NICE National Institute for Health and Care Excellence

Cancer Drugs Fund Review

Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (CDF review TA528) [ID1644]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CANCER DRUGS FUND REVIEW

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Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission** from GlaxoSmithKline

2. **Clarification questions and company responses**
   a. Appendix
   b. B3 and B6 responses

3. **Patient group, professional group and NHS organisation submission** from:
   a. British Gynaecological Cancer Society (BGCS)
   b. Ovacome
   c. Target Ovarian Cancer

4. **Public Health England Study Report**
   a. Overall survival refresh

5. **Evidence Review Group report** prepared by BMJ-TAG

6. **Evidence Review Group report – factual accuracy check**

7. **Technical engagement response from company** – GlaxoSmithKline
   a. New Evidence

8. **Technical engagement responses from experts:**
   a. Dr Jonathan Ledermann – clinical expert, nominated by GlaxoSmithKline
   b. Rachel Downing – patient expert, nominated by Target Ovarian Cancer

9. **Evidence Review Group critique of company response to technical engagement** prepared by BMJ-TAG

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

Cancer Drugs Fund Review of TA528

Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (ID1644)

Company evidence submission for committee

5 May 2021

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Contents

Tables and figures

Cancer Drugs Fund review submission

Executive Summary

This review demonstrates the clinical and economic value of niraparib as a maintenance therapy for adult patients with relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy. Ovarian cancer (OC) is responsible for one woman's death every three hours in England.[1,2] Around 70% of cases are diagnosed at an advanced stage, therefore the prognosis is frequently poor. Survival outcomes in the UK are below the G5 and European average, demonstrating a significant unmet need and an urgency for more effective treatments.[3,4]

Niraparib has shown to significantly extend progression-free survival (PFS), which is an important milestone for patients with OC.[5] Currently, the only PARP inhibitor (PARPi) available to patients in England via routine commissioning is olaparib for third- or subsequent-line maintenance treatment in a subgroup of patients who possess a breast cancer susceptibility gene (*BRCA*) mutation (approximately 20% of the relevant total population).[6] Although PARPis are now available as first-line and second-line maintenance treatment, funding is only available via the Cancer Drugs Fund (CDF). Niraparib is now the first PARPi to exit the CDF and has the benefit of having a broad marketing authorisation that covers both *BRCA* mutation and non *BRCA* mutation patients.[7]

An increasing number of patients will receive a PARPi in the first-line setting; however, not all eligible patients will do so. As a result, there is a diminishing, yet real unmet need for patients in the second-line, relapsed setting in routine commissioning, particularly in the short to medium term. The use of PARPi after PARPi is not clinical practice in the UK; patients will only receive a PARPi once in their treatment of OC. The number of eligible patients and budget impact of second-line treatment will therefore diminish over time.

The base-case incremental cost-effectiveness ratio (ICER) of niraparib versus routine surveillance (RS), with a simple discount, is £25,875 for the pooled intention-to-treat (ITT) population.

In light of the clinical and economic benefit, niraparib is considered a cost-effective maintenance treatment option for patients in the relapsed OC setting, regardless of their *BRCA* mutation status, where there is a high unmet need for an effective treatment to improve health outcomes for people suffering from this devastating disease.

A.1 Background

Niraparib is recommended for use within the CDF as an option for treating relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy in adults, only if:

- they have a germline breast cancer susceptibility gene (*BRCA*) mutation and have had 2 courses of platinum-based chemotherapy (PBC)[*]
- or they do not have a germline *BRCA* mutation and have had 2 or more courses of PBC* and
- the conditions in the managed access agreement for niraparib are followed.

The ICERs presented to the committee originally included a simple discount Patient Access Scheme (PAS) of [redacted]% and are presented below. The final agreed CDF PAS of [redacted]% gives lower ICERs than presented below.[‡]

The committee's preferred ICER range for the use of niraparib in people with a germline *BRCA* mutation was £20,694 (company's base-case) to £54,632 (Evidence Review Group's [ERG's] base-case) per quality-adjusted life year (QALY) gained. In people without a germline BRCA mutation it was £23,795 (company's base-case) to £81,674 (ERG's base-case) per QALY gained. The committee was aware that the ERG's base case was a worst-case scenario.

[*] The terms of engagement document refers to patients with and without a germline *BRCA* mutation with associated courses of platinum-based chemotherapy. These are denoted as g*BRCA*mut 2L (2 courses of PBC) and non-g*BRCA*mut 2L+ (2 or more courses of PBC) in this review.

[‡] The terms of engagement document states that an "updated PAS" generated ICERs between £23,795 and £81,674; these ICERs are derived using the original [redacted]% PAS price. An updated [redacted]% PAS was accepted for the CDF. Please refer to Section A.10.1

The committee's key uncertainty was around the overall survival (OS) of people taking niraparib. Evidence from the key trial, ENGOT-OV16/NOVA (NOVA), suggested that niraparib improves PFS and extends the chemotherapy-free interval compared with placebo. However, the effect on OS was unclear because these data were immature. The committee concluded that there is no reason to suppose that the OS benefit will be less than the PFS benefit, but was uncertain whether the OS benefit would be equal to or exceed the PFS benefit. Additional trial data would help resolve this uncertainty.

The committee noted that the company's ICERs were within the range considered cost-effective for both germline-*BRCA* mutation positive and negative populations, even if the company incorporated more conservative assumptions for PFS and OS. The committee acknowledged the high uncertainty associated with the ICERs but concluded that there was plausible potential for niraparib to be cost-effective pending results on overall survival from NOVA.[8]

A.2 Key committee assumptions

The committee's preferred assumptions as per the terms of engagement are summarised in Table 1.[8]

Table 1. Key committee assumptions as per the terms of engagement

Area	Committee preferred assumptions
Population	The committee concluded that those with and without *BRCA* mutation*** after 2 courses of platinum-based chemotherapy could only be recommended within the CDF. This is the population that should be considered within the CDF review. The company presented data for non-*BRCA* mutation*** subgroup who had HRD-positive tumours. The committee concluded that HRD testing is not a reliable means of identifying patients and decided not to make a specific recommendation for this group.

*** The terms of engagement document refers to *BRCA* positive and *BRCA* negative (or with and without a *BRCA* mutation) subgroups. The cohorts within the NOVA trial, and included within this submission, have a germline *BRCA* mutation specifically (referred to henceforth as g*BRCA*mut 2L [2 courses of PBC]) or do not have a germline *BRCA* mutation (referred to as non-g*BRCA*mut 2L+ [2 or more courses of PBC]).

	The committee noted that niraparib could not be considered plausibly cost-effective compared with olaparib in people with *BRCA* mutation*** who have had 3 or more courses of chemotherapy.††† **Those with and without *BRCA* mutation* after 2 courses of platinum-based chemotherapy are the relevant population for the CDF review.**
HRD positive tumour subgroup	The committee heard that the results for the HRD-positive subgroup are unreliable because the 2 available tests for HRD do not reliably identify patients who would and would not benefit from therapy and was not routinely available within the NHS. The committee concluded that HRD testing is not reliable as a means of identifying patients who would and would not benefit from niraparib treatment, and therefore it decided against making a specific recommendation for this group. **The CDF review is not expected to consider evidence according to HRD subgroups.**
Progression-free survival	The company prioritised statistical fit in their choice of PFS curve. This resulted in a curve that showed people still alive, without progression at 20 years. The ERG thought this clinically implausible and chose curves based on a distribution that predicted no patients remained alive and progression-free by 10 years. Clinical experts stated that it is biologically plausible that patients on niraparib could survive longer than 10 years. The company thought that the ERG's analysis underestimated the number of people alive and progression-free at 5 years and had worse visual fit. The company presented alternative modelling assumptions using flexible spline models. The committee welcomed this more conservative analysis but noted that this did not decrease the general uncertainty around the validity of the extrapolations. **The company should fully investigate the most appropriate PFS modelling using updated clinical trial data.**
Overall survival	The company estimate OS by assuming a 1:2 ratio of mean PFS gain to mean OS gain. This was based on data from study 19 among people with a *BRCA* mutation. The ERG preferred to assume a ratio of 1:1 (that all people have the same post-progression risk of death).‡‡‡ Committee concluded that it is not possible to resolve the uncertainty about the OS benefit with niraparib until mature data from NOVA become available. **The company should fully investigate the most appropriate OS modelling using updated clinical trial data.**

††† The ICERs presented with respect to olaparib reflected the original [redacted]% PAS price, not the updated [redacted]% PAS price

‡‡‡ The terms of engagement document states that this assumes that all people have the same post-progression risk of death. This is incorrect, as no OS survival curve was modelled for niraparib in the original TA528[9] submission to allow the risk of post-progression survival to be determined. A ratio of 1:1 means that the mean PFS gain is equal to the mean OS gain.

Time to treatment discontinuation	TTD in the company's model was shorter than PFS. The ERG preferred to assume that these were equal because niraparib is only stopped on disease progression or due to unacceptable toxicity. The committee concluded that the company's estimation of time to treatment discontinuation was more reflective of real-life clinical practice. **The TTD, as measured in the NOVA trial, should be used to within the economic model.**
Most plausible ICER	For the *BRCA* negative group*** the estimated ICERs with the updated PAS§§§ ranged from £23,795 (company) to £81,674 (ERG) per QALY gained. Committee noted that the ERG's base-case was a worst-case scenario. For the *BRCA* positive*** group this range was £20,694 (company's base-case) to £54,632 (ERG's base-case) per QALY gained. Committee considered that the ERG's estimates were likely worst-case scenarios including more pessimistic assumptions for TTD, PFS and OS. The ICERs remained in the range considered cost-effective when the company incorporated more conservative assumptions for PFS and OS.
End of life	Niraparib does not meet the end-of-life criteria

Abbreviations: BRCA, breast cancer susceptibility gene; CDF, Cancer Drugs Fund; ERG, Evidence Review Group; HRD, homologous recombination deficiency; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, Time to treatment discontinuation.

A.3 Other agreed changes

As per the terms of engagement, the company should not alter the decision-problem, submit additional evidence or make further alterations to the model during the CDF review period unless NICE requests or agrees to this in advance.[8]

As discussed by the Company during the CDF review kick-off meeting with NICE on March 30th, a pooled ITT population is presented as part of this review, in addition to the two ITT populations presented as part of the original submission (g*BRCA*mut 2L and non-g*BRCA*mut 2L+). The pooled ITT population is formed by combining the two randomised patient cohorts of the NOVA trial: g*BRCA*mut 2L+ and non-g*BRCA*mut 2L+. The g*BRCA*mut 2L+ and non-g*BRCA*mut 2L+ populations were randomised as separate cohorts, but with identical inclusion/exclusion criteria (Document B, Section

§§§ The terms of engagement document states that an "updated PAS" generated ICERs between £23,795 and £81,674; these ICERs are derived using the original [redacted]% PAS price. An updated [redacted]% PAS was accepted for the CDF. Please refer to Section A.10.1

B.2.3.3 pp. 40 - 45 of the original submission). It is, therefore, statistically feasible to combine the g*BRCA*mut2L+ and non-g*BRCA*mut 2L+ cohorts to present as the pooled ITT population. The pooled ITT population is aligned with the marketing authorisation for niraparib and reflects the current use in UK clinical practice.[10] Furthermore, the presentation of a pooled ITT population allows OS outcomes of patients treated with niraparib to be compared to published, UK-based, real world evidence (RWE) OS outcomes of patients treated with routine surveillance.

During the CDF review kick-off meeting, the Company discussed with NICE the possibility of re-considering the end of life (EOL) criteria to be applied in this review. The data to support this consideration is presented in Section A.13.

A.4 The technology

Table 2. Technology being reviewed

UK approved name and brand name	Niraparib (Zejula®)
Mechanism of action	Niraparib is a potent and selective PARP-1 and -PARP-2 inhibitor, which selectively kills tumour cells by preventing repair of damaged DNA. PARP-1 and -2 are DNA-binding enzymes that play a crucial role in DNA repair. Inhibiting PARP enzymes can cause an accumulation of DNA damage, which requires repair by other processes.[11,12] DNA damage repair deficiencies are common in patients with platinum-sensitive OC, and therefore, these patients are more sensitive to the effects of PARP inhibition.[135] In pre-clinical studies, niraparib concentrates in the tumour, delivering selective, greater than 90% durable PARP inhibition, and a persistent anti-tumour effect.[14,15] 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.[14]
Marketing authorisation/CE mark status	Since 2017 niraparib has been licensed for use in the EU, in the relapsed setting, to which this review applies.[7] A Type II variation application was submitted to the European Medicines Agency in February 2020 to extend the licensed indication to include the use of niraparib as a first-line maintenance treatment in advanced OC. Expanded marketing authorisation was granted in October 2020.[10]
Indications and any restriction(s) as described in the summary of product characteristics	Niraparib is indicated as a monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy;[10] this is the indication under consideration by this CDF review.

	Niraparib is also indicated as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy; however, the first-line maintenance treatment; this indication is outside the scope of this review. Niraparib is contraindicated in patients who are: • Hypersensitive to the active substance or to any of the excipients • Breast-feeding
Method of administration and dosage	Niraparib is taken as an oral monotherapy. The recommended starting dose for niraparib as a maintenance treatment for relapsed ovarian cancer, as per the SmPC, is three 100 mg capsules taken orally once daily, equivalent to a total daily dose of 300 mg. For patients with a baseline weight less than 58kg, a starting dose of 200mg can be considered.[10] Dose modifications are recommended in the management of adverse events.[10] The more commonly used dose, as observed in the NOVA trial and supported by clinical practice, is 200 mg per day (2 x 100 mg capsules). This is also reflected in the recommended starting dose for the first-line maintenance indication.[10]
Additional tests or investigations	Complete blood counts are monitored weekly for the first month, and blood pressure is monitored weekly for the first two months; complete blood counts and blood pressure are then monitored monthly for the next 10 months of treatment and periodically after this time.[10]
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 SmPC recommended starting dose of 300 mg daily, a 28-day cycle costs £6,700 per patient. At the more commonly used dose of 200 mg daily, a 28-day cycle costs £4,500 per patient.
Commercial arrangement (if applicable)	A PAS with a simple discount of [redacted]% is currently in operation for the second-line indication and would be operational after the CDF review date. [redacted]
Date technology was recommended for use in the CDF	July 2018
Data collection end date	NOVA data collection cut-off date: October 2020 SACT ITT data collection cut-off date: June 2019[16] SACT g*BRCA*mut 2L and non-g*BRCA*mut 2L+ data collection cut-off date: February 2021[17]

Abbreviations: BER, base excision repair; DNA, deoxyribonucleic acid; FIGO, The International Federation of Gynecology and Obstetrics; OC, ovarian cancer; PARP, poly (ADP-ribose) polymerase; PAS, patient access scheme; PFS, progression-free survival; SACT, systemic anti-cancer therapy; SmPC, Summary of Product Characteristics.

A.5 Clinical effectiveness evidence

NOVA provided the evidence base for NICE appraisal TA528[9] and the final data cut-off (DCO) (October 2020) from this study is used to support this review (Table 3).

