian cancer: a cost effectiveness analysis. *International Journal of Gynecologic Cancer* ijgc (2020) doi:10.1136/ijgc-2020-001550.

27. Tewari, K. S. *et al.* Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer. *J. Clin. Oncol.* **37**, 2317–2328 (2019).

28. Bristow, R. E. *et al.* Intraperitoneal cisplatin and paclitaxel versus intravenous carboplatin and paclitaxel chemotherapy for Stage III ovarian cancer: a cost-effectiveness analysis. *Gynecol. Oncol.* **106**, 476–481 (2007).

29. Armstrong, D. K. *et al.* Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer. *New England Journal of Medicine* **354**, 34–43 (2006).

30. Ledermann, J. *et al.* Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer. *New England Journal of Medicine* **366**, 1382–1392 (2012).

31. Ledermann, J. *et al.* Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol.* **15**, 852–861 (2014).

32. Ledermann, J. A. *et al.* Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet Oncol.* **17**, 1579–1589 (2016).

33. Friedlander, M. *et al.* Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. *Br. J. Cancer* **119**, 1075–1085 (2018).

34. Final Overall Survival Analysis From SOLO2 in Ovarian Cancer - The ASCO Post. https://ascopost.com/issues/september-10-2020-supplement-gynecologic-cancers-almanac/final-overall-survival-analysis-from-solo2-in-ovarian-cancer/.

35. Office for National Statistics. All-cause mortality. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths (2020).

36. Guy H., Walder L. & Fisher M. Cost-Effectiveness of Niraparib Versus Routine Surveillance, Olaparib and Rucaparib for the Maintenance Treatment of Patients with Ovarian Cancer in the United States. *Pharmacoeconomics* (2018) doi:10.1007/s40273-018-0745-z.

37. Susan Banerjee. Maintenance olaparib for patients (pts) with newly diagnosed, advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): 5-year (y) follow-up (f/u) from SOLO1. (2020).

38. Kathleen Moore. Maintenance olaparib following platinum-based chemotherapy in newly diagnosed patients (pts) with advanced ovarian cancer (OC) and a BRCA1/2 mutation (BRCAm): Phase III SOLO1 trial. Presidential Symposium 2. (2018).

39. NICE. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer. Final Appraisal Determination. TA528. (2018).

40. Giorgio Valabrega. Efficacy and Safety of Niraparib in Older Patients With Advanced Ovarian Cancer: Results From the PRIMA/ENGOT-OV26/GOG-3012 Trial. (2020).

41. NICE. Position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product. (2019).

42. Hall, H. Real-world treatment patterns in patients with advanced (stage III–IV) ovarian cancer in the USA and Europe. *Future Oncology* **16**, (2020).

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Technical engagement response form

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1680]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **9 October 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
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- Do not use abbreviations.
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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.21 to 3.1.30) for more information.

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About you

Your name	**Professor Donal O' Donoghue, RCP registrar**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Generalisability of the PRIMA results to UK clinical practice – dose used in trial versus clinical practice	
Based on the complete and partial response rates observed in the PRIMA trial after platinum-based chemotherapy, is the patient population of the trial reflective of the population that would be eligible for niraparib after response to first-line platinum-based chemotherapy in UK clinical practice?	Yes- The PRIMA population is representative of the UK population The PRIMA trial predominantly focused on a group of women with advanced ovarian cancer with a poorer prognosis: ie those patients who had residual disease after primary surgery or required neoadjuvant chemotherapy due to the initial inoperability of their disease. As a significant benefit in median progression free survival has been demonstrated even in this poorer prognostic subgroup we would extrapolate due to a class effect of PARP inhibitors that the benefit for women with no residual disease after primary surgery would also be seen (as has been demonstrated in the 2 other front line PARP inhibitor trials : SOLO1 –olaparib and PAOLA – olaparib and bevacizumab. and we feel that the population with no residual disease after primary surgery should also be able to access niraparib in the front line setting.
Is the niraparib dose used in PRIMA reflective of likely dosing in clinical practice?	Yes One third of patients in the PRIMA trial received a individualised starting dose (ISD), based on weight and platelet count and this led to a significant fall in haematological side effects – from 26% to 15% of patients. The ISD has been widely and safely utilised in the UK in women with recurrent ovarian cancer and would be the recommended method of dosing for niraparib in the front line setting.
The company assumed that the weighted average dose of niraparib received in month 18 of treatment would be the same for the duration of the treatment period with niraparib in	Yes Dosing of niraparib in the PRIMA trial indicates that the majority of dose reductions (for tolerability/toxicity) occur in the first 4-5 months and once dose is optimised between

the model. Is it reasonable to assume that the dose tolerated by month 18 would be expected to continue to be tolerated?	month 5-18 there are relatively few dose adjustments, and therefore this is a reasonable assumption by the company.
Is the company's post-hoc subgroup analysis of fixed versus individualised dosing robust enough to make a judgement on the issue around changing the dosing procedure?	Two thirds of patients stated on flat dosing and approximately one third of patients started on individualised dosing and of those [redacted]% started on 200mg. For the whole trial population by month 5 : [redacted]% were on 300mg, [redacted]% on 200mg and [redacted]% on 100mg. Overall 70% of patients on the niraparib arm required a dose reduction and 50% of patients were maintained on 100mg. This is very similar to the dose reduction rate within the NOVA trial (niraparib maintenance in platinum sensitive relapsed ovarian cancer and within this trial the progression free survival (PFS) in patients who were dose-reduced to 200mg was similar to those remaining at 300mg indicating no loss of effectiveness (Berek 2018 Annals Oncol). The company analysis taken together with experience in the relapsed setting supports the use of individualised dosing.
Issue 2: Generalisability of the PRIMA results to UK clinical practice – exclusion of population with no visible residual disease after primary debulking surgery	
There are a range of estimates for the proportion of people with stage III disease with NVRD. In clinical practice, what is the estimated proportion of people with stage III disease with NVRD: irrespective of type of debulking surgery; after IDS and after PDS? Is evidence available to support these estimates?	Across the UK there is significant variability in the rates of PDS and IDS in women with advanced ovarian cancer and the rates of complete resection (no visible residual disease) vary from surgeon to surgeon. It is reasonable to use the Edinburgh Ovarian Cancer database for estimation. This is difficult to accurately estimate for the whole of the UK as there is significant site-specific variation with regards to primary and interval debulking after 3-4 cycles of chemotherapy and rates of complete cytoreduction. In some sites primary surgery rates may be 80% with the majority (60-70%) achieving complete resection (NRVD); other sites may have 70-80% neoadjuvant chemotherapy

	and achieve NRVD. These will be sites that are carefully defining operability and undertaking supra-radical multivisceral surgery. Across the UK there remains considerable variation and in some sites complete cytoreduction rates may be approximately 40% or less with either approach. The BGCS are due to release an audit of UK resection rates in October 2020. The EORTC and CHORUS trials reported a decade ago demonstrated significantly lower complete cytoreduction rates in the UK -EORTC12% and CHORUS 17% (primary surgery) and 39% (interval)- however the general consensus is that surgical resections rates have improved over the past decade
Can the company provide further justification for the choice of the proportion of patients with stage III disease with NVRD after PDS?	-
Issue 3: Sources of evidence for estimating progression-free survival for people with stage III no visible residual disease after primary debulking surgery	
The company has used data from various sources in its base case and scenario analyses for estimating PFS for people with stage III disease and NVRD after PDS and the ERG have suggested an alternative approach. What is the most appropriate method for estimating the outcomes in the population excluded in PRIMA but included in the expected licensed population (people with stage III disease with NVRD after PDS)?	CHORUS demonstrated that IDS was not inferior to PDS and so it could be assumed that NVRD in both circumstances should be equivalent and benefit from maintenance PARPi should be similar. The only thing you can't demonstrate in the PDS population is platinum sensitivity but in SOLO1 60% had upfront surgery with 75% having NVRD. There is no data suggesting a difference in outcome for patients who achieve NRVD after primary surgery or IDS.
Is it appropriate to apply hazard ratios derived from data in PAOLA-1, SOLO-1 and the PRIMA stage III subgroup to the PRIMA ITT curves?	It is important to note that there are some significant differences in the treatment populations of these trials: SOLO1- was a group of patients who had BRCA mutations and the majority had primary debulking surgery and no residual visible disease; PAOLA 1 –this included patients with