Table 3. Primary source of clinical effectiveness evidence

Study title	NOVA (ENGOT-OV16/NOVA); ClinicalTrials.gov number: NCT01847274[5,18–20]
Study design	NOVA is a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial to assess the efficacy, safety, and tolerability of maintenance therapy with niraparib versus placebo.
Population	Patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer who had previously received at least two platinum-based regimens and were in response (partial or complete) to their most recent PBC. The two primary cohorts of the NOVA trial are: • Patients with a deleterious g*BRCA*mut or genetic variant, or a suspected deleterious mutation (g*BRCA*mut cohort) (n=203) • Patients with high-grade serous or high-grade predominantly serous histology, but without the hereditary g*BRCA*mut (non-g*BRCA*mut cohort) (n=350)
Intervention(s)	Niraparib (with or without food): 300 mg QD orally (3 x 100 mg capsules); n=372
Comparator(s)	Placebo: 3 appearance-matched capsules QD orally; n=181
Outcomes collected that address committee's key uncertainties	• OS (used in economic model) • TTD (used in economic model)
Reference to section in appendix	Appendix, Section A.18, Table 15

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; OS, overall survival; QD, once daily; TTD, time to treatment discontinuation

Results from the final DCO (October 2020) were presented at the Society of Gynecologic Oncology (SGO) 2021 conference.[21]

Unfortunately, interpretation of the OS data is challenged by the high rate of subsequent PARPi use and missing data, thus limiting its interpretation. The NOVA DCO October 2020 OS limitations are outlined full in Appendix, Section A.16. For the purpose of this review, the economic model was updated with the final OS data available for patients treated with niraparib in the NOVA trial (DCO October 2020). Whilst the placebo data from the NOVA trial are presented below, the placebo arm of the study is not included in the economic model because analyses of placebo data, in particular, were confounded by a high rate of subsequent PARPi use and missing

data. Confounding of the placebo data in NOVA has been confirmed by OC clinical expert opinion, such that this was anticipated due to the subsequent PARPi use.[22] Cross-over to a PARPi impacts the placebo arm greater than the niraparib arm as the magnitude of benefit is greater when switching from placebo to a PARPi compared to use of a second PARPi, thus confounding the data of the placebo arm and limiting the interpretation of OS in patients randomised to the placebo arm of the NOVA trial. Consequently, alternative data sources have been utilised within the economic model to estimate the OS of patients treated with RS. Placebo data from Study 19 (Phase III, placebo-controlled, RCT) and routine surveillance data from UK RWE published by Lord et al. 2020 have been used to model OS as scenario analyses; the results are presented in Section A.12.[23,24] KM data and summary statistics are presented in Appendix, Sections A.20 and A.21 for Study 19 and Lord et al. 2020, respectively.

Use of RWE to inform the Committee's decision-making is aligned with the fourth pillar of NICE's newly launched five-year plan: Leadership in data, research, and science. By providing published UK RWE from Lord et al. 2020, in addition to Systemic Anti-Cancer Therapy (SACT) data, the Company hope to support NICE in their ambition to "use real-world data to resolve issues of uncertainty and improve access to new innovations for patients".[25] NICE has identified the "proportion of our guidelines and recommendations that are informed by real-world data" as a metric of achieving this goal. NICE has committed to "reducing barriers to using data that is generated in routine clinical practice in health care decision-making, including addressing challenges with real world data discoverability, quality, and accessibility", and joined the GetReal Institute in April 2021 as a founding member to drive the use of RWE for better healthcare decision-making.[25,26]

Evidence for niraparib as part of the SACT data collection is summarised in Table 4. TTD SACT data were used to inform a scenario analysis in the economic model, as requested by NHS England. The results of the SACT data support the OS benefit observed in patients treated with niraparib when compared to patients treated with RS, sourced from other UK RWE data for validation purposes.

Table 4. Secondary source of clinical effectiveness evidence

Study title	SACT data cohort study[16,17]
Study design	SACT data cohort study
Population	SACT ITT data collection comprised of patients with a deleterious g*BRCA*mut or genetic variant, or a suspected deleterious mutation (g*BRCA*mut cohort) or with high-grade serous or high-grade predominantly serous histology, but without the hereditary g*BRCA*mut (non-g*BRCA*mut cohort) (n=[redacted])[14] SACT data collection reported per population above (g*BRCA*mut 2L; n=[redacted] and non-g*BRCA*mut 2L+; n=[redacted])[17]
Intervention(s)	Niraparib (with or without food): 300 mg QD orally (3 x 100 mg capsules)
Comparator(s)	Not applicable
Outcomes collected that address committee's key uncertainties	• OS (not modelled) • TTD (used in economic model as a scenario analysis)
Reference to section in appendix	Appendix, Section A.17 and Section A.19

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; OS, overall survival; QD, once daily; SACT, systemic anti-cancer therapy; TTD, time to treatment discontinuation

A.6 Key results of the data collection

During the CDF data collection period data matured for the OS and TTD endpoints of NOVA. Data are available from the final DCO (October 2020), with a median follow-up of 66 months.[21] This new data cut provides an additional 49.1 months follow-up compared with the data provided in TA528.[9]

In addition to the NOVA trial, RWE data are available for the OS and TTD endpoints from SACT. OS and TTD data collected in SACT are outlined in Appendix Section A.19. Between 1 June 2018 and 31st May 2019, n=[redacted] were enrolled to receive treatment with niraparib, forming the pooled ITT cohort (consisting of g*BRCA*mut 2L and non-g*BRCA*mut 2L+ patients), through the SACT framework with data available until June 2019.[16] The final CDF report included data available until November 2019, with a subsequent OS data refresh provided until February 2021.[17,27]

Availability of baseline characteristics for patients enrolled in SACT was minimal; however, two key prognostic factors, age and Eastern Cooperative Oncology Group (ECOG) status, are less favourable compared to the characteristics of patients in the NOVA trial. Furthermore, the ECOG performance status score was missing or

unknown for approximately [redacted]% of patients included in the SACT cohort (g*BRCA*mut: [redacted]%; non-g*BRCA*mut: [redacted]%).[27] These differences are expected when comparing real-life cohorts to clinical trial cohorts; clinical advisors (n=7) in attendance at a recent advisory board (9th April 2021) agreed that patients in clinical trials are self-selected to do well as they are generally younger and better performing than those treated in practice.[28]

A summary of baseline characteristics of patients included in the SACT cohort is presented in Table 14, alongside the niraparib NOVA cohort. The Company was keen to further understand the differences between the NOVA and SACT populations. However, we understand a research study was not agreed to by NHS England and Improvement (NHSE&I) and SACT because the product is still in the CDF. It has therefore not been possible to analyse the differences between the respective populations in further detail and consequently the assessment of the two patient populations is limited.

Sections A.6.1 to A.6.3 present the key results from the final NOVA DCO (October 2020) (Appendix, Section A.18 Table 15) and SACT dataset (Appendix, A.19 Table 16), based on the information that is available.

A.6.1 *Progression-free survival*

ENGOT-OV16/NOVA

As part of this CDF review, the pooled ITT cohort is presented and is based on the NOVA DCO June 2016, when the primary PFS endpoint, based on the determination of progression made by the Independent Review Committee (IRC), was met. No additional analysis was conducted beyond June 2016. PFS KM data are presented in Appendix, Section A.18, Figure 10.

In the pooled ITT cohort, median PFS was [redacted] and [redacted] months for the placebo and niraparib treatment arms, respectively. Across placebo and niraparib arms [redacted]% and [redacted]% of patients had progressed or died, respectively. Treatment with maintenance niraparib significantly reduced the risk of progression or death compared to placebo with a hazard ratio (HR) of [redacted] (95% confidence interval [CI]: [redacted]).

PFS data were presented for the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohorts in the original submission (please refer to Document B of original Company submission, Section B.2.6.2, pp. page 56-60).

A.6.2 *Overall survival*

ENGOT-OV16/NOVA

At the time of the original submission, NOVA OS data were highly immature and hence did not inform the submission. Following maturity of the data during the CDF period, OS data are now available from NOVA (DCO October 2020). This mature data addresses one of the key uncertainties from the Committee in the original submission (Section A.2). As discussed in Section A.5 and Appendix, Section A.16 analysis of OS data is confounded by missing data and a high rate of subsequent PARPi use in the placebo arm in particular, thus limiting its interpretation and reliability.

In the pooled ITT cohort, median OS was [redacted] and [redacted] months for the placebo and niraparib treatment arms, respectively. Across placebo and niraparib arms, [redacted]% and [redacted]% of patients had died, respectively. Treatment with maintenance niraparib [redacted] with a HR of [redacted] (95% CI: [redacted]). KM data are presented in Appendix, Section A.18, Figure 11.

OS KM data and summary statistics for the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ are presented in Appendix, Section A.18.

Systemic Anti-Cancer Therapy dataset

OS data collected in the SACT dataset is available until June 2019 for the SACT ITT cohort.[16] For the SACT ITT cohort, n=[redacted] patients had a niraparib treatment record in SACT and the median follow-up time was [redacted] months. Median survival was not reached and over the follow-up period [redacted]% of patients had died. KM data are presented in Appendix, Section A.19 Figure 17.

OS KM data and summary statistics are presented for the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohorts in Appendix, Section A.19. The OS SACT data are not used to inform the economic model due to limited availability of baseline characteristics from SACT thus limiting a comparison with NOVA.

A.6.3 *Time to Treatment Discontinuation*

ENGOT-OV16/NOVA

Following the maturity of the data during the CDF period, mature TTD data are available from the NOVA trial (DCO October 2020). Mature TTD data provides more reliable evidence to inform niraparib treatment duration. Therefore, this updated data supports one of the Committee assumptions which states that niraparib TTD as measured from NOVA should be used within the economic model (Section A.2).

In the pooled ITT cohort, median TTD with niraparib was [redacted] months. At the time of data cut-off [redacted]% of patients had discontinued treatment. KM data are presented Appendix, Section A.18 Figure 14.

TTD KM data and summary statistics for the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohorts are presented in Appendix, Section A.18 .

Systemic Anti-Cancer Therapy dataset

TTD data collected in the SACT dataset is available until June 2019 for the SACT ITT cohort.[16]

For the SACT ITT cohort, median treatment duration was [redacted] months. Over the follow-up period [redacted]% of patients discontinued treatment with niraparib. A summary of treatment outcomes for patients that have ended treatment is presented in Appendix, Section A.19 Table 17. KM data are presented in Appendix, Section A.19 Figure 20.

Median TTD in SACT is lower than that observed in NOVA (DCO October 2020). SACT TTD data provides RWE to inform niraparib treatment duration. An NHS England request was for GSK to explore the SACT TTD in the modelling. Therefore, in order to fulfil this request, the data are presented in the model. To be conservative, the SACT data are used to inform a scenario analysis only in the economic model.

TTD KM data and summary statistics from the SACT dataset for the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohorts are presented in Appendix, Section A.19.

A.7 Evidence synthesis

No synthesised evidence is presented.

A.8 Incorporating collected data into the model

A.8.1 *Model structure*

A decision analytic model was developed in Microsoft Excel® to estimate the costs and QALYs of a cohort of patients eligible for niraparib. To ensure consistency, this is the same model structure as used in TA528 with updates performed to address key uncertainties from the Committee (Section A.2). Please refer to Section B.3.2.2, pp. 98-99 of the Company submission Document B for further details on the model structure.[9] The updates performed are described in the following sections. As in Section A.6 the pooled ITT cohort is presented in this section as the base-case and corresponding information for the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ populations can be found in Appendix, Section A.22.

A.8.2 *Progression-free survival*

Long-term PFS estimates for niraparib and routine surveillance were based on extrapolations of PFS patient-level data assessed by IRC from the NOVA DCO June 2016. At this cut off, the primary PFS endpoint was met and no additional analysis was conducted beyond June 2016. Survival analysis was conducted following NICE Decision Support Unit guidance. Updated parametric distributions to inform the base case were selected based on clinical plausibility and statistical and visual fit of the curves fitted to the PFS KM data for niraparib and routine surveillance, and with consideration of the updated NOVA 2020 OS data.

PFS - Pooled ITT

Long-term parametric extrapolations of PFS per IRC data for niraparib and routine surveillance were considered for the pooled ITT population. Aligned with the Company response to the ACD (see ACD response, *"ID1041 Niraparib ACD stakeholder comments form v3.0",* Comment 3, pp. 3-6)[29], and acknowledging that the Committee welcomed the conservative analysis of using a flexible survival distribution, as opposed to standard parametric survival analysis, a flexible distribution was adopted in order to fit curves to the pooled ITT PFS data (see Appendix, Section A.23).

The best fitting distribution for both treatment arms was chosen by considering clinical plausibility, statistical fit (Akaike information criterion [AIC]) and visual fit. Clinical plausibility was assessed based upon the proportion of patients progression-free at 5 and 10 years. All curves for niraparib and routine surveillance for the pooled ITT population are presented in Appendix, Section A.23 Figure 33 and Figure 34.

The normal k=1 curve reported the second lowest total sum of niraparib and routine surveillance AIC scores (Table 19). The proportion of niraparib patients progression-free at 5 and 10 years for the normal k=1 spline curve are [redacted] and [redacted]%, respectively. From the mature data estimates of Study 19, it is clear that the normal k=1 spline curve provides clinically plausible PFS estimates for niraparib in relation to the long-term evidence for olaparib from Study 19 for ITT patients; 13% on treatment and hence progression-free at 5 years.[30]

One-year estimates of the proportion of patients progression-free in the placebo arm of Study 19 for ITT patients and the normal k=1 curve are 12% and [redacted]%, respectively, making the normal k=1 spline curve clinically plausible for routine surveillance as well as niraparib. Therefore, the spline normal k=1 was modelled as the base case. Figure 1 demonstrates that this curve fits the KM for pooled ITT niraparib and routine surveillance well.

Using the normal k=1 spline distribution, only [redacted]% and [redacted]% of niraparib and routine surveillance patients, respectively, are estimated to be progression-free after 20 years. Applying a 20-year cap (patients could not be progression-free after 20 years) and ensuring PFS is less that OS for niraparib and routine surveillance, the mean PFS was calculated as the AUC using the trapezium rule as [redacted] and [redacted] years, respectively. After discounting was applied, the mean PFS equates to [redacted] years and [redacted] years, respectively.

Figure 1. Spline normal k = 1 curve and KM for niraparib and routine surveillance PFS for pooled ITT, NOVA DCO June 2016

Curves used to model PFS in the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohorts are presented in Appendix, Section A.22.1.

A.8.3 *Overall survival*

At the time of the original submission, NOVA OS data were highly immature and hence did not inform the submission. Following maturity of the data during the CDF period, OS data are available from NOVA (DCO October 2020). This mature data addresses one of the key uncertainties from the Committee in the original submission (Section A.2).

As described previously in Section A.5 (limitations are outlined full in Appendix, Section A.16), the interpretability of the placebo arm OS results from the October 2020 DCO is limited due to confounding by missing data and a high rate of subsequent PARPi use specifically in the placebo arm. Therefore, similar to the original submission, a simulation method was used in the economic assessment. However instead of simulating the active arm, like in the original submission, the base-case analysis uses the extrapolated mature niraparib OS data from DCO October 2020 to anchor the assumptions around the OS outcomes for the placebo arm. This review considers a 1:1 PFS:OS relationship, aligned with the ERG's assumption (Section A.2) and acceptance by the Committee (Section A.1).

Two alternative approaches are presented in the scenario analyses, whereby analyses were conducted in which long-term extrapolations from Lord et al. 2020 (ITT) and separately from Study 19 placebo arm (ITT, *BRCA*mut and *BRCA*wt) are instead used to model routine surveillance OS.[23,24]

Long-term OS estimates for niraparib in the base case and scenario analyses were based on parametric survival distributions fit to OS patient-level data from NOVA (DCO October 2020).

OS - Pooled ITT

The lognormal curve was considered the most plausible niraparib OS curve based on statistical fit of extrapolations of niraparib OS from NOVA (DCO October 2020) (see Appendix, Section A.24, Table 21). This was validated by an OC clinical expert such that ~[redacted]% of patients alive at ~8 years is deemed clinically plausible in the relapsed setting while on PARPi treatment.[22]

Using the lognormal distribution in the base case (Figure 2), the mean OS was calculated as the AUC using the trapezium rule. Mean OS for niraparib was calculated as [redacted] years. Based on a mean PFS benefit for niraparib of [redacted] years, mean OS for routine surveillance was calculated as [redacted] years ([redacted] – 1*[redacted]; assuming OS benefit for niraparib is equal to the mean PFS benefit). This estimated value for routine surveillance mean OS is clinically plausible, lying between mean OS values obtained from long-term extrapolations of Lord et al. 2020 and Study 19; 2.47 years and 3.29 years, respectively.[23,24] After discounting was applied, the mean OS equates to [redacted] years and [redacted] years for niraparib and routine surveillance, respectively.

Figure 2. Lognormal curve and KM for niraparib OS for pooled ITT, NOVA DCO October 2020

Scenario analysis – Study 19 as routine surveillance

In the scenario analysis in which long-term extrapolations of OS data from Study 19 were used to model routine surveillance OS, the lognormal curve was considered the most plausible curve based on statistical and visual fit (see Appendix, Section A.24, Table 22). Using the lognormal distribution (Figure 3) routine surveillance mean OS was calculated as the AUC using the trapezium rule as 3.29 years or 3.11 years after discounting was applied.

Figure 3. Lognormal curve and KM for niraparib OS from NOVA DCO October 2020 and placebo OS from Study 19 for pooled ITT

Scenario analysis – Lord et al. (2020) as routine surveillance

In the scenario in which long-term extrapolations of OS data from Lord et al. (2020) were used to model routine surveillance OS, the lognormal curve was considered the most plausible curve based on statistical and visual fit (see Appendix, Section A.24, Table 23). Using the lognormal distribution (Figure 4) routine surveillance mean OS was calculated as the AUC using the trapezium rule as 2.47 years or 2.36 years after discounting was applied.

Figure 4. Lognormal curve and KM for niraparib OS from NOVA DCO October 2020 and placebo OS from Lord et al. 2020 for pooled ITT

Curves used to model OS in the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohorts are presented in Appendix, Section A.22.2.

A.8.4 *Time on maintenance treatment*

Following data collection during the CDF period, long-term TTD estimations for niraparib and routine surveillance were based on parametric survival distributions fit to TTD patient-level data from NOVA (DCO October 2020). Mature TTD data provides more reliable evidence to inform niraparib treatment duration. Therefore, this updated data further supports and maintains one of the key Committee assumptions which states that niraparib TTD as measured from NOVA should be used within the economic model (Section A.2). Distributions were selected based on clinical plausibility, statistical fit and visual fit of the fitted curves to the niraparib KM data, since patients on routine surveillance incur no treatment costs.

TTD - Pooled ITT

The log-logistic and lognormal curves were considered the most plausible niraparib TTD curves based on statistical fit (see Appendix, Section A.25, Table 24), clinical plausibility and visual fit as they do not cross the selected PFS curve. The proportion of patients remaining on treatment after 1 year for the lognormal and log-logistic distributions based on NOVA DCO October 2020 is [redacted]% and [redacted]%, respectively.

As an alternative TTD (which is explored in sensitivity analysis [see Appendix, Section A.25.1]), the SACT TTD data provides RWE from England to inform niraparib treatment duration and was used to help decide which TTD extrapolation to select. SACT TTD data suggest that [redacted]% of patients remain on treatment after 1 year. The lognormal curve was selected as it aligns with the lognormal curve selected to model SACT TTD (see Appendix, Section A.25.1).

Using the lognormal distribution in the base case, only [redacted]% of patients are estimated to be on treatment after 20 years. Applying a 20-year cap (patients could not be on treatment after 20 years) and ensuring TTD is less that OS for niraparib (Figure 5), as per the original submission (see Company submission Document B, Section B.3.3.3, pp. 123-132), the mean time on maintenance treatment (TOMT) was calculated as the AUC using the trapezium rule. The pooled ITT mean TOMT for niraparib and routine surveillance were [redacted] years and [redacted] years, respectively. After discounting, these equate to [redacted] years and [redacted] years for niraparib and routine surveillance, respectively.

Figure 5. Lognormal TTD curve and KM for niraparib and routine surveillance for pooled ITT, NOVA DCO October 2020

Scenario analysis – SACT used for niraparib TTD

A scenario analysis was conducted in which long-term extrapolations of TTD data in the ITT cohort from SACT were used to model niraparib TTD. In this scenario the lognormal curve was considered the most plausible curve based on statistical and visual fit (see Appendix, Section A.25.1, Table 25). Using the lognormal distribution (Figure 35) niraparib mean TTD was calculated as the AUC using the trapezium rule as [redacted] years, and [redacted] years after discounting.

Curves used to model TTD in the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohorts are presented in Appendix, Section A.22.3.

A.8.5 *Health-related quality of life*

Health-related quality of life (HRQoL) data has been updated and is presented in the appendix (see Appendix, Section A.26).

A.8.6 *Niraparib dosing regimen*

Niraparib dosing data has been updated and is presented in the appendix (see Appendix, Section A.27).

A.9 Key model assumptions and inputs

Table 5 summarises all assumptions and input changes to the economic model since the original TA528 submission. Assumptions and inputs related to scenario analysis are summarised in Appendix, Section A.29.

Table 5. Key model assumptions and inputs

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption	Source/Justification
PFS source [See Company submission Document B, Section B.3.3.1., pp. 103-112]	Evidence from NOVA – DCO June 2016	No change	IRC PFS was the primary endpoint in the NOVA trial and this endpoint was met in DCO June 2016, therefore no additional data has been collected.
PFS extrapolations – Pooled ITT	N/A	Fully fitted flexible spline (normal k=1) curve	In acknowledgment of the Committee welcoming the conservative analysis using a flexible survival distribution as opposed to standard parametric survival analysis (Section A.2), the best fitting spline curve (normal k=1) was adopted for PFS for pooled ITT.
Niraparib OS source [See Company submission Document B, Section B.3.3.2., pp. 112-118]	Mean OS benefit twice the mean PFS benefit	Evidence for niraparib from NOVA DCO October 2020	Included the final niraparib OS data (DCO October 2020) from the NOVA trial. This updated data addresses one of the key uncertainties from the Committee in the original submission (Section A.2).
Routine surveillance OS source [See Company submission Document B, Section B.3.3.2., pp. 112-118]	Evidence from Study 19	Base case: Mean OS benefit equal to mean PFS benefit Scenario analysis (pooled ITT): Evidence from Lord et al. 2020 Scenario analysis (pooled ITT, g*BRCA*mut 2L and non-g*BRCA*mut 2L+): Evidence from Study 19	Due to confounded routine surveillance OS data from NOVA DCO October 2020, a relationship between PFS and OS is employed, but in reverse, such that routine surveillance OS is estimated based on niraparib OS extrapolation minus the PFS benefit of niraparib. This review considers a 1:1 PFS:OS relationship, aligned with the ERG's assumption (Section A.2) and acceptance by the committee (Section A.1). Scenario analyses using OS evidence from Study 19 and RWE from Lord et al. 2020 were explored to investigate sensitivity around modelling RS OS.
Niraparib OS extrapolations – Pooled ITT	N/A	Full fitted lognormal parametric curve	The best fitting parametric curve (lognormal) was selected based on statistical, clinical and visual plausibility.

TOMT source [See Company submission Document B, Section B.3.3.3., pp. 123-132]	Evidence from NOVA DCO June 2016	Base case: Evidence from NOVA DCO October 2020 Scenario analysis (pooled ITT): SACT dataset	Mature TTD data from NOVA provides more reliable evidence to inform niraparib treatment duration. This updated data further supports and maintains one of the key Committee assumptions which states that niraparib TTD as measured from NOVA should be used within the economic model (Section A.2).
TOMT extrapolations – Pooled ITT	N/A	Fully fitted lognormal parametric curve	The best fitting parametric curve was selected based on statistical, clinical, and visual plausibility.
Utility data source [] [See Company submission Document B, Section B.3.4.6, pp. 141-142]	Treatment-specific utility values from NOVA DCO June 2016	Treatment-specific utility values from NOVA DCO October 2020	Included the most up to date utility data from the NOVA trial to reflect HRQoL in clinical practice.
Niraparib dosing data source [See Company submission Document B, Section B.3.5.3.1, pp.144-145]	Evidence from NOVA DCO June 2016	Evidence from NOVA DCO October 2020	Included the most up to date niraparib dosing data from the NOVA trial to reflect dosing in clinical practice.
Niraparib dosing regimen [See Company submission Document B, Section B.3.5.3.1, pp.144-145]	Based on planned daily dosing data	Based on actual monthly dose consumed	Included the most up to date niraparib dosing data from the NOVA trial. Actual monthly consumed dose was included to provide more accurate dosing data for niraparib in clinical practice.
Niraparib price [See ACD response, "ID1041 Niraparib ACD stakeholder comments form v3.0", Comment 2, pp. 2-3]	[redacted]% simple discount	[redacted]% simple discount	In line with PAS currently in place.

Abbreviations: DCO, data cut off; gBRCAmut, germline breast cancer susceptibility gene mutation; HRQoL, health-related quality of life; ITT, intention to treat; OS, overall survival; PFS, progression-free survival; RWE, real world evidence; TOMT, time on maintenance treatment

A.10 Cost-effectiveness results (deterministic)

A.10.1 *Replication of the key cost-effectiveness result(s) considered by the committee to demonstrate plausible potential for cost-effectiveness at entry to the CDF*

The key cost-effectiveness results considered by the Committee to demonstrate plausible potential for cost-effectiveness at entry to the CDF have been replicated in Table 6. These results are based on the original simple discount PAS of [redacted]% and align with those presented in the terms of engagement as summarised in Table 1.[8] Following the final committee meeting, and prior to entry to the CDF, the PAS was revised to [redacted]%. The results incorporating the active PAS are also presented in Table 6.

Table 6. Cost-effectiveness results (deterministic): replication of the analysis that demonstrated plausible potential for cost effectiveness at CDF entry

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
[redacted]*% PAS*							
g*BRCA*mut 2L							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,694
Non-g*BRCA*mut 2L+							
Routine surveillance	[redacted]	2.868	[redacted]	-	-	-	-
Niraparib	[redacted]	5.132	[redacted]	[redacted]	2.265	[redacted]	23,795
[redacted]*% PAS*							
g*BRCA*mut 2L							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,153
Non-g*BRCA*mut 2L+							
Routine surveillance	[redacted]	2.868	[redacted]	-	-	-	-
Niraparib	[redacted]	5.132	[redacted]	[redacted]	2.265	[redacted]	17,585

A.10.2 *Cost-effectiveness incorporating the data collected during the CDF data collection period, with all model inputs and parameters unchanged from cost-effectiveness analysis in Section A.10.1*

Cost-effectiveness results that incorporate the mature NOVA data collected during the CDF (OS and TTD, NOVA DCO October 2020), with all other model inputs and parameters unchanged from the original cost-effectiveness analysis, are presented in Table 7. All analyses include a [redacted]% PAS discount off the list price of niraparib.

Details of the impact of each update made during this review are presented in Appendix, Section A.28. The use of long-term extrapolated NOVA niraparib OS data has resulted in an increase in the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ ICERs, due to a decrease in incremental QALYs and life years gained. The use of long-term extrapolated TTD data from the NOVA trial has resulted in a decrease to the ICER for g*BRCA*mut 2L, due to decreased costs for niraparib treatment resulting from decreased TOMT. Conversely, an increase in TOMT in non-g*BRCA*mut 2L+ causes an increase to the ICER. Updating the distribution used to obtain long-term extrapolations of PFS in non-g*BRCA*mut 2L+ results in an increase to the ICER due to the curve providing a more conservative estimate of niraparib PFS.

Various scenarios were explored in these analyses in addition to those presented in the original submission (see Section A.12):

- Using long-term OS extrapolations from Lord et al. 2020 for routine surveillance with long-term OS extrapolations from NOVA DCO October 2020 for niraparib (pooled ITT only)
- Using long-term OS extrapolations from Study 19 for routine surveillance with long-term OS extrapolations from NOVA DCO October 2020 for niraparib
- Using long-term TTD extrapolations from SACT
- Using long-term OS extrapolations from Lord et al. 2020 for routine surveillance with long-term OS extrapolations from NOVA DCO October 2020 for niraparib and using long-term TTD extrapolations from SACT
- Using long-term OS extrapolations from Study 19 for routine surveillance with long-term OS extrapolations from NOVA DCO October 2020 for niraparib and using long-term TTD extrapolations from SACT

Table 7. Cost-effectiveness results (deterministic): analysis demonstrating plausible potential for cost effectiveness at CDF entry – incorporating updated clinical evidence – [redacted]% PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Pooled ITT*							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,388
g*BRCA*mut 2L							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,086
non-g*BRCA*mut 2L+							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	40,069

*Due to unavailability of NOVA 2016 dosing data for pooled ITT, NOVA 2020 data is used in these analyses.

A.10.3 *Cost-effectiveness results incorporating data collected during the CDF data collection period plus any associated changes to the company's preferred assumptions*

In addition to the updated clinical evidence, the dosing data for niraparib and utility data have been updated with data from NOVA DCO October 2020.

The cost-effectiveness results that incorporate data collected during the CDF data collection period (OS and TTD) plus the aforementioned additional changes to dosing and utilities are presented in Table 8. The updated dosing regimen for niraparib results in lower costs associated with niraparib treatment and slightly lower ICERs in all populations. The updated treatment-specific utility values increase the incremental QALYs, resulting in reduced ICERs in all populations. Updating the dosing and utility values reduces the ICER to £25,875, £19,599 and £36,449 per QALY in the pooled ITT, g*BRCA*mut 2L and non-g*BRCA*mut 2L+ populations, respectively.