	PDS and IDS regardless of residual disease status and therefore a slightly better prognostic group.
How are the confounding factors, such as bevacizumab use in PAOLA-1 and BRCA mutation status in SOLO-1 likely to affect the 'NVRD effect' and 'treatment effect'?	Should not effect NVRD for PDS BRCA mutations should increase platinum sensitivity and would increase rate of response and therefore reduce the rate of residual disease in those patients undergoing IDS (neoadjuvant chemotherapy). Majority of benefit with bevacizumab believed to be in the maintenance phase
Is it reasonable to assume a class effect between olaparib and niraparib in order to estimate the 'NVRD effect' and 'treatment effect'?	Yes- all the trials of maintenance therapy in the front line and relapsed setting have demonstrated a benefit of PARP inhibitor therapy in women with BRCA mutated; HRD and to a lesser extent HR proficient tumours. This is a class effect
Is the assumption that patients with stage III disease and NVRD after IDS have similar prognosis to patients with stage III disease and NVRD after PDS in line with what is seen in clinical practice?	Yes – CHORUS trial, Kehoe et al Lancet 2015
Issue 5: Estimation of overall survival using a Δ progression-free survival: Δ overall survival ratio	
The company used Study 19 (which evaluated olaparib as second line treatment in BRCA+ patients with 7-year follow-up) to estimate a PFS:OS ratio and therefore assumed a class effect between olaparib and niraparib. Is it appropriate to assume this class effect as a basis for estimating the PFS:OS ratio?	Yes Of note Study 19 was enriched for mBRCA/ HRD due to the selection of platinum sensitivity at relapse but also included non-BRCA ovarian cancer
Is it appropriate to assume that niraparib has a constant survival advantage over routine surveillance over the entire time horizon of the model?	Patients may derive significant benefit and it is plausible that the survival advantages would persist with time; and may even be greater for some subgroups (BRCA and HRD deficient groups).
The company provided a scenario analysis with PFS:OS ratios ranging from 1:1 up to 1:3. What is likely to be the most	Was <1.0 for SOLO-1 (TA528)

appropriate ratio to use when estimating OS from PFS in this population?	Appropriate ratio probably closer to 1.1 than 1.3
The company's MA base case OS curve predicts that [redacted] of patients would be alive at 30 years in the niraparib arm of the model, when they would be 91 years old. This estimate compares with [redacted] in the company's curve for the ITT population (and [redacted] with no cure assumption). Is it clinically plausible that this proportion of people would be alive at this stage?	It is difficult to predict what percentage of the normal population would be alive at 91. But it is plausible that some would be, even in the placebo arm. And one would assume that the percentage of total would be slightly greater in the Niraparib arm.
The ERG noted that the HR used by the company to generate the 1:2 ΔPFS:ΔOS relationship is not reflective of the treatment effect for niraparib compared with routine surveillance observed in PRIMA. The hazard ratio of [redacted] used by the company to generate the 1:2 ΔPFS:ΔOS relationship suggests [redacted] relative treatment effect for niraparib compared with routine surveillance than that observed in PRIMA (HR of 0.70 [95% CI 0.44 to 1.11]). Can this discrepancy in treatment effect between the hazard ratio generated from the ΔPFS:ΔOS ratio and the data in PRIMA be explained?	
In the company's model, at 39 years (the time horizon used in the model) 100% of people in the routine surveillance arm are dead, but 1% of people in the niraparib arm remain alive (at age 100). How clinically plausible is this estimate?	It is difficult to predict what percentage of the normal population would be alive at 91. But it is plausible that some would be, even in the placebo arm. And one would assume that the percentage of total would be slightly greater in the Niraparib arm.
Issue 6: Company's model structure	
Given that patients can experience multiple disease progressions, would a 4-state model (progression-free, progression-free 2, progressed disease and death) be more suitable for decision making, as data are available from	PFS2 data are immature but suggest benefit of 1st line Niraparib is maintained. I am not sure that PFS2 is adds to the model from the 3-state model

PRIMA for progression-free and 2nd progression-free survival?	
Issue 7: Estimation of long-term remission	
The ERG agrees with the company that the appropriate use of mixture cure models relies on the existence of mature data from studies with long follow-up times that exceed anticipated point of cure time, as well as sufficient numbers of patients at risk at the end of follow-up in order to robustly estimate a cure fraction. What is the most appropriate method for estimating the point of long-term remission, given the immature data available from PRIMA?	Reasonable to use the Edinburgh Ovarian Cancer data and previously published data from similar populations such as Du Bois 2009
The company have assumed long-term remission is achieved in people who have had progression-free disease for 7 years. Does this align with what is seen in clinical practice?	In the vast majority of cases this would be reasonable to assume. The majority of patients (80%) with stage 3c/4 disease will relapse , usually within 18 months.
The company justified using data from Du Bois *et al.,* 2009 to estimate the proportion of people in long-term remission in the stage III NVRD after PDS population because it included a large sample size, assessment of a range of surgical outcomes and long follow-up (144 months) allowing for PFS and OS data to be extracted at 5, 7 and 10 years. The ERG suggest that this data could also be taken from the NVRD PFS curves estimated in the model, which would be consistent with the approach used in the ITT population. No comparative analysis has been provided between the De Bois *et al.,* study and the population in PAOLA-1 (where treatment effect for patients with stage III disease and NVRD after PDS was estimated), nor with the population in PRIMA. Is the approach to estimating the proportion of people in long-term remission in the stage III disease and NVRD after PDS	

population using external data from Du Bois *et al.,* 2009 appropriate?	
Is the ERGs assumption of removing long-term remission from the model appropriate?	Perhaps if it does have minimal effect on ICER
In UK clinical practice, is it correct that after 10 years in progression free disease, patients in this population are discharged?	yes
Issue 8: Modelling of progression-free survival	
The company uses data from the University of Edinburgh Ovarian Cancer database on TFST as a proxy for data on PFS, which it uses to validate long-term model estimates. Is TFST a reasonable alternative for PFS in this population?	Yes – probably most relevant clinically
Issue 9: Time to treatment discontinuation	
Can it be assumed that all people who have no radiological evidence of residual disease after 3 years will stop treatment?	yes
Based on clinical expert opinion and evidence from SOLO-1, the company assumed that [redacted] of participants who had not discontinued treatment at 3 years would carry on receiving niraparib. Based on clinical experience with similar treatments, what is the expected proportion of patients who would continue to receive niraparib at the end of the 3-year treatment period?	We estimate this to be a small percentage probably <10%
What length of time is it reasonable to assume niraparib would continue to be given to people who did not discontinue treatment at 3 years?	This is difficult to be sure, but we estimate approximately 5 years
What dose of niraparib was included in the model for people who continued to receive treatment after 3 years?	Most will be on 200mg or less (>70%) even if they started at 300mg