Table 8. Cost-effectiveness results (deterministic): new company base case – [redacted]% PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Pooled ITT							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,875
g*BRCA*mut 2L							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,599
non-g*BRCA*mut 2L+							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,449

A.11 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed for 1,000 iterations to explore the uncertainty around key model inputs. In each iteration, model inputs were randomly varied from specified distributions, as summarised in Section A.31.

Mean incremental results were recorded and are displayed in Table 9. Results are illustrated through an incremental cost-effectiveness plane (ICEP) which is presented in Figure 6, Figure 7 and Figure 8 for the ITT, g*BRCA*mut 2L and non-g*BRCA*mut 2L+ populations. Assuming a willingness-to-pay threshold of £30,000 per QALY gained, the probability of niraparib being the most cost-effective treatment option was 69%, 90% and 24%, in the ITT, g*BRCA*mut 2L and non-g*BRCA*mut 2L+ populations, respectively.

Table 9. Updated base-case results (probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Pooled ITT							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,069
g*BRCA*mut 2L							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,137
non-g*BRCA*mut 2L+							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	41,591

Figure 6. Scatterplot of probabilistic results for pooled ITT

Figure 7. Scatterplot of probabilistic results for gBRCAmut 2L

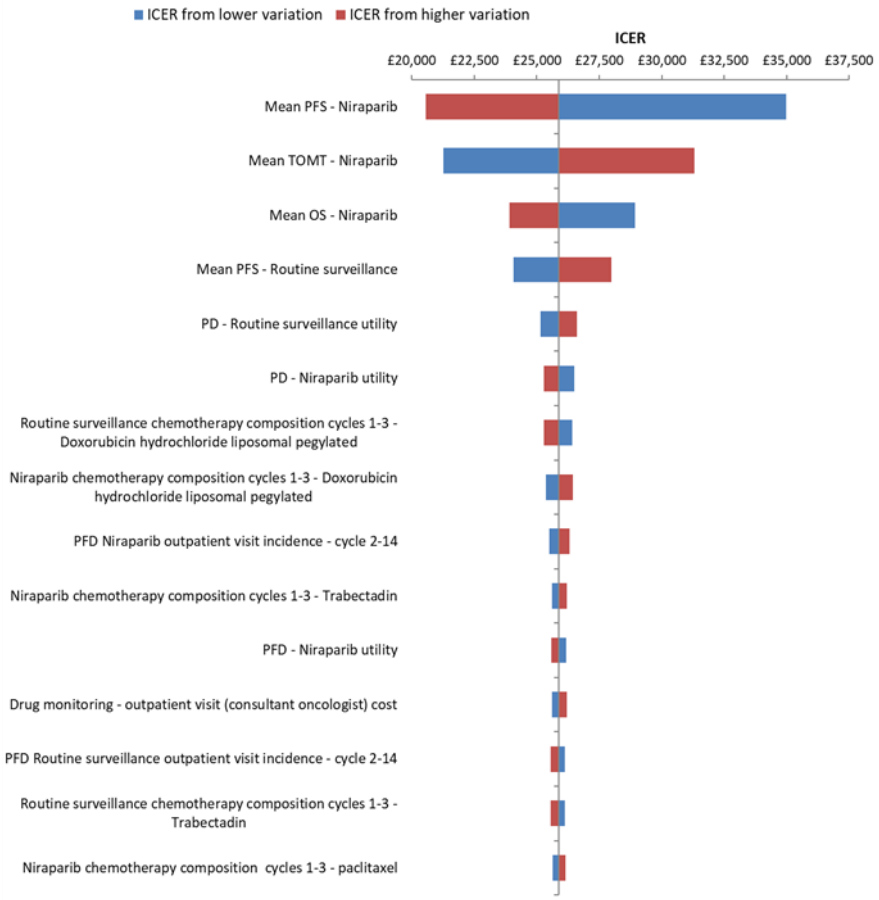
Figure 8. Scatterplot of probabilistic results for non-gBRCAmut 2L+

A.12 Key sensitivity and scenario analyses

Pooled ITT

A tornado diagram is presented in Figure 9, with the top 15 most sensitive parameters presented. Results were most sensitive to mean PFS and TOMT for niraparib. Results were also sensitive to mean OS for niraparib and mean PFS for RS. In all instances the ICER was less than £35,000 per QALY.

Figure 9. Tornado diagram of niraparib versus routine surveillance for pooled ITT



Various scenario analyses were conducted to assess alternate model settings and structural uncertainty of the base case analysis. Key scenarios are presented in Table 10.

Table 10. Key scenario analyses – Pooled ITT

	Scenario and cross reference	Scenario detail	Brief rationale	ICER
Base case				25,875
1	Extrapolated trial data from Lord et al. 2020 for RS OS *Section A.8.3*	Extrapolated trial data from Lord et al. 2020 was modelled to inform the OS estimates for RS in the ITT population. OS KM was extrapolated using the lognormal distribution	The ICER decreases as the RS OS from Lord et al. 2020 is shorter than modelled using the PFS:OS relationship	23,147
2	Extrapolated trial data from Study 19 for RS OS *Section A.8.3*	Extrapolated trial data from Study 19 modelled to inform the OS estimates for RS in the ITT population. OS KM was extrapolated using the lognormal distribution	The ICER increases as the RS OS from Study 19 is longer than modelled using the PFS:OS relationship	35,579
3	Niraparib TTD data sourced from SACT *Appendix, Section A.25.1*	TTD SACT data was used to inform the niraparib mean TOMT. TTD KM was extrapolated using the lognormal distribution	The ICER decreases as patients included in the SACT dataset remained on treatment for less time when compared to the NOVA dataset.	15,893
4	Extrapolated trial data from Lord et al. 2020 for RS OS (*Section A.8.3)* and niraparib TTD data from SACT (*Appendix, Section A.25.1)*	See scenarios 1 and 3 for details	The ICER decreases as the RS OS from Lord et al. 2020 is shorter than modelled using the PFS:OS relationship and as patients in the SACT dataset remained on treatment for less time when compared to the NOVA dataset	14,238
5	Extrapolated trial data from Study 19 for RS OS (*Section A.8.3)* and niraparib TTD data from SACT (*Appendix, Section A.25.1)*	See scenarios 2 and 3 for details	Although RS OS from Study 19 is longer than modelled using the PFS:OS relationship, the ICER decreases as patients in the SACT dataset remained on treatment for less time when compared to the NOVA dataset.	21,782

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention to treat; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; RS, routine surveillance; SACT, systematic anti-cancer therapy; TOMT, time on maintenance therapy; TTD, time to treatment discontinuation

g*BRCA*mut 2L

A tornado diagram is presented in Appendix, Section A.30, Figure 38, with the top 15 most sensitive parameters presented. Results were most sensitive to mean PFS and TOMT for niraparib. Results were also sensitive to the mean PFS for RS. In all instances the ICER was less than £49,000 per QALY.

Various scenario analyses were conducted to assess alternate model settings and structural uncertainty of the base case analysis. Key scenarios are presented in Table 11.

Table 11. Key scenario analyses – gBRCAmut 2L

	Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER (£)
Base case				19,599
1	Extrapolated trial data from Study 19 for RS OS *Appendix, Section A.22*	Extrapolated trial data from Study 19 modelled to inform the OS estimates for RS in the gBRCAmut 2L population. OS KM was extrapolated using the lognormal distribution.	The ICER increases as the RS OS from Study 19 is longer than modelled using the PFS:OS relationship.	22,347
2	Niraparib TTD data sourced from SACT *Appendix, Section A.25.1*	TTD SACT data was used to inform the niraparib mean TOMT. TTD KM was extrapolated using the lognormal distribution	The ICER decreases as patients included in the SACT dataset remained on treatment for less time when compared to the NOVA dataset.	8,720
3	Extrapolated trial data from Study 19 for RS OS (*Appendix, Section A.22)* and niraparib TTD data from SACT (*Section A.8.4)*	See scenarios 1 and 2 for details	Although RS OS from Study 19 is longer than modelled using the PFS:OS relationship, the ICER decreases as patients included in the SACT dataset remained on treatment for less time when compared to the NOVA dataset.	9,904

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; RS, routine surveillance; TOMT, time on maintenance treatment; TTD, time to treatment discontinuation

Non-gBRCAmut 2L+

A tornado diagram is presented in Appendix, Section A.30, Figure 39, with the top 15 most sensitive parameters presented. Results were most sensitive to mean PFS for niraparib and RS. Results were also sensitive to the mean OS for niraparib. In all instances the ICER was less than £52,500 per QALY.

Various scenario analyses were conducted to assess alternate model settings and structural uncertainty of the base case analysis. Key scenarios are presented in Table 12.

Table 12. Key scenario analyses – non-gBRCAmut 2L+

Scenario and cross reference		Scenario detail	Brief rationale	Impact on base-case ICER (£)
Base case				36,449
1	Extrapolated trial data from Study 19 for RS OS *Section A.22*	Extrapolated trial data from Study 19 modelled to inform the OS estimates for RS in the non-gBRCAmut 2L+ population. OS KM was extrapolated using the lognormal distribution	The ICER increases as the RS OS from Study 19 is longer than modelled using the PFS:OS relationship.	39,608
2	Niraparib TTD data sourced from SACT *Appendix, Section A.25.1*	TTD SACT data was used to inform the niraparib mean TOMT. TTD KM was extrapolated using the lognormal distribution	The ICER decreases as patients included in the SACT dataset remained on treatment for less time when compared to the NOVA dataset.	25,699
3	Extrapolated trial data from Study 19 for RS OS (*Appendix, Section A.22)* and niraparib TTD data from SACT (*Section A.8.4)*	See scenarios 1 and 2 for details	Although RS OS from Study 19 is longer than modelled using the PFS:OS relationship, the ICER decreases as patients included in the SACT dataset remained on treatment for less time when compared to the NOVA dataset.	27,923

Abbreviations: non-gBRCAmut, non-germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; RS, routine surveillance; TOMT, time on maintenance treatment; TTD, time to treatment discontinuation

A.13 End-of-life criteria

During the CDF review engagement meeting, the Company discussed with NICE the possibility of reintroducing consideration for the EOL criteria to be applied in this review (Table 13):

- The non-g*BRCA*mut 2L+ population meets the EOL criteria; for which SACT and published RWE Lord et al. 2020 support this.
- Conversely the g*BRCA*mut 2L population does not meet the EOL criteria.

Approximately 80% of patients with advanced OC do not have a g*BRCA* mutation, and as such the non-g*BRCA*mut 2L+ population forms the majority of patients with relapsed OC treated in clinical practice[6]; this highlights the significant unmet need in this group of patients.

Table 13. End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Yes, SACT non-g*BRCA*mut 2L+ niraparib arm median OS was [redacted] (95% CI [redacted]) months.[17] In addition, Lord et al. 2020 ITT RS arm median OS was 19.3 (95% CI ± 2.4) months.[24]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Yes, mean OS estimated from the model for the non-g*BRCA*mut 2L+ population when using the PFS:OS 1:1 relationship is [redacted] and [redacted] years for niraparib and RS, respectively. Therefore the difference in terms of life extension is 0.97 years. When considering the scenario analysis of modelling RS based on Study 19 the mean OS estimated for RS is 2.83; the difference in terms of life extension in this scenario is [redacted] years. Both indicate that there is an additional 3-month OS gain.

Abbreviations: non-gBRCAmut, non-germline breast cancer susceptibility gene mutation; OS, overall survival; RS, routine surveillance

A.14 Key issues and conclusions based on the data collected during the CDF review period

In the base case analysis, niraparib was associated with [redacted] incremental QALYs, and £[redacted] incremental costs per patient, compared with RS in the pooled ITT population. The corresponding ICER is £25,875 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. The economic evaluation confirms a robust and favourable cost-effectiveness profile. Niraparib can therefore be considered a cost-effective treatment option for patients with relapsed OC.

There are currently no routinely commissioned oral maintenance treatment options available to patients in the second-line setting and only a subgroup of patients are able to access treatment in third- or subsequent-lines. Niraparib is an effective and well-tolerated maintenance treatment to meet the needs of eligible patients and has the benefit of having a broad marketing authorisation, covering both g*BRCA* mutation and non-g*BRCA* mutations. Moreover, non-g*BRCA*mut patients are particularly affected by both the absence of routinely commissioned treatments as well as reduced life expectancy; this cohort of patients meet the EOL criteria set out by NICE.

Analysis of OS data from the NOVA trial is confounded by missing data and a high rate of subsequent PARPi use in the placebo arm in particular, thus limiting its interpretability. Therefore mature placebo data from Study 19 and routine surveillance data from UK RWE published by Lord et al. 2020 have been used as scenario analyses. RWE OS outcomes are considered generalisable to UK clinical practice, as assessed by clinical experts. The use of alternative OS data supports the base-case OS assumptions in the economic model.

This review demonstrates the clinical and economic value of niraparib as a maintenance therapy for patients with relapsed OC, regardless of a patient's *BRCA* status, by extending PFS and OS, whilst preserving patients' quality of life. Niraparib can serve to meet the high unmet need for an effective treatment and improve health outcomes for people suffering from this devastating disease.

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Cancer Drugs Fund review

Cancer Drugs Fund review of technology appraisal 528 of niraparib as maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1644]

Response to clarification questions

May 2021

File name	Version	Contains confidential information	Date
[ID1644]_clarification_letter_response_redacted	v.1	Yes	26/05/21

Section A: Clarification on effectiveness data

A1. Priority question. Please provide the clinical study report (CSR) or equivalent document for the final data cut-off (October 2020) for the NOVA trial.

Response:

The CSR for the final data cut-off (October 2020) for the NOVA trial is currently in development. Unfortunately, the CSR is not finalised and will not be available until Q4 2021. The complete CSR for the September 2016 data cut for the NOVA trial has been provided.

A presentation took place at the Society of Gynaecologic Oncology (SGO) Annual Meeting on Women's Cancer March 19–25, 2021 titled "Long-term safety and secondary efficacy endpoints in the ENGOT-OV16/NOVA phase 3 trial of niraparib in recurrent ovarian cancer", Matulonis et al.[1] The presentation included the key long-term efficacy and safety outcomes data from the final data cut-off (October 2020) for the NOVA trial which have been included within this CDF review. The data used to inform this presentation has been included in the dossier and incorporated into the cost-effectiveness model. A PDF of the complete presentation is provided with this response.

A2. Priority question. Please provide available data on the number of patients who received PARPi therapy as subsequent therapies in:

- the niraparib and placebo arms for the gBRCAmut 2L subgroup and non-gBRCAmut 2L+ cohort from the NOVA trial;
- the placebo arm of the BRCAmut and BRCAwt subgroups from Study 19.

Response:

Crossover to PARPi therapy was not permitted in NOVA. However, patients could receive subsequent PARPi after disease progression on withdrawal from the study, per their oncologist's clinical judgement.[2]

Table 1 outlines the number of patients who were treated with subsequent PARPi therapy in the NOVA trial. Due to study discontinuation, post-progression therapy

information was not available for 25% (138/553) of the NOVA pooled intention to treat (ITT) population. Table 1 outlines that number of patients who received subsequent PARPi in row one, however this is likely an underestimate of true subsequent PARPi therapy usage considering the number of patients for whom subsequent PARPi therapy information was unavailable.

Table 1. Proportion of patients in the NOVA trial in the gBRCAmut 2L and non-gBRCAmut 2L+ cohorts who received subsequent PARPi therapy[3]

	gBRCAmut 2L (n = 100)		**Non-gBRCAmut 2L+ (n = 350)**	
	Niraparib n = 70 (%)	**Placebo n = 30 (%)**	**Niraparib n = 234 (%)**	**Placebo n = 116 (%)**
Number of patients who received subsequent PARPi n (%)	[redacted]	[redacted]	15 (6.4)	15 (12.9)
Missing information n (%)	[redacted]	[redacted]	51 (21.8)	31 (26.7)
Number of patients who received subsequent PARPi n (% of patients for whom subsequent PARPi therapy information was available)	[redacted]	[redacted]	15 (8.2)	15 (17.6)

Abbreviation: 2L, second-line; g*BRCA*mut, germline breast cancer susceptibility gene mutation; PARPi, poly (ADP-ribose) polymerase inhibitor

Footnote: Row three of Table 1 outlines the percentage of patients who received subsequent PARPi therapy using the number of patients for whom subsequent PARPi therapy information was available as the denominator i.e. for niraparib g*BRCA*mut 2L 18 patients received subsequent PARPi therapy and subsequent PARPi therapy information was available for 53 patients, therefore 18/53 = 34%

Similarly, crossover to PARPi therapy in the Study 19 trial was not permitted.[4] Table 2 outlines the number of patients who were treated with subsequent PARPi therapy in Study 19.

Table 2. Number of patients who received PARPi as subsequent treatment in Study 19 trial[4]

	BRCAmut (n = 136)		**BRCAwt (n = 118)**	
	Olaparib n = 74 (%)	**Placebo n = 62 (%)**	**Olaparib n = 57 (%)**	**Placebo n = 61 (%)**
Number of patients who received subsequent PARPi n (%)	0	14 (22.6)	0	3 (4.9)

Abbreviations: *BRCA*wt, wild type breast cancer susceptibility gene; *BRCA*mut, breast cancer susceptibility gene mutation; PARPi, poly (ADP-ribose) polymerase inhibitor

In the NOVA trial, a larger proportion of patients in the placebo arm of both the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohort crossed over to subsequent treatment with a PARPi compared to both cohorts randomised to placebo in the Study 19 trial.

The large proportion of patients switching to subsequent PARPi resulted in the confounding of the overall survival (OS) data and challenges the interpretability of the OS data from NOVA (data cut-off [DCO] October 2020), particularly within patients randomised to placebo.

A3. Priority question. There are several discrepancies in the data presented for the gBRCAmut 2L subgroup between Table 15, Figure 12, Figure 15 and the data presented in the text of the appendix to the company's evidence submission. According to Figure 12 and Figure 15, there were 70 and 30 patients treated with niraparib and placebo, respectively, in the gBRCAmut 2L subgroup. However, according to the original appraisal of niraparib, this subgroup included 79 patients treated with niraparib and 37 patients treated with placebo. In addition, the proportion of patients who had died and the median time to treatment discontinuation (TTD) on niraparib in the gBRCAmut 2L subgroup differs between Table 15 and what is reported in the text. Please clarify these discrepancies and highlight which are the correct data. Please also provide the number of patients in each treatment arm in each population in Table 15.

Response:

The NOVA patient baseline characteristics are presented in Table 10 of the original submission (Document B, Table 10, pp. 48-49).[5] Patients are classified by the number of lines of previous chemotherapy, and the number of lines of previous platinum-based chemotherapy (PBC). In order to capture those patients who are truly second-line, having completed two previous lines of PBC as first and second-line, only those patients who had two lines of chemotherapy in total were included in the g*BRCA*mut 2L cohort.

With respect to the 79 g*BRCA*mut 2L+ patients treated with niraparib, there are 9 patients who have had two previous lines of PBC but three previous lines of chemotherapy in total i.e. also 1 line of non-platinum-based chemotherapy; these

patients have been excluded from the g*BRCA*mut 2L cohort as they are considered to be third-line, so the total number of true g*BRCA*mut 2L niraparib patients is 70.

Similarly, with the 37 patients in the g*BRCA*mut 2L+ placebo cohort, 7 patients had two previous lines of PBC but three previous lines of chemotherapy in total i.e. also 1 line of non-platinum-based chemotherapy; these patients were also excluded from the g*BRCA*mut 2L cohort as they are considered to be third-line, so the total number of true g*BRCA*mut 2L placebo patients is 30.

Within the original submission, the baseline characteristics for the g*BRCA*mut 2L+ subgroup were outlined for the 79 patients treated with niraparib and 37 patients treated with placebo. The number of patients in each treatment arm included in the g*BRCA*mut 2L cohort analysis, ensuring that all patients received only two previous lines of PBC, are presented in Table 3. These patient numbers (n=70 and n=30 for niraparib and placebo cohorts, respectively) match those used in the analyses presented in the original submission (Appendix L, Figure 62, pp. 2)[5] and presented in this review submission.

Table 3. Number of patients in each treatment arm in the gBRCAmut 2L cohort

	gBRCAmut 2L (n = 100)	
	Niraparib	**Placebo**
Number of patients who received only two previous line of previous PBC	70	30

Abbreviations: PBC, platinum-based chemotherapy

In relation to the latter part of the clarification question, Table 15 from the company CDF review submission has been revised to present the correct outcome data for the g*BRCA*mut 2L cohort. The numbers of patients in each treatment arm have also been added as requested, and are presented in **Error! Not a valid bookmark self-reference.**.

Table 4. Key efficacy outcomes from NOVA - DCO October 2020 (Correction of Table 15 in CDF submission)

Endpoint	**Placebo**	**Niraparib**
Overall survival – pooled ITT cohort[a] (n = 553)		
Number of patients	181	372

Endpoint	Placebo	Niraparib
Events (%)	[redacted]	[redacted]
Median (95% CI) (months)	[redacted]	[redacted]
HR (95% CI), *p-value*	[redacted]	
Overall survival – gBRCAmut 2L cohort[a] (n = 100)		
Number of patients	30	70
Events (%)	[redacted]	[redacted]
Median (95% CI) (months)	[redacted]	[redacted]
HR (95% CI), *p-value*	[redacted]	
Overall survival – non-gBRCAmut 2L+ cohort[a,b] (n = 350)		
Number of patients	116	234
Events (%)	[redacted]	[redacted]
Median (95% CI) (months)	36.47 [redacted]	31.11 [redacted]
HR (95% CI), *p-value*	1.10 (0.83 – 1.46), *p* =NR	
Time to treatment discontinuation – pooled ITT cohort[a] (n = 553)		
Number of patients	181	372
Events (%)	[redacted]	[redacted]
Median (95% CI) (months)	[redacted]	[redacted]
HR (95% CI), *p-value*	[redacted]	
Time to treatment discontinuation – gBRCAmut 2L cohort[a] (n = 100)		
Number of patients	30	70
Events (%)	[redacted]	[redacted]
Median (95% CI) (months)	[redacted]	[redacted]
HR (95% CI), *p-value*	[redacted]	
Time to treatment discontinuation – non-gBRCAmut 2L+ cohort[a] (n = 350)		
Number of patients	116	234
Events (%)	[redacted]	[redacted]
Median (95% CI) (months)	[redacted]	[redacted]
HR (95% CI), *p-value*	[redacted]	

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; HR, hazard ratio; NE, non-evaluable; NR, not reported; OS, overall survival; TTD, time to treatment discontinuation. a. NOVA PLD analysis[3] analysis, simple cox model. b. Matulonis 2021[1]

Section B: Clarification on cost-effectiveness data

IMPORTANT: For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model. Furthermore, if the company chooses to update its base case results, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response along with a log of changes made to the company base case.

Response:

The base case results have been revised by capping TTD by PFS, as per the ERG's suggestion in Question B7. This update reduces the ICER to £23,676, £19,475 and £28,942 per QALY gained, for the pooled ITT, g*BRCA*mut 2L and non-g*BRCA*mut 2L+ populations, respectively. Full cost-effectiveness results, sensitivity and scenario analyses incorporating this revised base case assumption are provided in Appendix A. All other results in this document are presented in a stepwise fashion, applied to the company base case submitted in the CDF review submission, in response to the question posed. This is to ensure full transparency of each individual change on the results.

Model Structure

B1. In the Final Appraisal Document (FAD) for TA528, it is stated that, "*the committee heard that the company had explored other model structures, including a partitioned survival model, and found that the cost-effectiveness results differed by no more than £1,000 per QALY gained, as long as the same assumptions for survival were used*". The ERG believe a partitioned survival model, where costs and utilities are applied to the proportions occupying a health state per model cycle and discounted per model cycle is a more robust approach. Please supply the partitioned survival model referred to in the FAD and include the data and assumptions used in the means-based model for the company's CDF base case to allow a comparison of the results. Please ensure that the partitioned survival model is able to replicate the

base case results referred to in the FAD, where a difference of no more than £1,000 per QALY gained is observed.

Response:

The model to be used as the basis for this CDF review was outlined in the Terms of Engagement document.[6] This document highlighted that the economic model named *"ID1041 Niraparib CEM_Response to ACD v0.2 16.03.18 [ACIC]"* should be used. The model submitted for this CDF review *"[ID1644]_Cost_effectiveness_model_[ACIC]"* is the updated version of the decision analytic model specified in the Terms of Engagement document.[6]

As part of the original submission, the Committee discussed the choice of model structure and assessed the ERG's proposal that a partitioned survival model (PSM) should be used in place of a decision analytic model. The Company provided extensive rationale to support the use of a decision analytic model, outlined in Section B.3.2.2 of the original submission (Document B, Table 10, pp. 98-99) and in response to ERG Question B1 of the original submission (see Committee Papers, Company ERG questions response, B1, pp. 316-323).[5] The company referred the ERG to a previous oncology submission in which a decision analytic model was adopted by the School of Health and Related Research at the University of Sheffield (ScHARR) during the NICE Multiple Technology Appraisal (MTA) for ovarian cancer treatments (TA91).[7] The choice of model structure was based on this existing accepted model.

Further, in the FAD for TA528 it is stated that the Committee concluded that *"the choice of model structure is not critical to the decision making"* and that *"the committee accepted that the model was adequate for decision-making and that the choice of model structure was not critical."* Therefore the cost-effectiveness model structure was not included as an uncertainty which needed to be addressed in the FAD for TA528 or in the Terms of Engagement for this CDF review.[6,8] As such, the existing model structure has been used as part of this review.

Nonetheless, in order to explain the difference between the two structures and the impact this could have on the results, a narrative has been provided below.

As per the response to the ERG questions in the original submission, the PSM and decision analytic methods differ only in terms of how discounting is performed. The partitioned survival analysis approach implements discounting within each cycle,

whilst the submitted model approach discounts continuously using the exponential distribution. Theoretically, one could develop exactly the same survival curves, implement them into a PSM structure or the submitted decision analytic model structure with the same time horizon, and the only difference in results would be due to how discounting is applied. This difference is negligible and the Company provided an example in Excel (Appendix 3 – Exponential Discounting, attached with this response for reference) to show that discounting costs and QALYs continuously by the exponential method with an instantaneous discount rate of 3.44% gives no noticeable differences compared to cyclic discounting at 3.5% per annum.

The Company did not provide a separate partitioned survival model in the original appraisal. It was demonstrated that a difference of no more than £1,000 per QALY gained would be observed in the results between the submitted decision analytic model structure and a PSM via sensitivity analysis. For the sensitivity analysis, instead of applying the trapezium rule (used in the submitted decision analytic model), the proportion of patients in each cycle was summed to give the mean time in state (proposed by the ERG to be used in the partitioned survival model).

The trapezium rule could be applied in both a decision analytic model structure and PSM, such that the only difference between the ERG's suggested methodology and this sensitivity analysis would be due to discounting, where the impact is negligible (<1%), see Appendix 3 – Exponential Discounting (attached with this response for reference).

SACT data

B2. Priority question: TTD data for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups from SACT are available. Please provide a scenario analysis where SACT TTD data is used for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroup analyses.

Response:

TTD summary statistics for the Systemic Anti-Cancer Therapy (SACT) dataset for the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohorts were presented in the Appendix, Section A.19, of the company CDF review submission. TTD KM data is presented in

Figure 1 and

Figure 2 for the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohorts from SACT, respectively.

Figure 1. TTD KM for niraparib SACT gBRCAmut 2L cohort

Time intervals (months)	0 - 21	3 - 21	6 - 21	9 - 21	12 - 21	15 - 21	18 - 21	21
Number at risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; KM, Kaplan-Meier; SACT, Systemic Anti-Cancer Therapy dataset; TTD, time to treatment discontinuation

Source: Niraparib for treating ovarian cancer – data review[9]

Figure 2. TTD KM for niraparib SACT non-gBRCAmut 2L+ cohort

Time intervals (months)	0 - 21	3 - 21	6 - 21	9 - 21	12 - 21	15 - 21	18 - 21	21
Number at risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; KM, Kaplan-Meier; SACT, Systemic Anti-Cancer Therapy dataset; TTD, time to treatment discontinuation

Source: Niraparib for treating ovarian cancer – data review[9]

Using these data, as requested, scenario analyses have been conducted in which long-term extrapolations of TTD from SACT were used to model niraparib TTD for the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohorts, respectively.

For the g*BRCA*mut 2L cohort, the lognormal curve was considered the most plausible curve based on statistical and visual fit (Table 5). Using the lognormal distribution (Figure 3) niraparib mean TTD was calculated as the area under the curve (AUC) using the trapezium rule as [redacted] years and [redacted] years after discounting.

For the non-g*BRCA*mut 2L+ cohort, the lognormal curve was considered the most plausible curve based on statistical and visual fit (Table 5). Using the lognormal distribution (Figure 4) niraparib mean TTD was calculated as the AUC using the trapezium rule as [redacted] years and [redacted] years after discounting.

On this basis, please find scenario analyses results in Table 6 where SACT TTD data is used for the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohorts, respectively. This update reduces the ICER to £18,520 and £24,204 per QALY gained, for the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohorts, respectively. Using SACT TTD data provides real world evidence to inform niraparib treatment duration. These scenarios can be accessed via the switches in cell C20 and C21 on the Survival sheet of the economic model.

For both the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ populations the median TTD in SACT is shorter than that observed in NOVA (DCO October 2020). As described in the CDF submission (A.6.3) an NHS England request was explicitly made for GSK to explore the SACT TTD in the modelling. To be conservative, the SACT TTD data are used to inform scenario analysis only in the economic model.

It should be noted that using the SACT TTD in combination with the updated company base case (Appendix A) results in further reduced ICERs from £18,520 to £18,372 and from £24,204 to £24,197 for the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohort respectively, as outlined in Table 4 and Table 5 of Appendix A.