Issue 10: Utility values	
Are the utility values that the company have used clinically plausible?	N/A not able to see this information
Issue 11: Subsequent treatments	
Are the proportions of people receiving subsequent treatment in PRIMA representative of UK clinical practice?	>80% seems a very reasonable number and this reflects UK clinical practice.
Issue 12: Cancer Drugs Fund	
Is there further data being collected that could reduce uncertainty surrounding longer-term effectiveness and health outcomes in the relevant population(s)?	Ongoing follow-up for PRIMA and SOLO-1 Plans for extension of MONITOR-UK which would further address this in a real world population
When will these additional data become available?	?5 years
How suitable is the technology for use in the Cancer Drugs Fund (CDF)?	Suitable – very important, effective and well-tolerated treatment for this patient group

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1680]

Notes from meeting with clinical expert

7 October 2020

In attendance

Dr Shibani Nicum, Consultant Medical Oncologist

Emily Eaton Turner, Technical Adviser (NICE)

Albany Meikle, Technical Analyst (NICE)

Treatment options and severity of the disease

Most people (80%) present with advanced disease (stage 3 and 4) and ~80% of people will relapse within 18 months, so the population of interest all have severe disease. Relapse is generally over 3 to 5 years in cycles and as time passes, the time between relapses decreases. When disease becomes platinum resistant then life expectancy is less than 12 months. The aim of new treatment is to prevent (cure patients) or delay relapses. If relapses (each progression free survival) are delayed, you then see an incremental improvement in overall survival. People with stage 4 disease generally do less well, as do people who have residual disease after treatment (surgery and/or chemotherapy) (a 'higher risk' group). Olaparib is available in the CDF for people who have had a response to first line chemotherapy and have a BRCA mutation. Niraparib would potentially be an option for a wider group of patients who have responded to first line chemotherapy ie BRCA1/2 mutated and also the wild type group based on the results of PRIMA.

Regular blood monitoring

In month one of niraparib treatment the bloods are monitored weekly. After month 1; bloods are monitored monthly for the next 11 months and then as needed from 12 months onwards. The risk of low platelets has been improved through individualised niraparib dosing. Blood tests can be performed by a GP or at hospital and do not contribute to additional oncology appointments. Monitoring of blood test results is performed by a multi-disciplinary team, which does not require a change in structure as these practices are already in place (as niraparib is widely used in the recurrent setting).

Stopping rules

The PRIMA trial suggested discontinuation at 3 years unless continuation was deemed appropriate by a clinician. In practice, it would be expected that treatment would be stopped at 3 years if there was no visible residual disease. If there was

residual disease (controlled, without progression), treatment would likely be continued. Treatment would likely continue until disease progression and the next line of therapy is given. The rationale for this approach is that in this setting niraparib is a treatment for residual disease and is maintaining control of disease.

If there is no visible residual disease after 3 years of treatment, it would be expected that the treatment had targeted the undetectable cancerous cells and treatment could be stopped. The proportion of people who would continue to receive treatment after 3 years (population with controlled visible residual disease) is likely to vary across the country based on different success rates of resection. Approximately [redacted]% is a reasonable estimate of this proportion.

Impact on patients of receiving maintenance treatment

For many patients there is a psychological advantage to being given a maintenance treatment, rather than 'waiting' for disease recurrence/ progression with routine surveillance. PARP inhibitors are generally well tolerated with little discontinuation seen. It is an oral treatment which is an advantage for patients who do not need regular visits to hospital as with other maintenance treatments (available via the CDF). Oral administration is also advantageous for capacity issues, which is an ongoing consideration, but particularly during the COVID-pandemic.

Proportion of stage III NVRD after PDS

There is variation across the country for the success rate of cytoreduction. This is shown in the EORTC and CHORUS trials. It is expected that the proportions of people achieving no visible residual disease after primary surgery in CHORUS (17%) is greater now than it was when CHORUS was published 10 years ago. However, data to reliably estimate this proportion is not available. The BGCS are due to release an audit of UK resection rates in October/November 2020.

Generalisability of interval debulking surgery and primary debulking surgery

The achievement of complete cytoreduction (no visible residual disease) is the most important factor for prognosis. There is no recent published data on the differences in prognosis between people who undergo radical primary debulking surgery and interval debulking surgery and achieve NVRD –The TRUST trial will provide this data but only finished recruitment in April 2020. The CHORUS trial demonstrated that PDS was equivalent to IDS and achieving no visible residual disease is clearly the most important prognostic factor and it would be expected that prognosis would be similar in these 2 groups.

Niraparib dosing

Individualised dosing is beneficial for managing the adverse events of treatment. PRIMA data is likely to be robust enough to make a recommendation for individualised dosing, as although fixed dosing was used for approximately two thirds

of participants in PRIMA, many people in this group had their dose reduced (70% of the PRIMA population also has a dose reduction in the first few months) and still there was an overall benefit seen with this therapy.

The experience with niraparib in recurrent ovarian cancer has shown that a lower dose is effective (as shown in the NOVA trial). The NOVA trial included people with very good prognosis and niraparib showed a treatment benefit even in those patients who had a dose reduction (69% of the trial population). For the majority of people, a reduction in dose will be unlikely to negatively affect the inhibition of PARP receptors (e.g in PRIMA 50% of the trial population received 100mg and an overall benefit was still demonstrated). I am supportive of individualised dosing and do not think that it will impact the treatment effect.

In practice in the recurrent setting the gynae oncology community support and use individualised dosing of niraparib. Once on a dose of niraparib that is well tolerated, most people remain stable on the tolerated dose.

Plausibility of OS estimates

The company's base case for the marketing authorisation population estimates that [redacted] of patients will be alive at 30 years in the model (at 91 years old). It is likely that this is an [redacted] based on what is expected in clinical practice, due to the age of the cohort of patients. It is expected that in people who have achieved 7 to 10 years without disease progression, most causes of death will not be due to ovarian cancer. A realistic estimate of people expected to be alive at 30 years in the model is likely to be around 5 to 7% and this is likely to be higher in the niraparib arm

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy

ERG critique of the company's response to the technical engagement process

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1 Introduction

This document provides a review and critique of the company's response to the technical engagement (TE) process. The company's response addressed eleven issues raised in the TE report. The ERG discusses these in turn below.

1.1 Issue 1: Generalisability of the PRIMA results to UK clinical practice – dose used in trial versus clinical practice

Question 1. Complete and partial response in PRIMA

The ERG's clinical experts stated that the proportions of patients with a complete response (CR) and partial response (PR) after first line chemotherapy enrolled in PRIMA are reasonable compared with what would be expected in UK clinical practice. However, the ERG notes that there is likely to be variability in response across the country and between relevant trials. In PRIMA around 70% had a CR and 30% a PR after first line therapy. In PAOLA-1, which informs the extrapolation of the PRIMA trial to the MA population in the company's base case, the proportion of patients with a CR and PR were 78% and 22%, respectively, and in SOLO-1 the equivalent proportions were 82% and 18% with CR an PR, respectively.

Question 2. Niraparib dose used in PRIMA

The ERG's clinical experts stated that the individualised dosing strategy in which patients start on 300 mg or 200 mg niraparib depending on weight and platelet count, is the most relevant dosing strategy for clinical practice as it is reflected in the marketing authorisation for niraparib in this indication. Just over one third (35.2%) of patients enrolled in PRIMA started on individualised dosing, and 64.8% started on the fixed 300 mg dose of niraparib.