Table 5. Goodness of fit statistics for the SACT niraparib TTD parametric distributions - gBRCAmut 2L and non-gBRCAmut 2L+

Curve	**gBRCAmut 2L**		**non-gBRCAmut 2L+**	
	AIC	BIC	AIC	BIC
Exponential	530.55	533.60	3,359.11	3,363.86
Weibull	532.26	538.37	3,329.83	3,339.34
Gompertz	531.84	537.95	3,359.22	3,368.74
Log-logistic	528.28	534.39	3,284.71	3,294.22
Lognormal	**524.83**	**530.94**	**3,270.21**	**3,279.72**
Generalised gamma	524.90	534.07	3,268.51	3,282.78

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; gBRCAmut, germline breast cancer susceptibility gene mutation
Lower AIC/BIC indicates better fit. **Selected curve**

Figure 3. Lognormal curve and KM for niraparib TTD from SACT gBRCAmut 2L

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; KM, Kaplan-Meier; SACT, Systemic Anti-Cancer Therapy dataset; TTD, time to treatment discontinuation.

Figure 4. Lognormal curve and KM for niraparib TTD from SACT non-gBRCAmut 2L+

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; KM, Kaplan-Meier; SACT, Systemic Anti-Cancer Therapy dataset; TTD, time to treatment discontinuation.

Table 6. Cost-effectiveness scenario results (deterministic) of cohort specific SACT TTD data applied to the company base case submitted in the review submission – [redacted]% PAS

Technologies	Total costs (£)	Total LYG (years)	Total QALYs	Incremental. costs (£)	Incremental LYG (years)	Incremental QALYs	Incremental ICER (£/QALY)
g*BRCA*mut 2L							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,520
non-g*BRCA*mut 2L+							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24,204

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life years; SACT, Systemic Anti-Cancer Therapy dataset; TTD, time to treatment discontinuation

B3. Please provide cost-effectiveness results for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups using SACT data. The ERG suggests the following approach if possible:

Niraparib arm:

- Extrapolation of SACT OS and TTD data;
- To estimate a "SACT" PFS curve, explore the following options as alternative scenarios:
    - SACT TTD as a surrogate for PFS;
    - Estimate a PFS:TTD ratio for niraparib from NOVA and apply it to the SACT TTD curve to estimate a niraparib PFS curve.

Routine surveillance arm

- For PFS, use the NOVA HR for PFS to generate the routine surveillance PFS curve;
- For OS, use a PFS:OS ratio of 1:1 as per the company base case (in the PSM model, this will be assuming the niraparib post-progression survival based on the SACT PFS and OS analysis is the same for routine surveillance).

The ERG acknowledges that the approach outlined above introduces several issues, however it is useful for the committee to see a "real world" base case using SACT data for niraparib. An alternative to the above approach which yields similar results would also be considered appropriate.

Response:

The feasibility of this analysis is being explored. We will endeavour to provide further information on this analysis by June 14th.

Survival analysis

B4. Priority question: The approach to extrapolating PFS for the gBRCAmut 2L subgroup has not changed with the companies CDF submission with no additional

justification for it supplied. In the Terms of Engagement, it is noted that, "*the company should fully investigate the most appropriate PFS modelling using updated clinical trial data*".

Please clarify why splines/other flexible approaches were not explored for modelling of PFS for the gBRCAmut 2L subgroup as was done for the ITT and non-gBRCAmut 2L+ subgroup analyses? Please note, that in the company's response to the ACD for TA528, spline models were explored and presented for the gBRCAmut 2L subgroup.

a) Please provide the scenarios using spline models for PFS for the gBRCAmut 2L subgroup.

b) Please provide diagnostic plots (such a log-cumulative hazard plots, quantile-quantile plots and residual plots as recommended by DSU TSD 14) to investigate the hazards from NOVA and demonstrate that the PFS lognormal extrapolation for the gBRCAmut 2L subgroup is appropriate.

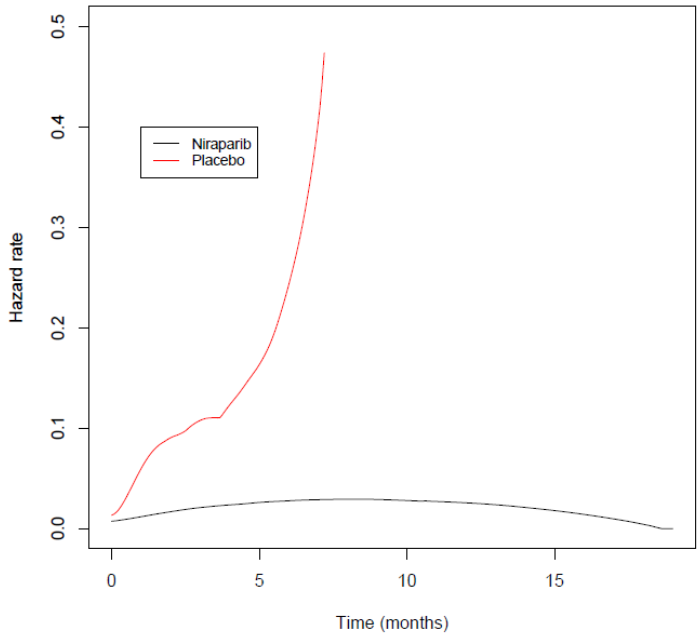
Response:

In the company's original submission, niraparib OS was estimated using the PFS:OS relationship, based on a Study 19 routine surveillance anchor. This methodology has been updated for this review, such that niraparib OS data from NOVA (DCO October 2020) is used as the anchor to estimate routine surveillance. The clinical plausibility of the PFS curves in the original submission was re-assessed following this update to OS. The niraparib PFS generalised gamma curve for the non-g*BRCA*mut 2L+ population was found to cross with the best fitting curve (lognormal) for niraparib OS, making it a clinically implausible PFS curve. Therefore, a more conservative approach using the normal k=1 flexible distribution was adopted. However, for the g*BRCA*mut 2L population, the niraparib PFS lognormal curve remains a plausible curve based on clinical and visual fit, and absence of curves crossing, when lognormal niraparib OS is modelled using data from NOVA (DCO October 2020).

The hazard function plot and log-cumulative plots are provided in Figure 5 and Figure 6, respectively. The hazard rate for niraparib initially increases and then decreases at approximately seven months, indicating one turning point. As per Decision Support Unit (DSU) Technical Support Document (TSD) 14, the log curves are suitable parametric distributions for modelling this type of curve.[10] In addition, the

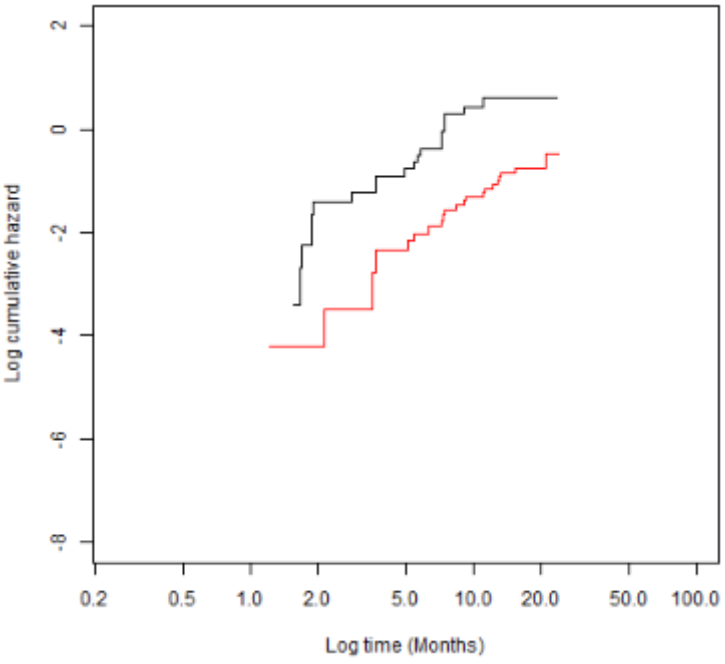
log-cumulative plot has reasonably straight lines which also indicates that parametric distributions are suitable.

Figure 5. Hazard functions of PFS from NOVA (DCO June 2016) for niraparib and routine surveillance in the gBRCAmut 2L population



Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; DCO, data cut-off; PFS, progression-free survival

Figure 6. Log-cumulative hazard plot of PFS from NOVA (DCO June 2016) for niraparib and routine surveillance in the gBRCAmut 2L population



Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; DCO, data cut-off; PFS, progression-free survival

Table 7 summarises the AIC and BIC scores for the flexible spline distributions for the g*BRCA*mut 2L population. The proportion of niraparib patients surviving at key time points are presented in Table 8.

The normal k=0 and odds k=0 distribution, which are equivalent to the lognormal and log-logistic curves, respectively, are statistically the best fitting curves when compared to the other flexible spline distributions. The statistical plausibility of these curves in relation to the other flexible spline distributions provides additional support for selecting the parametric lognormal curve in the base case.

Of the remaining flexible spline curves, those that predict a higher proportion of niraparib patients alive and progression-free at 10 years than the base case curve (lognormal) would not be considered; hazards, k= 3; odds k=1, 2 and 3; normal, k=1, 2 and 3. This is aligned with the Company response to the ACD (see ACD response, "ID1041 Niraparib ACD stakeholder comments form v3.0", Comment 3, pp. 3-6).[11]

Study 19 reports that ~16% of olaparib patients were on treatment and therefore progression-free after 5 years.[12] At 5 years, the odds k=0 and hazard k=1 curves estimate that 18.62% and 21.36% of patients remain progression-free at 5 years, making them both clinical plausible distributions when compared to Study 19. However, between 10 and 20 years, the hazard k=1 curve estimates a significant decrease in the proportion of patients who remain progression-free; it is likely that patients who remain progression-free after 10 years will have a reduced risk of progression in the following years. The odds k=0 (log-logistic) curve represents this situation more accurately with a less significant rate of decrease from year 10 compared with hazard k=1.

Whilst we maintain that the PFS lognormal extrapolation is the most appropriate base case for the g*BRCA*mut 2L population, please find scenarios using the odds k=0 and hazards k=1 flexible curves in Table 9. Using these alternative curves increases the ICER to £19,745 and £22,199 per QALY gained, respectively, for the g*BRCA*mut 2L population. These scenarios can be accessed via the switches in cells F47:F49 on the Model setup sheet of the economic model.

Table 7: Goodness of fit statistics for flexible spline models for niraparib and routine surveillance in the gBRCAmut 2L population

	Hazards k=0	Hazards k=1	Hazards k=2	Hazards k=3	Odds k=0	Odds k=1	Odds k=2	Odds k=3	Normal k=0	Normal k=1	Normal k=2	Normal k=3
Niraparib	214.80	214.79	216.76	218.44	212.85	214.63	216.62	218.45	212.85	214.63	216.62	218.45
RS	135.75	134.19	N/A	126.42	130.89	132.71	134.21	126.47	130.44	132.12	133.85	125.63
Sum	350.56	348.98	N/A	344.86	344.80	347.48	350.96	344.93	343.29	346.75	350.47	344.08

Abbreviations: AIC, Akaike Information Criterion; gBRCAmut, germline breast cancer susceptibility gene mutation; RS, routine surveillance

Table 8: Proportion surviving and progression-free at key timepoints for the lognormal and flexible spline models for niraparib in the gBRCAmut 2L population

Year	Company's base case (lognormal)	Hazards k=0	Hazards k=1	Hazards k=2	Hazards k=3	Odds k=0	Odds k=1	Odds k=2	Odds k=3	Normal k=0	Normal k=1	Normal k=2	Normal k=3
Niraparib													
5	21.75%	7.35%	21.36%	22.00%	27.86%	18.62%	27.27%	27.00%	31.31%	21.75%	25.80%	26.91%	30.60%
10	8.97%	0.18%	5.78%	6.29%	11.93%	7.72%	14.82%	14.56%	19.06%	8.97%	12.55%	13.65%	17.64%
15	4.74%	0.00%	1.69%	1.95%	5.70%	4.44%	9.99%	9.77%	13.79%	4.74%	7.50%	8.42%	11.98%
20	2.85%	0.00%	0.52%	0.64%	2.91%	2.97%	7.47%	7.28%	10.84%	2.85%	4.98%	5.74%	8.83%

Abbreviations: AIC, Akaike Information Criterion.

Table 9: Cost-effectiveness scenario results (deterministic) of the flexible odds k=0 and hazards k=1 curve for PFS applied to the company base case submitted in the review submission in the gBRCAmut 2L population – [redacted]% PAS

Technologies	Total costs (£)	Total LYG (years)	Total QALYs	Incremental. costs (£)	Incremental LYG (years)	Incremental QALYs	Incremental ICER (£/QALY)
Odds k=0 (log-logistic)							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,745
Hazards k=1							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,199

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; PAS, patient access scheme; PFS, progression-free survival

B5. Priority question: There was a potential discrepancy between PFS as assessed by BICR and investigator assessed (IA) TTD, resulting in treatment costs that are not aligned with treatment benefit in the original company submission for TA528. Please provide a scenario for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups where investigator assessed (IA) PFS from NOVA is used for the extrapolation of PFS for niraparib and routine surveillance in the economic model.

Response:

For the original submission, we can confirm that the Committee concurrently assessed time to treatment discontinuation (TTD) and the NOVA primary endpoint of PFS per independent review committee (IRC) . As stated in the FAD for TA528, the Committee concluded 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".*[8] As part of the committee meeting, *"clinical experts explained that time to treatment discontinuation in the trial would more closely reflect treatment discontinuation in clinical practice than independent retrospective assessment of progression-free survival. The committee concluded that the company's estimation of time to treatment discontinuation was more reflective of real-life clinical practice and therefore the most appropriate."*

On this basis, the use of TTD and PFS per IRC was accepted and not included as an uncertainty which needed to be addressed in the FAD for TA528 or in the Terms of Engagement for this CDF review.[6,8] In line with the Committee's preferred assumptions, as outlined in the Terms of Engagement document, TTD within the economic model follows TTD as measured in the NOVA trial.[6] This is used alongside IRC PFS as part of this review.

In addition, the health state utilities derived for use in the submission are defined as pre-progression and post-progression based on the date of progression determined by IRC PFS. Therefore, disease progression outcomes are aligned with health-related quality of life (HRQoL). HRQoL should follow the true progression status, which is the IRC PFS.

Furthermore, use of IA PFS is not considered appropriate as it is not a primary or secondary endpoint of the NOVA trial.

B6. Priority question: The extrapolation of niraparib overall survival (OS) based on Kaplan-Meier (KM) data from NOVA appears to overpredict survival for the gBRCAmut 2L subgroup. Please clarify why splines/other flexible approaches were not explored for the modelling of overall survival?

a) The ERG has explored the other standard parametric distributions for niraparib OS and found none fit the observed data well. Please explore flexible spline models in scenario analyses.

Response:

The feasibility of this analysis is being explored. We will endeavour to provide further information on this analysis by June 14th.