In addition, the ERG notes that further investigation of the lower dose of niraparib (100 mg) and its impact on clinical outcomes for ovarian cancer may be useful (ERG report 3.2.3).

Question 3. Tolerability of niraparib dose used long term

The ERG agrees with the company's response given to question 3. See also the ERG response to question 28. Based on the company's response to clarification question B17, the ERG considers it reasonable to assume that the dose of niraparib tolerated by month 18 would be expected to continue to be tolerated.

Question 4. Fixed versus individualised dosing

The subgroup analyses indicate that niraparib may be slightly less effective in the subgroup of patients on individualised dosing than in the fixed dose subgroup but individualised dosing also led to fewer dose interruptions and dose reductions due to AEs than the fixed dose. However, these subgroup analyses should be considered exploratory in nature, because they are *post-hoc* unstratified analyses, the difference between the subgroups were not statistically significant and PRIMA was not powered to detect a difference between these groups.

1.2 Issue 2: Generalisability of the PRIMA results to UK clinical practice – exclusion of population with no visible residual disease after primary debulking surgery

Question 5. Proportion of patients with stage III disease and NVRD

There are large variations in surgical outcomes between surgeons, centres and across different regions of the UK. In the study by Hall *et al*. 2019[1], which compared the outcomes of patient treated within two neighbouring UK cancer centres for advanced ovarian cancer, the proportion of patients with NVRD after cytoreductive surgery (irrespective of stage of disease) was 59% and 85%, depending on surgical expertise. The ERG's clinical experts estimated that the proportion of patients with stage III and NVRD is likely to be 50-60% in the UK. In comparison, only [redacted] of patient in the MA cohort of the Edinburgh database had NVRD (irrespective of stage of disease) compared with 46.5% in the PRIMA trial. This large variation in surgical outcomes is echoed by the company and in other stakeholder comments for this appraisal. In addition, as highlighted by the company, there are no centralised guidelines for reporting of surgical outcomes or robust data collection mechanisms to report the proportion of patients who are classified as stage III NVRD in standard practice. The ERG notes that any adjustment of the PRIMA trial data to more accurately reflect the timing and outcomes of surgery seen in UK practice, is reliant on accurate and reliable estimates of those outcomes in clinical practice. Due to the uncertainty around the proportions of patients with stage III and NVRD after PDS and/or IDS in UK practice, the ERG does not consider that an adjustment of the PRIMA data to compensate for the exclusion of patients with stage III NVRD post PDS will plausibly decrease the uncertainty or improve the precision around the estimate of efficacy of niraparib in the intended population.

Question 6. Proportion of patients with stage III disease with NVRD after PFS

The ERG is concerned about the applicability of the proportion of patients with stage III NVRD post PDS estimated from the Edinburgh dataset due to the large variation in surgical outcomes across the country. Based on the updated analysis of the Edinburgh dataset [redacted] were stage III NVRD post PDS compared with the ERG's and the company's clinical experts who estimate the proportion to be between 25% and 40% of the patient population. The Edinburgh dataset also shows that [redacted] of patient in the PRIMA-simulated cohort had NVRD irrespective of PDS or IDS compared with 46.5% in PRIMA. As highlighted in the response to question 5, the proportion of patients with NVRD after debulking surgery varies across UK practice and basing this estimate on one small region in the UK is unlikely to be representative of the surgical outcomes seen across the country.

1.3 Issue 3: Sources of evidence for estimating progression-free survival for people with stage III no visible residual disease after primary debulking surgery

Question 7. Method for estimating the outcomes in the population excluded in PRIMA

Based on the uncertainty around the proportion of the population excluded from the PRIMA trial, the ERG does not consider the company has provided reasonable justification that any adjustment of the PRIMA trial results will lead to a more reliable or representative estimate of the efficacy of niraparib in UK clinical practice. However, if the committee considers an adjustment justified, the approach suggested by the ERG will provide a more robust estimate of the efficacy of niraparib in a population potentially more representative of UK patients, compared with the company's approach.

The ERG has serious concerns about the validity of the company's current approach and the data informing it, as described in the ERG report, Section 2.4.4. The impact of some of the key issues with the it are described in response to question 8, 9, and 10 below.

To refute the assumption of similar prognosis and treatment effect in stage III patients with NVRD after IDS and PDS, the company references the ICON8 trial and a subgroup analysis of PAOLA-1 between patients of high and low risk of progression. The ICON8 trial[2] shows a marked difference in OS between patients who have had PDS and IDS and the ERG agrees with the company that patients selected for PDS and IDS are likely to have some differences in disease characteristics. However, as expanded on in response to question 11, ICON8, as well as other relevant trials (Vergote *et al.* 2010[3] and Kehoe *et al.* 2015) do not provide quantifiable data for the subgroup comparing the outcomes of patients with stage III NVRD post PDS and IDS. Nonetheless, the ERG acknowledges that the

outcomes may differ between these subgroups, with NVRD potentially being a stronger prognostic factor for patients who have PDS than for those who have IDS. [3]

Based on the subgroup analysis of PAOLA-1 the company concludes that it is appropriate to expect that the treatment effect of PARPi maintenance treatment will be different between patients who have undergone PDS and IDS. As described in the ERG report (section 2.4.4) and in response to question 9, there are several factors which are likely to confound the generalisability of these results to what would be expected for niraparib in PRIMA or in UK clinical practice. One of the main confounders being the concomitant use of bevacizumab in both arms of PAOLA-1, which is likely to lead to an overestimate of the potential 'treatment effect' compared with the expected effect without concomitant bevacizumab.

Due to the lack of evidence showing a substantial and quantifiable prognostic difference between patients with stage III NVRD after PDS and IDS, the ERG considers it a reasonable assumption that the prognosis for these patient groups are similar (i.e. it is the NVRD status that drives the difference in prognosis rather than the type of surgery that attains it). This assumption allows reweighting outcome data for patients within PRIMA, an approach which has several advantages over the methods used by the company. The ERG's approach uses the different prognosis of stage III NVRD patients and the treatment effect in this population observed in the PRIMA trial rather than estimating them from secondary sources, which implicitly adds additional uncertainty that the ERG considers unwarranted.

Question 8. Applying HRs to curves for which proportional hazards don't hold

Although the PHs assumption seems to hold for the 'NVRD effect' and 'treatment effect' HRs, the company is applying these HRs directly to the PFS curves in PRIMA even though PHs have been demonstrated not to hold for this outcome within PRIMA. No assessment has been provided of the potential impact of and how to interpret the results of applying these HRs to independent curves for which PHs do not hold.

Question 9. Confounding of 'NVRD effect' and 'treatment effect'

The ERG considers the 'NVRD effect' and 'treatment effect' estimated by the company based on PAOLA-1 and SOLO-1 to have limited generalisability to the PRIMA trial due to confounding caused by differences in populations, interventions and trial design, including concomitant bevacizumab use

in PAOLA-1 and SOLO-1 being limited to patients with a BRCA mutation. Importantly, no adjustments have been made by the company for any differences between PRIMA, PAOLA-1 and SOLO-1.