B7. Priority question: Please clarify why TTD is not capped by PFS.

a) Please provide a scenario for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups where TTD is capped by PFS.

Response:

We agree that capping TTD by PFS is appropriate and reflective of clinical practice as discussed at the first committee meeting for the original submission i.e. a patient would not remain on niraparib following progression (see ACD response, *"ID1041 Niraparib ACD stakeholder comments form v3.0",* Comment 3 and 5, pp. 3-4 and 8).[11]

On this basis, in line with this suggestion by the ERG, GSK has revised its base case results in Table 10 with TTD capped by PFS. This update reduces the ICER to £23,676, £19,475 and £28,942 per QALY gained, for the pooled ITT, g*BRCA*mut 2L and non-g*BRCA*mut 2L+ populations, respectively. This revised base case setting has been programmed in for when the 'CEM with refreshed base case' is selected in cell D9 on the Model setup sheet of the economic model. This setting can be altered independently via the switch in cell C22 on the Survival sheet.

Table 10. Cost-effectiveness revised company base case results (deterministic) with TTD capped by PFS – [redacted]% PAS

Technologies	Total costs (£)	Total LYG (years)	Total QALYs	Incremental. costs (£)	Incremental LYG (years)	Incremental QALYs	Incremental ICER (£/QALY)
Pooled ITT							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,676
g*BRCA*mut 2L							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,475
non-g*BRCA*mut 2L+							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,942

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PFS, progression-free survival; QALYs, quality-adjusted life years; TTD, time to treatment discontinuation

Health related quality of life

B8. Priority question: Please provide a scenario where health state utilities based on progression status (as presented in Table 26 of Appendix A.26) are used instead of treatment specific utilities.

Response:

As discussed in the review submission, in line with the Company's original submission ACD response (see Comment 6 of the ACD response, *"ID1041 Niraparib ACD stakeholder comments form v3.0",* pp. 8),[11] treatment specific utilities from the NOVA ITT population are the most appropriate for the base case to capture the quality of life benefit that patients on niraparib and routine surveillance can expect. Niraparib patients have a higher quality of life whilst progression-free compared to routine surveillance patients due to reduction in disease related symptoms such as pain levels.[13] Additionally, insights from clinicians and patient groups are that having the opportunity of maintenance therapy, which extends the period without disease progression, can offer patients psychological as well as physical health benefits; illustrated by lower individual Functional Assessment of Cancer Therapy ovarian cancer symptom index (FOSI) measures for "worry" recorded in niraparib treated NOVA patients compared to placebo.[13]

However, please find a scenario applying non-treatment specific health state utilities in Table 11. This update increases the ICER to £27,772, £20,657 and £40,662 per QALY gained, for the pooled ITT, g*BRCA*mut 2L and non-g*BRCA*mut 2L+ populations, respectively. This scenario can be accessed via the switch in cell D6 on the Utilities sheet of the economic model.

Table 11. Cost-effectiveness scenario results (deterministic) of non-treatment specific health state utilities applied to the company base case submitted in the review submission – [redacted]% PAS

Technologies	Total costs (£)	Total LYG (years)	Total QALYs	Incremental. costs (£)	Incremental LYG (years)	Incremental QALYs	Incremental ICER (£/QALY)
Pooled ITT							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,772
g*BRCA*mut 2L							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,657
non-g*BRCA*mut 2L+							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	40,662

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Resource use and costs

B9. Priority question: The ERG is unclear why the niraparib dose for the first 5 cycles of the model has changed from the original submission as a result of a later data cut from NOVA (Table 27, Appendix A.27 and Table 63 of the ERG report [Table 48 of the original company submission]). The ERG considers that the dose data informing the first 5 cycles of the model would be complete at the time of the 2016 DCO, especially as no further PFS data was collected after 2016. Please clarify why the mean niraparib dose in the first 5 cycles of the model has changed and why cycle 1 is not the full dose of 84 tablets, as was presented in the original company submission (Table 48).

a) Please provide a scenario where the dose data presented in the Table 48 of the original company submission is used.

Response:

The planned niraparib dose, as presented in the original submission, is calculated as the prescribed daily dose. The prescribed daily dose is a weighted average based upon the proportion of patients prescribed 300 mg, 200 mg or 100 mg per day at each cycle and multiplied by 28 days (the cycle length applied in the model).

The updated NOVA 2020 dosing data utilises the mean actual dose taken per cycle. The actual mean dose is calculated as the dispensed dose minus the returned dose each cycle; the actual dose, therefore, reflects the mean dose taken rather than the dose prescribed and is applied directly per cycle in the model. The actual mean dose most accurately represents the dose of niraparib actually taken by patients and therefore should be used in the base case.

Dose titration may be used to manage adverse events. In the NOVA study, niraparib dose adjustment tended to occur early with the mean dose reaching a plateau by Cycle 4. As such, it is not uncommon for a patient's dose to be down-titrated in the first few weeks of treatment and therefore, the mean actual dose per cycle in Cycle 1 is below the starting dose of 300 mg per day x 28 days; for example, Cycle 1 mean actual dose: [redacted] mg for non-g*BRCA*mut 2L+ per cycle versus Cycle 1 mean planned dose: 8400.00 mg.[3] Full details of the actual mean dose per cycle are

provided in Table 27 and Table 28 of the CDF review submission Appendix, Section A.27.

A scenario applying NOVA 2016 planned dosing data across all cycles (Table 48 of the original company submission) is shown in Table 12. This update increases the ICER to £22,650 and £39,202 per QALY gained, for the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ populations, respectively. This scenario can be accessed via the switch in cell F40 on the Model Setup sheet of the economic model.

Table 12. Cost-effectiveness scenario results (deterministic) of planned niraparib dose NOVA 2016 applied to the company base case submitted in the review submission – [redacted]% PAS

Technologies	Total costs (£)	Total LYG (years)	Total QALYs	Incremental. costs (£)	Incremental LYG (years)	Incremental QALYs	Incremental ICER (£/QALY)
g*BRCA*mut 2L							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,650
non-g*BRCA*mut 2L+							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	39,202

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

* The ITT population was not presented in the original submission; as such, planned niraparib dosing data for the ITT population were not analysed.

Probabilistic sensitivity analyses

B10. Priority question: In the NICE methods guide it is stated that probabilistic methods provide the best estimates of mean costs and outcomes for non-linear models. In the ERG report for TA528, the ERG was concerned about the approach to probabilistic sensitivity analyses (PSA) and found it to be unreliable. In the current CDF submission, the PSA results for the non-gBRCAmut 2L+ subgroup are different to the deterministic results suggesting a non-linear model. Please clarify why the PSA results are not similar to deterministic results and correct if necessary.

Response:

Following exploration of the difference in the PSA and deterministic results for the non-g*BRCA*mut 2L+ population, an error was identified which has now been corrected.

In the base case, niraparib OS data from NOVA (DCO October 2020) is used as the anchor to estimate RS OS. In the economic model, the niraparib PFS curve is capped by the niraparib OS curve. A cap is applied to the RS PFS curve such that the RS PFS does not exceed RS OS curve; however, a RS OS curve is not drawn when niraparib is used as an OS anchor and a mean ΔPFS:ΔOS relationship is used to inform RS OS. This resulted in the RS PFS curve not being capped by RS OS and consequently exceeding the niraparib PFS curve when extreme values were inputted as part of the PSA; in turn, mean RS OS was greater than mean niraparib OS which is clinically highly implausible. This led to extreme probabilistic results in the North West quadrant of the scatterplot, Figure 8 of the CDF review submission, with extreme negative incremental QALYs, in turn causing an incorrect disparity between the probabilistic and deterministic results. This has now been fixed in Column DA of the 'Flexible splines curve' sheet in the economic model, such that the RS PFS curve is capped by the niraparib OS curve. This update does not affect the deterministic results.

On this basis, please find corrected PSA results for the submitted company base case in Table 13. The associated incremental cost-effectiveness plane (ICEP) is shown in Figure 7. The non-g*BRCA*mut 2L+ probabilistic ICER is £37,692 per QALY gained which is now closer to the deterministic ICER submitted company base case of £36,449 per QALY gained.

Table 13. Cost-effectiveness scenario results (probabilistic) corrected to cap RS PFS by niraparib OS applied to the company base case submitted in the review submission for non-gBRCAmut 2L+ – [redacted]% PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
non-g*BRCA*mut 2L+							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,692

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; QALYs, quality-adjusted life years; RS, routine surveillance

Figure 7. Scatterplot of probabilistic results for non-gBRCAmut 2L+

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; QALY, quality-adjusted life year

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Cancer Drugs Fund review

Cancer Drugs Fund review of technology appraisal 528 of niraparib as maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1644]

Response to clarification questions Appendix A

May 2021

File name	Version	Contains confidential information	Date
[ID1644]_response_appendix_redacted	V1	Yes	26/05/21

Appendix A: Revised base case results

This appendix contains full cost-effectiveness results, sensitivity and scenario analyses for the revised company base case. The base case results have been revised by capping TTD by PFS as per the response to Question B7 with results shown in Table 1. The base case ICERs are £23,676, £19,475 and £28,942 per QALY gained, for the pooled ITT, g*BRCA*mut 2L and non-g*BRCA*mut 2L+ populations, respectively. This revised base case setting has been programmed in for when the 'CEM with refreshed base case' is selected in cell D9 on the Model setup sheet of the economic model. This setting can be altered independently via the switch in cell C22 on the Survival sheet.

Table 1. Cost-effectiveness revised company base case results (deterministic) – [redacted]% PAS

Technologies	Total costs (£)	Total LYG (years)	Total QALYs	Incremental. costs (£)	Incremental LYG (years)	Incremental QALYs	Incremental ICER (£/QALY)
Pooled ITT							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,676
g*BRCA*mut 2L							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,475
non-g*BRCA*mut 2L+							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,942

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PFS, progression-free survival; QALYs, quality-adjusted life years; TTD, time to treatment discontinuation

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed for 1,000 iterations to explore the uncertainty around key model inputs. In each iteration, model inputs were randomly varied from specified distributions, as summarised in Section A.31 of the company CDF review submission.

Mean incremental results were recorded and are displayed in Table 2. Results are illustrated through an incremental cost-effectiveness plane (ICEP) which is presented in Figure 1, Figure 2 and Figure 3 for the ITT, g*BRCA*mut 2L and non-g*BRCA*mut 2L+ populations, respectively. Assuming a willingness-to-pay threshold of £30,000 per QALY gained, the probability of niraparib being the most cost-effective treatment option was 81%, 94% and 48%, in the ITT, g*BRCA*mut 2L and non-g*BRCA*mut 2L+ populations, respectively.

Table 2. Cost-effectiveness revised company base case results (probabilistic) – [redacted]% PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Pooled ITT							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24,417
g*BRCA*mut 2L							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,545
non-g*BRCA*mut 2L+							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,173

Figure 1. Scatterplot of probabilistic results for pooled ITT

Abbreviations: ITT, intention-to-treat; QALY, quality-adjusted life years

Figure 2. Scatterplot of probabilistic results for gBRCAmut 2L

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; QALY, quality-adjusted life years

Figure 3. Scatterplot of probabilistic results for non-gBRCAmut 2L+

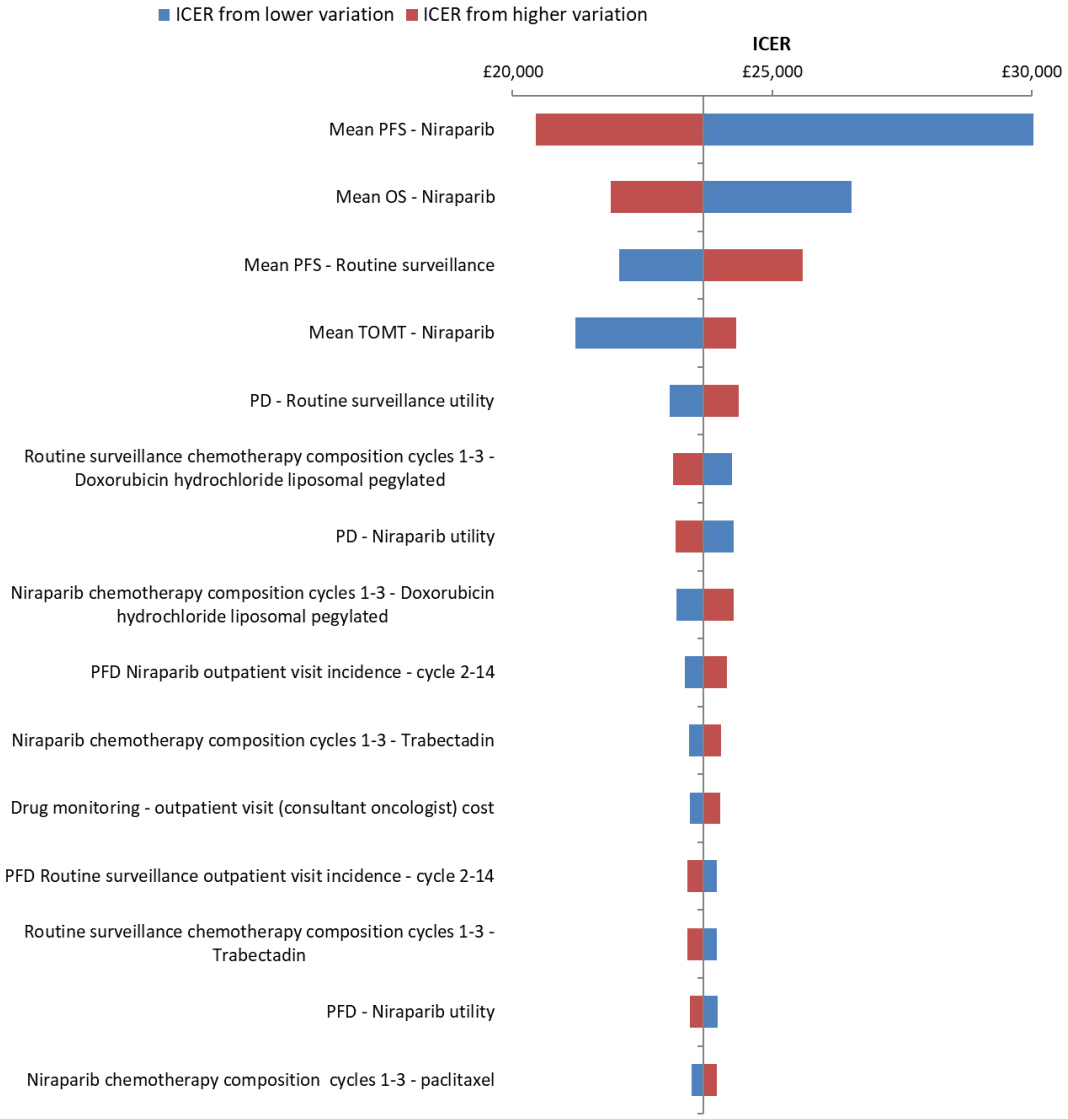
Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; QALY, quality-adjusted life years

Key sensitivity and scenario analyses

Pooled ITT

A tornado diagram is presented in ***Figure 4***, with the top 15 most sensitive parameters presented. Results were most sensitive to mean PFS and OS for niraparib. Results were also sensitive to mean PFS for RS. In all instances the ICER was less than £30,451 per QALY.