As described in the ERG report (Section 2.4.4), the 'treatment effect' calculated based on PAOLA-1 in patients given olaparib plus bevacizumab is likely to be overestimated compared with the equivalent 'treatment effect' expected with niraparib in patients not receiving concomitant bevacizumab. That is because of a potential synergistic effect of maintenance treatment with PARPi and bevacizumab.[4, 5] In addition, concomitant bevacizumab treatment is likely to also confound the 'NVRD effect' calculated based on PAOLA-1. As bevacizumab has been shown to be more effective compared with routine surveillance in patients at high risk of progression than in patients at a lower risk of progression (e.g. patients with stage III and NVRD)[6] it would be expected that the relative improvement of patients treated with bevacizumab would be smaller in the subgroup of patients with stage III NVRD after PDS than in the rest of the PAOLA-1 population. This means that the 'NVRD effect' calculated based on subgroups of the placebo arm in PAOLA-1 could be an underestimate compared with what would be expected in a population not receiving bevacizumab maintenance therapy.

The impact on the 'NVRD effect' of the SOLO-1 trial only including BRCA+ patients is not clear. Patients with a BRCA mutation have a better prognosis than patients with BRCA wild type (BRCAwt) and the overall population. The PARPi specific treatment effect has also been established to be larger in the BRCA+ population than in BRCA- or the overall population. As the BRCA+ subgroup overall has a better prognosis, it could potentially hide or obscure the "true" 'NVRD effect', or it may not have an impact on the relative 'NVRD effect' at all. The impact of focusing on BRCA+ patients on the 'treatment effect' on the other hand is likely to lead to an overestimate of the effect as treatment with PARPis like olaparib and niraparib are known to lead to longer PFS compared with placebo in BRCA+ patients compared with BRCA- patients or a mixed population.

Question 10. PARPi class effect

The ERG's clinical experts agreed that there is likely to be a class effect for PARPi in terms of PFS. However, there are no data available comparing mature OS data for the different PARPi. The assumption of a PARPi class effect has been necessary in previous appraisals due to the lack of long-term data for any of the PARPi other than olaparib as a second line therapy as assessed in Study 19. In addition, there is no evidence available to support the assumption that the efficacy of olaparib in

combination with bevacizumab compared with bevacizumab monotherapy will be similar or the same as niraparib versus placebo in populations with differences in prior therapy.

Question 11. Assumption of similar prognosis between patients with stage III NVRD after PDS and IDS

The ERG highlights that the assumption of similar prognosis for patients with stage III disease and NVRD after PDS and IDS is only relevant if the committee deems an adjustment of the PRIMA ITT data is required in order to make the results more reflective of what is expected in the patient population in UK clinical practice. The ERG reiterates that the most reliable estimate for the efficacy of niraparib relevant to the patient population in UK clinical practice is based on the ITT results of the PRIMA trial without any adjustment for the population excluded from the trial, as described in response to question 5. However, if an adjustment is deemed to be required, using the approach suggested by the ERG, which is contingent on the assumption of similar prognosis for stage III NVRD after PDS as after IDS, is likely to provide more robust and reliable results than the approach provided by the company, as described in response to question 7.

The ERG considers that the primary driver of a better prognosis in the population of interest is achieving NVRD irrespective of the type of surgery used to achieve this. The ERG agrees that there is a difference in prognosis between NVRD and VRD and it is likely that the different surgical techniques results in different proportions of patients achieving NVRD or VRD and this may result in different long-term outcomes for the overall populations.

As the company has highlighted, the studies by Vergote *et al*. 2010 and Kehoe *et al.* 2015 show no significant difference in PFS or OS depending on PDS and IDS in the overall population. However, the proportion of patients who had NVRD after PDS and IDS differed. In Vergote 2010, the proportion of patients with NVRD was 19% and 51% after PDS and IDS, respectively, and in Kehoe 2015 the equivalent proportions were 17% and 39%. This indicates that the prognosis may differ between patients with NVRD after IDS and PDS, with NVRD potentially being a stronger prognostic factor for patients who have PDS than for those who have IDS. In support of a differential prognosis for stage III NVRD after PDS and IDS the company also references PAOLA-1 and SOLO-1. However, none of these studies provide robust evidence of a substantial difference in PFS or OS for the specific subgroups of patients with stage III disease and NVRD after PDS compared with IDS. The ERG therefore considers it a reasonable assumption that patients with stage III disease and NVRD after PDS and IDS have a similar prognosis, which is consistent with feedback from the ERG's clinical experts and other clinical expert stakeholder comments for this appraisal.

1.4 Issue 5: Estimation of overall survival using a Δ progression-free survival: Δ overall survival ratio

Use of a PFS to OS ratio to model OS

The company mentions that previous OC technology appraisals (TA528 and TA598) have utilised OS to PFS ratios to inform the modelling of OS. The company also mentions that the review conducted by the DSU, and referred to by the ERG in their original report (Section 3.2.4.3.2), is not an appropriate source of evidence for decision making given that it was not specific to OC and was conducted prior to the emergence of PARP inhibitors.

The ERG notes that the DSU review was not used by the ERG as a source to estimate the PFS to OS ratio for the modelling of OS in the model. The review aimed to examine the evidence available concerning the relationship between PFS and OS in advanced or metastatic cancer, with a view to determining the extent to which PFS can be considered a robust (and quantifiable) surrogate endpoint for OS. The review concluded that even where robust evidence supporting a correlation between the treatment effect on PFS and OS is available (regardless of type of cancer and treatments available), it remains unclear how that should be converted into a quantified relationship between the surrogate and the final outcome within a cost-effectiveness model.

Furthermore, TA598 (olaparib for first-line maintenance treatment of BRCA+ ovarian, fallopian tube and peritoneal cancer) identified a systematic review (searches run between 1 January 1996 to 30 June 2012) on the relationship between PFS and OS in epithelial ovarian cancer.[4] The review found a modest relationship between the HRs for PFS and OS (r^2 =0.52), and a moderate association between median PFS and median OS (r^2 = 0.72). The ERG in TA598 noted therefore, that the relationship between median times to PFS and OS in this population do not indicate there is an equivalent relationship between the HRs for these two outcomes.

In its original report (Section 3.2.4.3.2), the ERG notes a systematic review by Sundar *et al*. evaluating the relationship between PFS and post-progression survival in advanced ovarian cancer including 37 trials (15,850 patients) which concluded that, "… increases in median PFS generally lead to little change in post-progression survival. Percentage gains in PFS are generally associated with no percentage gains or with very slight percentage gains or losses in post-progression survival". The authors concluded that, if the effect of a treatment for ovarian cancer extends PFS by x months, it is reasonable to estimate that the treatment will also extend OS by x months, meaning that, "*the*

magnitude of the improvement in PFS is the magnitude of the improvement in OS." [7, 8] Similar findings were reported elsewhere. [7, 8]

Therefore, the ERG's original conclusion remains that there is not sufficient evidence available in literature to suggest that the use of PFS as a surrogate outcome for OS is appropriate, and importantly, OS gains that exceed PFS gains should be interpreted with extreme caution and substantiated with robust, mature data. Crucially, the results generated from the company's modelling approach are inconsistent with the OS data observed in PRIMA. Firstly, the HR of [redacted] used by the company in the ITT model to generate the 1:2 ΔPFS:ΔOS relationship suggests a much higher relative treatment effect for niraparib vs RS than that observed in PRIMA - HR of 0.70 (95% CI: 0.44 to 1.11). Secondly, Figure 1 shows that at [redacted] months, the OS RS and OS niraparib curves [redacted] ([redacted]% alive in the RS arm and [redacted]% alive in the niraparib arm). At this point the number of patients at risk is low and therefore, results should be interpreted with caution; however, these still represent around [redacted]% of the niraparib patients and [redacted]% of the RS patients. Nonetheless, at the same timepoint in the model, the niraparib and RS OS curves are on a [redacted] trajectory, suggesting that the relative treatment effect for niraparib does not diminish over time (Figure 1).

Figure 1. Overall survival KM curves in PRIMA and modelled OS curves (Figure 18, ERG report)

The company asserts that Study 19 provides the best available evidence to inform long-term OS predictions for PARPi in the OC setting and that it demonstrates that as the data matures the treatment effect on OS improves relative to RS. Therefore, the company concludes that the OS treatment effect for niraparib should be expected to improve as the PRIMA data matures.

The ERG in TA598 noted that, "*The ERG does not disagree that the SOLO-1 OS curves may be similar to that observed in Study 19, but it is also possible that no additional OS benefit is observed after the*

curves in SOLO-1 have converged. […] One potentially important difference between the two studies is that that the criteria for stopping treatment were very different. In Study 19, patients could continue their treatment indefinitely until relapse, whereas in SOLO-1, patients could only continue their treatment beyond two years after initiation if: they had a partial response at two years; had not experienced a relapse; and, in the opinion of the treating physician the patient could derive further benefit from olaparib treatment." The committee for TA598 concluded that, "*No significant differences in overall survival have been observed between the olaparib and placebo arms in SOLO1. Given the magnitude of the effect on PFS, it would be reasonable to expect that olaparib will extend life, but the size of that effect is uncertain*."

Similarly, the ERG notes that the PRIMA protocol indicated that patients should discontinue treatment at 3 years unless indicated by the consulting physician. Even though the trend in OS curves in Study 19 might provide an indication of how OS curves in PRIMA would evolve over time, it is also possible that the results observed during the PRIMA trial period will not change in the future.

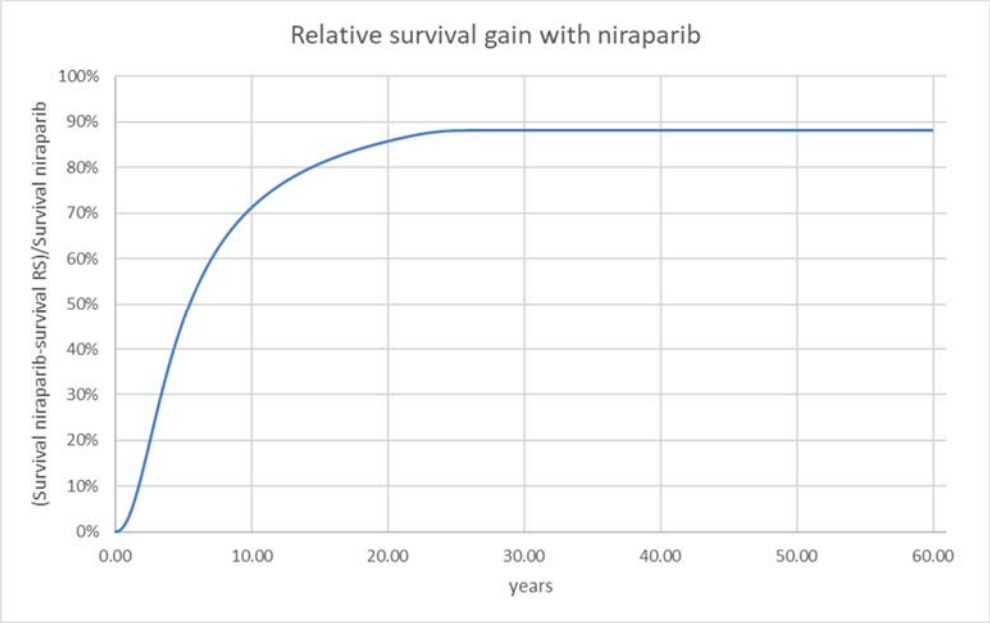
When explaining why the OS niraparib KM data from PRIMA was not used to fit OS curves in the model while the OS RS KM data were fitted, the company stated that the immaturity in the RS OS KM data from PRIMA was overcome with the use of long-term real word data, which allowed the company to validate the RS OS curve extrapolations. The company added that real-world data are not currently available for niraparib to inform long-term OS curves, and thus, survival analysis techniques cannot be used. The company added that using a PFS to OS ratio is a flexible method that, "*allows the user to select an appropriate ΔPFS:ΔOS relationship in order to produce clinically plausible long-term survival predictions for niraparib relative to routine surveillance*."

The ERG notes the inconsistency in the company's argument. The lack of long-term external data to validate OS curves for niraparib presents the same challenges regardless of the method used to estimate the long-term OS curve. The OS curve derived through a PFS to OS ratio should still be validated by clinical expert opinion or external data to ascertain clinical plausibility. Therefore, once a reference has been established around what is considered clinically plausible, the company should have used a more robust method to estimate OS for niraparib, and importantly, used the available observed data from PRIMA. This method would have allowed the analysis not to rely on the assumption of a **constant** relative treatment effect as is the case with the use of HRs.

In their response to TE, the company also argued that the application of a HR to the RS OS arm to sustain the PFS:OS relationship in the model does not lead to a constant survival advantage for

niraparib compared to RS because OS in the model is restricted by the risk of death from all-cause mortality for both treatment arms. The ERG disagrees with the company's statement. The ERG produced Figure 2, which shows the relative survival gain for niraparib vs RS in the model, when long-term remission is not assumed. The graph shows that the relative survival gain with niraparib increases over time and then stabilises around 23 years in the model, approximately when OS in the model is restricted by the risk of death from all-cause mortality for both treatment arms.

Figure 2. Relative survival gain with niraparib (no long-term remission assumption)



Furthermore, the company applied a HR to a log-logistic model (used to fit the OS RS curve). From a methodological point of view, the application of an HR to a log-logistic model (i.e. to a non-PHs model) is not appropriate (DSU; TSD 14).[9]

The company also states that assuming a constant survival advantage in the model between niraparib and RS might be appropriate as the PHs assumption cannot be rejected for the PRIMA OS data across study arms. The ERG notes that: 1) the company deemed the OS niraparib data from PRIMA to be too immature to draw any reliable conclusions for long-term survival; and 2) the fact that the PHs assumption is not rejected during the trial period (30 months) does not provide any information as to whether the PH assumption would hold in the future if the trial were to continue for the 39 years of the economic analysis.

Therefore, the ERG reinforces its previous opinion that using a surrogate outcome to estimate OS for niraparib is inappropriate given the availability of OS data from PRIMA.

Estimate of PFS to OS ratio used in the model

The company considers that the 1:2 ratio is the most appropriate ratio to be used in the model and that the 1:1.13 ratio [corresponding to the OS HR of 0.70 (95% CI: 0.44 to 1.11) in PRIMA] should be considered the lower bound for the analysis. The company uses the Sundar *et al*. review's conclusion that, "*if the effect of a treatment for ovarian cancer extends PFS by x months, it is reasonable to estimate that the treatment will also extend OS by x months*" and states that because the review included chemotherapy trials only, then the 1:1 ratio is that associated with chemotherapy treatments and PARPis should improve this relationship further.

The ERG notes that the Sundar *et al*. study evaluated how many months a new drug for OC might add to OS if the number of months the drug added to PFS (relative to a standard drug) was already known. Therefore, the ERG's conclusion from the Sundar *et al*. review is that any increase in OS derived from PARPis relative to standard chemotherapy is likely to be due to an increase in PFS. The ERG considers the company's view that this increase in OS (relative to PFS) would be greater for PARPis to be speculation.

The company reports five sources of evidence to substantiate using a PFS to OS ratio ranging from 1:2 to 1:4. These are: Vergote 2010; Kehoe 2015; Tewari 2019; Bristow 2007; and Armstrong 2006. Upon review of these sources, the ERG did not find any new evidence in support of the use of a PFS to OS ratio. Furthermore, the ERG notes that all the reported studies compared chemotherapy regimens, or surgical procedures, therefore, contradicting the company's argument that chemotherapy studies should not be used to inform the appropriateness (or lack thereof) of a PFS to OS ratio for PARPis.

The company raised its concern with the use of a 1:0.66 PFS to OS ratio in one of the ERG's exploratory analysis and requested more details on the ERG's rationale for using this estimate.

The 1:0.66 ratio was used by the company in TA598 and was estimated as a PFS2 to OS surrogate measure. The company in TA598 acknowledged that for SOLO-1, the high rate of subsequent PARPi use after progression on RS was likely to confound the post-progression survival period of the study. Therefore, to account for the effect of subsequent PARPi use on OS, the company assumed that the effect of treatment on OS was proportional to the effect observed on PFS2, which covers the period from randomisation to second progression or death.

The ERG notes that data on subsequent treatment use from PRIMA are highly immature and therefore, the ERG cannot ascertain what proportion of patients on RS received subsequent PARPis. Importantly, given the ERG's restriction to use a PFS to OS ratio in the model (which the ERG disagrees with), it was considered relevant to provide the committee with a range of possible scenarios. As per the ERG's original report, a range of ratios (1:0.66; 1:1; 1:1.13) were added to the scenarios included by the company in their model (1:1; 1:1.25; 1:1.5; 1:1.75; 1:2.5; and 1:3).

For clarity, the ERG produced Table 1 which shows the PFS to OS ratios used in the ERG's exploratory analysis and in the company's base case, together with the corresponding OS HRs applied to the RS OS curve in the model. All PFS to OS ratios used in the ERG's analysis result in a survival gain for niraparib vs RS, with the company's 1:2 ratio resulting in the application of a HR of [redacted] between the RS and niraparib OS curves. The ERG notes, again, that the OS PRIMA results have shown a not statistically significant 0.70 (95% CI: 0.44 to 1.11) HR between niraparib and RS.

Table 1. PFS to OS ratios and corresponding survival gains in the model

PFS to OS ratio (α parameter) in the equation: Niraparib mean OS = (RS mean OS + [Mean PFS difference x α])	Resulting hazard ratio applied to the OS RS curve to derive the OS niraparib curve in the model (a HR <1 indicates a survival benefit for niraparib vs RS)	Total undiscounted life years gained with niraparib vs RS
α=0.66	0.84	0.79
α=1	0.74	1.50
α=1.13	0.70	1.83
α=2	[redacted]	[redacted]
Abbreviations: PFS, progression-free survival; OS, overall survival; RS, routine surveillance; HR, hazard ratio.		

1.5 Issue 6: Company's model structure

The company states that including a second progression state in the model would not be appropriate and is unlikely to impact the cost-effectiveness results.

The ERG in TA598 was concerned that the use of a three-state model did not capture multiple disease progressions; subsequent treatments received; and the impact of second progressions on patients' quality of life.

Without having more mature data from PRIMA, it is difficult for the ERG to assess the likely impact of including a second progression state in the model. It is possible that including a second

progression state in the model would not impact the cost-effectiveness results; however, it is also possible that including PFS2 data in the model could greatly impact the results. The ERG notes that analysis of the time to second progression in PRIMA resulted in a [redacted] and that [redacted]; however, it is not possible to ascertain if niraparib delays second progression events without having more mature PFS2 data.

1.6 Issue 7: Estimation of long-term remission

The company acknowledged the ERG's concern surrounding the modelling of long-term remission and therefore decided to remove this assumption from the analyses.

Nonetheless, the company added that the potential for patients to achieve long-term remission is still valid to this decision problem thus, the company agreed with the ERG's exploratory analyses in which patients who are progression-free at 7 or 10 years stop incurring disease management costs.

1.7 Issue 8: Modelling of progression-free survival

The ERG does not have anything to add to the company's response.

1.8 Issue 9: Time to treatment discontinuation

Questions 25 through 27 raised by NICE call for clinical expert opinion.

The ERG agrees with the company's explanation about the dose of niraparib included in the model (question 28). For clarity, the ERG also reproduced Table 29 from the ERG's report (Table 2).

Table 2. Total acquisition costs for niraparib per cycle applied in the base case analysis (taken from the revised model) (Table 29, ERG report)

Model cycle	Proportion of patients across dose (mg) categories			Total cost per day (per dose [mg])			Total cost per cycle
	100	200	300	100	200	300	
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]				[redacted]
3	[redacted]	[redacted]	[redacted]				[redacted]
4	[redacted]	[redacted]	[redacted]				[redacted]
5	[redacted]	[redacted]	[redacted]				[redacted]
6	[redacted]	[redacted]	[redacted]				[redacted]

7	[redacted]	[redacted]	[redacted]				[redacted]
8	[redacted]	[redacted]	[redacted]				[redacted]
9	[redacted]	[redacted]	[redacted]				[redacted]
10	[redacted]	[redacted]	[redacted]				[redacted]
11	[redacted]	[redacted]	[redacted]				[redacted]
12	[redacted]	[redacted]	[redacted]				[redacted]
13	[redacted]	[redacted]	[redacted]				[redacted]
14	[redacted]	[redacted]	[redacted]				[redacted]
15	[redacted]	[redacted]	[redacted]				[redacted]
16	[redacted]	[redacted]	[redacted]				[redacted]
17	[redacted]	[redacted]	[redacted]				[redacted]
18	[redacted]	[redacted]	[redacted]				[redacted]
18+	[redacted]	[redacted]	[redacted]				[redacted]

Abbreviations: mg, milligram

1.9 Issue 10: Utility values

The company presents a study by Valabrega[10] which divided the PRIMA population into <65 years; ≥65 years; <75 years; and ≥75 years categories, to analyse the impact of age on treatment efficacy; safety; and quality of life. Figure 9 in the company's response to TE indicates that patients' EQ-5D-5L reported values: 1) did not change considerably over 56 weeks; and 2) were similar for the 4 age groups at baseline.

The company uses these results to justify not employing age-adjusted utility values in the economic model. The ERG disagrees with the company's assessment and notes that: 1) the lack of a substantial change in the mean EQ-5D values over the approximately 1-year follow up period in Valabrega is expected, and does not contradict the use of age adjusted utilities, as the bigger changes in utility due to age are observed over the years, and not over 1 year; 2) without more information on patients' age's distribution it is difficult to ascertain why the baseline mean utility values in Figure 9 seem broadly the same across all age groups, however, it is possible that the highest concertation of data points is around the age thresholds, which would make the mean baseline across age groups in the study categories similar.

Using a lifetime horizon in the model means patients can live for an additional 39 years, compared with 1 year at the end of the Valabrega study. Therefore, the changes in QoL data observed during the study do not capture the impact of aging in the economic analysis. The company's approach,

thus, overestimates the utility of survivors and the cost effectiveness of the more effective treatment in the model (niraparib).

1.10 Issue 11: Subsequent treatments

Question 30 raised by NICE calls for clinical expert opinion. Nonetheless, the ERG notes that the proportion of patients who progressed in PRIMA who also received subsequent chemotherapy amount to [redacted] for niraparib and RS, respectively. The number of patients receiving subsequent treatments in PRIMA is lower than what is expected in UK practice and lower than what has been reported in other trials for the same disease area. For example, the ERG in TA598 reported that the CSR for SOLO-1 suggests that 90% and 93% of the patients who progressed received subsequent chemotherapy in the olaparib and placebo arms, respectively.

Importantly, the ERG notes that the proportion of patients receiving subsequent PARPi treatment in the RS arm of PRIMA is low ([redacted]). The proportion of patients receiving a PARPi after RS in SOLO-1 was redacted in the TA598 documents, however this was reported to be high, and a scenario analysis was provided by the company in TA598 as a response to TE, estimating that 51% is likely to be the maximum percentage of patients who would receive a PARP inhibitor after RS.

The ERG acknowledges that the PRIMA data are immature and therefore data on subsequent treatments need to be interpreted with caution. Nonetheless, the ERG stresses the importance of interpreting the future results for more mature OS and PFS2 data together with the more mature data on subsequent treatments received in PRIMA.

1.11 Issue 12: Cancer Drugs Fund

The company reported that next available data cuts from PRIMA will not be available before [redacted]. The ERG, therefore, notes that there [redacted] in 2022, when the standard 2-year CDF review process would take place, if niraparib were to be included in the CDF in 2020. Furthermore, the ERG notes that real world evidence from the systemic anti-cancer therapy (SACT) database collected through the CDF would include a maximum follow-up period of 2 years, which would represent a slightly shorter follow-up period that that currently available for OS data from PRIMA (approximately 30 months).

2 Company's updated results

The results of the company's updated base case analysis are presented in Table 3 for the ITT population from the PRIMA trial; and in Table 4 for the MA population. The values in Table 3 and Table 4 are discounted at 3.5% per annum, unless otherwise stated. All results include the simple list price discount of [redacted]% for niraparib. A list of the changes incorporated in the company's updated base case results is provided in Appendix 1 of the company's response to TE.

Table 3. Company's base case results, ITT population

Treatment	Total Costs	Total LYG, undiscounted	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
RS	[redacted]	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,178

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance

Table 4. Company's base case results, MA population

Treatment	Total Costs	Total LYG, undiscounted	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
RS	[redacted]	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,184

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RS, routine surveillance

3 ERG's exploratory analysis

Given the uncertainty around the survival benefit associated with niraparib, the ERG does not have a preferred base case ICER. The exploratory analyses provided by the ERG in its original report are replicated below. The preferred assumptions for the economic model have not changed from the ERG's previously conducted analyses and are the following:

- Use of the ITT population in the model;
- Removal of long-term remission approach from the model and assuming PFS patients stop incurring costs at 10 years;
- Applying age-related utility decrements in the model;
- Assuming no treatment discontinuation with niraparib as per SmPC;
- Including the cost of heart rate and blood pressure monitoring;
- Using alternative resource use estimates for PFS.

In addition to the changes listed above, the ERG considered three different scenarios:

1. Use of a PFS to OS ratio of 1:0.66 as per TA598;
2. Use of a PFS to OS ratio of 1:1;
3. Use of a HR between RS OS and niraparib OS of 0.70 as observed in PRIMA.

Results of these analyses are reported in Table 5. The ERG notes that the ICERs presented in Table 5 are slightly higher (a difference smaller than £70) than those presented in Table 50 of the ERG's original report, due to a small error found in the previously ran analyses.

When the PFS to OS ratio of 1:0.66 is used in the model, the ICER amounts to £79,146 per QALY gained. When it is assumed that the magnitude of the improvement in PFS with niraparib is the same as the magnitude of the improvement in OS (i.e. 1 month of extra PFS leads to 1 month of extra OS - PFS to OS ratio of 1:1), the ICER decreased to £45,265 per QALY gained.

The ERG notes that the OS HR for niraparib vs RS observed in PRIMA was of 0.70 (95% CI: 0.44 to 1.11), albeit not statistically significant. When a HR of 0.70 is used in the model, this leads to an ICER of £38,284 per QALY gained. This, in its turn corresponds to a PFS to OS ratio of 1:1.13 (1 month of extra PFS leads to 1.13 months of extra OS). However, given the lack of maturity and statistical significance of the HR in PRIMA, and the shape of the OS curves (see section 4.2.6.1.1 of the ERG report), it is possible that the survival benefit with niraparib is much smaller or higher than that observed in PRIMA.

The ERG concludes that without having more mature OS data from PRIMA it is not possible to make inferences on the survival benefits of niraparib without a paramount level of uncertainty.

The ERG reinforces is concern that for all the analyses presented, it was assumed that niraparib has a constant survival advantage over RS for the duration of the 39-year model (given the use of a HR). The ERG notes that this is unlikely to represent clinical reality and likely to considerably overestimate the cost-effectiveness of niraparib. The ERG again, notes that this could be surpassed with fitting an OS model to the OS KM niraparib data from PRIMA (provided survival predictions are valid).

Table 5. Results of ERG's exploratory analysis for the ITT population

		Niraparib	RS	Inc. value
1	**Use of a PFS to OS ratio of 1:0.66 as per TA598 (HR between RS OS and niraparib OS of 0.84)**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	Total undiscounted life years	[redacted]	[redacted]	[redacted]
	ICER	-	-	£79,146

2	**Use of a PFS to OS ratio of 1:1 (HR between RS OS and niraparib OS of 0.74)**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	Total undiscounted life years	[redacted]	[redacted]	[redacted]
	ICER	-	-	£45,265
3	**Use of a HR between RS OS and niraparib OS of 0.70 (PFS to OS ratio of 1:1.13)**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	Total undiscounted life years	[redacted]	[redacted]	[redacted]
	ICER	-	-	£38,284
	Abbreviations: ICER. Incremental cost-effectiveness ratio; Inc. incremental; ITT, intention to treat; OS, overall survival; PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life year; RS, routine surveillance; TA, technology appraisal			

References

1. Hall M, Savvatis K, Nixon K, Kyrgiou M, Hariharan K, Padwick M, et al. Maximal-Effort Cytoreductive Surgery for Ovarian Cancer Patients with a High Tumor Burden: Variations in Practice and Impact on Outcome. *Ann Surg Oncol* 2019; **26**: 2943-51.
2. Clamp A. ICON8: Overall survival results in a GCIG phase III randomised controlled trial of weekly dose-dense chemotherapy in first line epithelial ovarian, fallopian tube or primary peritoneal carcinoma treatment. . 2020. p. S551-S89.
3. Vergote I, Trope CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med* 2010; **363**: 943-53.
4. National Institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy: technology appraisal guidance [TA598]. 2019.
5. Ray-Coquard I, Pautier P, Pignata S, al. e. Phase III PAOLA-1/ENGOT-ov25 trial: Olaparib plus bevacizumab (bev) as maintenance therapy in patients (pts) with newly diagnosed, advanced ovarian cancer(OC) treated with platinum-based chemotherapy (PCh) plus bev. *Annals of Oncology* 2019; **30**: v851-v934.
6. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med* 2011; **365**: 2484-96.
7. Sundar S, Wu J, Hillaby K, Yap J, Lilford R. A systematic review evaluating the relationship between progression free survival and post progression survival in advanced ovarian cancer. *Gynecol Oncol* 2012; **125**: 493-9.
8. Wilkerson J, Fojo T. Progression-free survival is simply a measure of a drug's effect while administered and is not a surrogate for overall survival. *Cancer J* 2009; **15**: 379-85.
9. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011.
10. Valabrega G, editor Efficacy and Safety of Niraparib in Older Patients With Advanced Ovarian Cancer: Results From the PRIMA/ENGOT-OV26/GOG-3012 Trial. 2020.