Figure 4. **Tornado diagram of niraparib versus routine surveillance for pooled *ITT***



Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OS, overall survival; PD, progressed disease; PFD, progression-free disease; PFS, progression-free survival; TOMT, time on maintenance treatment

Various scenario analyses were conducted to assess alternate model settings and structural uncertainty of the base case analysis. Key scenarios are presented in Table 3.

Table 3. Key scenario analyses – Pooled ITT

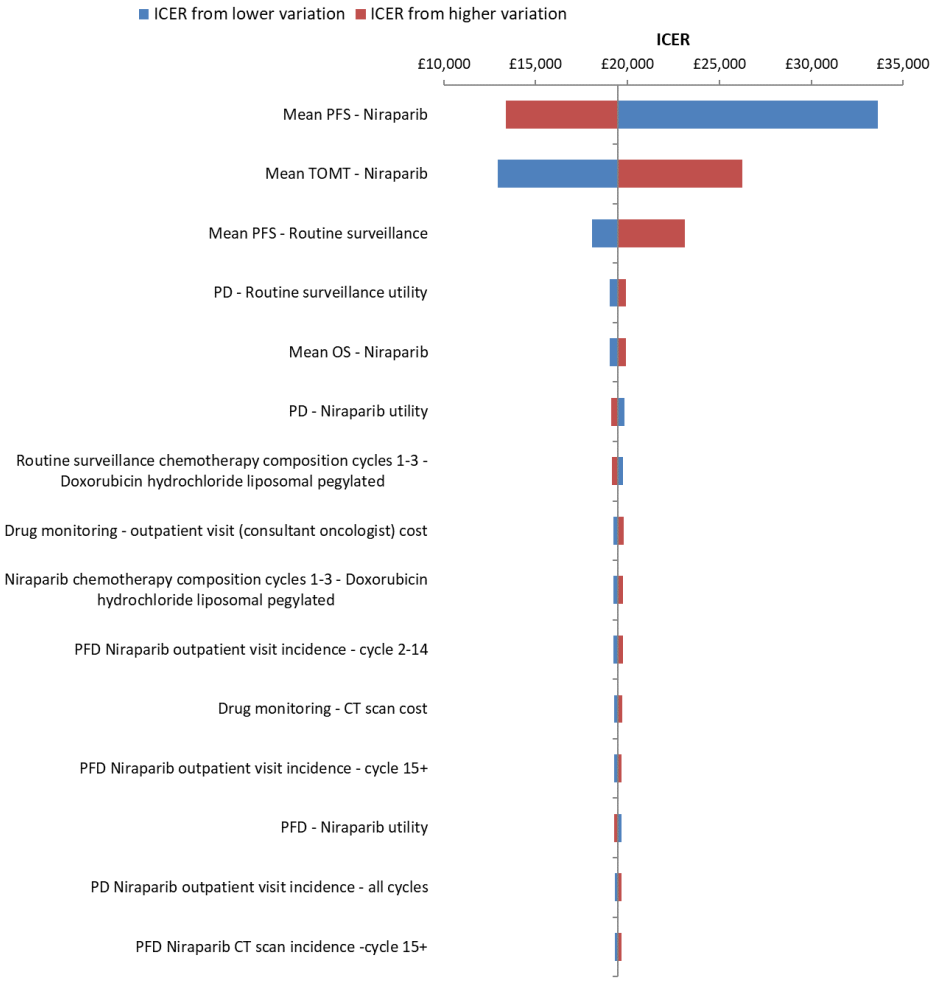
Scenario and cross reference		Scenario detail	Brief rationale	ICER (£)
Base case				**23,676**
1	Extrapolated trial data from Lord et al. 2020 for RS OS *Section A.8.3 of CDF review submission*	Extrapolated trial data from Lord et al. 2020 was modelled to inform the OS estimates for RS in the ITT population. OS KM was extrapolated using the lognormal distribution	The ICER decreases as the RS OS from Lord et al. 2020 is shorter than modelled using the PFS:OS relationship	21,185
2	Extrapolated trial data from Study 19 for RS OS *Section A.8.3 of CDF review submission*	Extrapolated trial data from Study 19 modelled to inform the OS estimates for RS in the ITT population. OS KM was extrapolated using the lognormal distribution	The ICER increases as the RS OS from Study 19 is longer than modelled using the PFS:OS relationship	32,540
3	Niraparib TTD data sourced from SACT *Appendix, Section A.25.1, of CDF review submission*	TTD SACT data was used to inform the niraparib mean TOMT. TTD KM was extrapolated using the lognormal distribution	The ICER decreases as patients included in the SACT dataset remained on treatment for less time when compared to the NOVA dataset.	15,889
4	Extrapolated trial data from Lord et al. 2020 for RS OS (*Section A.8.3 of CDF review submission*) and niraparib TTD data from SACT (*Appendix, Section A.25.1, of CDF review submission*)	See scenarios 1 and 3 for details	The ICER decreases as the RS OS from Lord et al. 2020 is shorter than modelled using the PFS:OS relationship and as patients in the SACT dataset remained on treatment for less time when compared to the NOVA dataset	14,234
5	Extrapolated trial data from Study 19 for RS OS (*Section A.8.3 of CDF review submission*) and niraparib TTD data from SACT (*Appendix, Section A.25.1, of CDF review submission*)	See scenarios 2 and 3 for details	Although RS OS from Study 19 is longer than modelled using the PFS:OS relationship, the ICER decreases as patients in the SACT dataset remained on treatment for less time when compared to the NOVA dataset.	21,776
6	Non-treatment specific health state utilities *B8 ERG clarification question*	Non-treatment specific health state utilities applied i.e. not treatment specific	The ICER increases as the incremental QALY gain is smaller than modelled using the treatment specific utilities.	25,413

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention to treat; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; RS, routine surveillance; SACT, systematic anti-cancer therapy; TOMT, time on maintenance therapy; TTD, time to treatment discontinuation

g*BRCA*mut 2L

A tornado diagram is presented in Figure 5, with the top 15 most sensitive parameters presented. Results were most sensitive to mean PFS and TOMT for niraparib. Results were also sensitive to the mean PFS for RS. In all instances the ICER was less than £33,601 per QALY.

Figure 5. Tornado diagram of niraparib versus routine surveillance for gBRCAmut 2L



Abbreviations: CT, computerised tomography; gBRCAmut, germline breast cancer susceptibility gene; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFD, progression-free disease; PFS, progression-free survival; TOMT, time on maintenance treatment

Various scenario analyses were conducted to assess alternate model settings and structural uncertainty of the base case analysis. Key scenarios are presented in Table 4.

Table 4. Key scenario analyses – gBRCAmut 2L

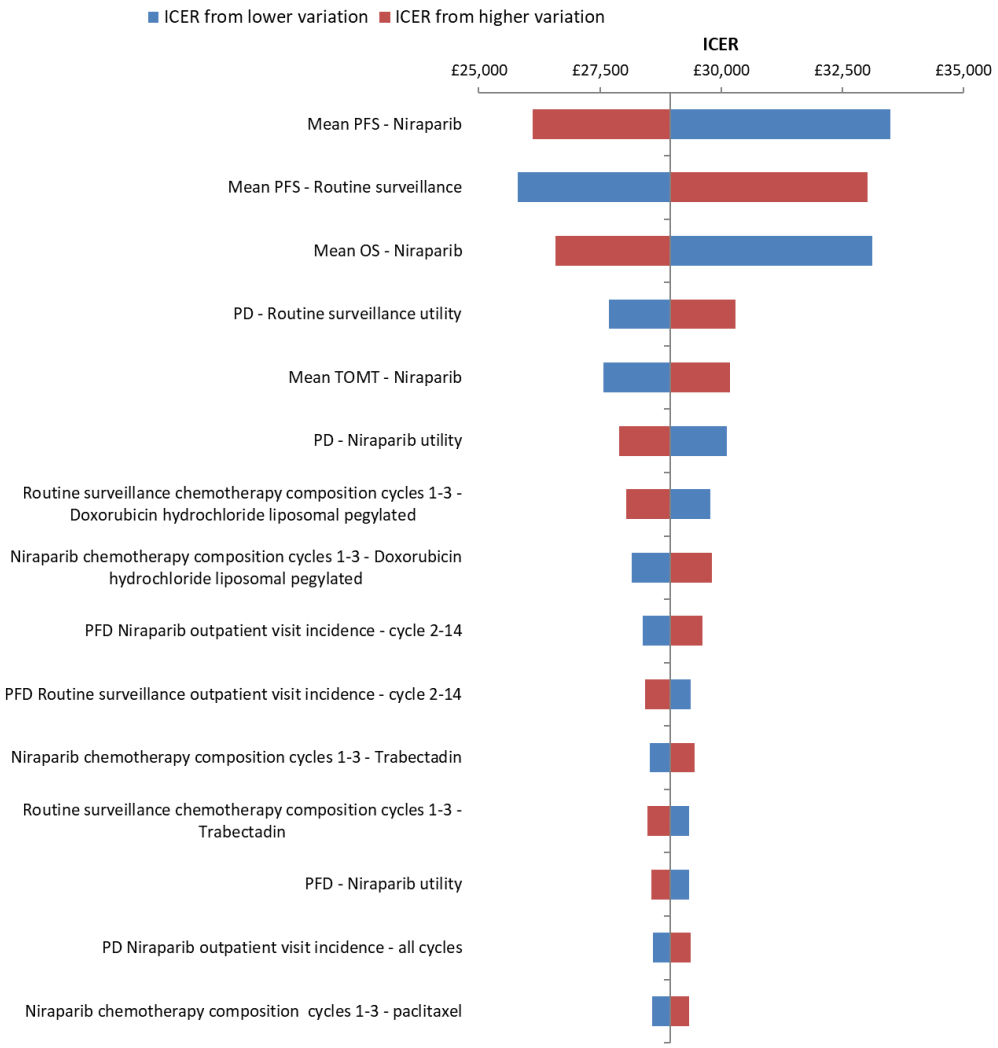
Scenario and cross reference		Scenario detail	Brief rationale	ICER (£)
Base case				**19,475**
1	Extrapolated trial data from Study 19 for RS OS *Appendix, Section A.22, of CDF review submission*	Extrapolated trial data from Study 19 modelled to inform the OS estimates for RS in the gBRCAmut 2L population. OS KM was extrapolated using the lognormal distribution.	The ICER increases as the RS OS from Study 19 is longer than modelled using the PFS:OS relationship.	22,205
2	Niraparib TTD data sourced from SACT gBRCAmut 2L *B2 ERG clarification question*	TTD SACT gBRCAmut 2L data was used to inform the niraparib mean TOMT. TTD KM was extrapolated using the lognormal distribution	The ICER decreases as patients included in the SACT dataset remained on treatment for less time when compared to the NOVA dataset.	18,372
3	Extrapolated trial data from Study 19 for RS OS (*Appendix, Section A.22, of CDF review submission)* and niraparib TTD data from SACT gBRCAmut 2L (*B2 ERG clarification question)*	See scenarios 1 and 2 for details	Although RS OS from Study 19 is longer than modelled using the PFS:OS relationship, the ICER decreases as patients included in the SACT dataset remained on treatment for less time when compared to the NOVA dataset.	20,943
4	PFS extrapolated using the odds k=0 flexible curve *B4 ERG clarification question*	NOVA 2016 PFS data extrapolated using the odds k=0 flexible curve	The ICER increases as the incremental PFS benefit is smaller than modelled using the lognormal curve.	19,621
5	PFS extrapolated using the hazards k=1 flexible curve *B4 ERG clarification question*	NOVA 2016 PFS data extrapolated using the hazards k=1 flexible curve	The ICER increases as the incremental PFS benefit is smaller than modelled using the lognormal curve.	22,058
6	Non-treatment specific health state utilities *B8 ERG clarification question*	Non-treatment specific health state utilities applied i.e. not treatment specific	The ICER increases as the incremental QALY gain is smaller than modelled using the treatment specific utilities.	20,527
7	Planned niraparib dose NOVA 2016 *B9 ERG clarification question*	Planned niraparib dosing data from NOVA 2016 used rather than the actual niraparib dosing from NOVA 2020	The ICER increases as the niraparib dose received is greater than modelled using the actual niraparib dose.	22,507

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; RS, routine surveillance; TOMT, time on maintenance treatment; TTD, time to treatment discontinuation

Non-gBRCAmut 2L+

A tornado diagram is presented in Figure 6, with the top 15 most sensitive parameters presented. Results were most sensitive to mean PFS for niraparib and RS. Results were also sensitive to the mean OS for niraparib. In all instances the ICER was less than £33,486 per QALY.

Figure 6. Tornado diagram of niraparib versus routine surveillance for* non-*gBRCAmut 2L+



Abbreviations: CT, computerised tomography; gBRCAmut, germline breast cancer susceptibility gene; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFD, progression-free disease; PFS, progression-free survival; TOMT, time on maintenance treatment

Various scenario analyses were conducted to assess alternate model settings and structural uncertainty of the base case analysis. Key scenarios are presented in

Table ***5***.

Table 5. Key scenario analyses – non-gBRCAmut 2L+

Scenario and cross reference		Scenario detail	Brief rationale	ICER (£)
Base case				**28,942**
1	Extrapolated trial data from Study 19 for RS OS *Section A.22 of CDF review submission*	Extrapolated trial data from Study 19 modelled to inform the OS estimates for RS in the non-gBRCAmut 2L+ population. OS KM was extrapolated using the lognormal distribution	The ICER increases as the RS OS from Study 19 is longer than modelled using the PFS:OS relationship.	31,449
2	Niraparib TTD data sourced from SACT non-gBRCAmut 2L+ *B2 ERG clarification question*	TTD SACT non-gBRCAmut 2L+ data was used to inform the niraparib mean TOMT. TTD KM was extrapolated using the lognormal distribution	The ICER decreases as patients included in the SACT dataset remained on treatment for less time when compared to the NOVA dataset.	24,197
3	Extrapolated trial data from Study 19 for RS OS (*Appendix, Section A.22, of CDF review submission)* and niraparib TTD data from SACT non-gBRCAmut 2L+ (*B2 ERG clarification question)*	See scenarios 1 and 2 for details	Although RS OS from Study 19 is longer than modelled using the PFS:OS relationship, the ICER decreases as patients included in the SACT dataset remained on treatment for less time when compared to the NOVA dataset.	26,291
4	Non-treatment specific health state utilities *B8 ERG clarification question*	Non-treatment specific health state utilities applied i.e. not treatment specific	The ICER increases as the incremental QALY gain is smaller than modelled using the treatment specific utilities.	32,287
5	Planned niraparib dose NOVA 2016 *B9 ERG clarification question*	Planned niraparib dosing data from NOVA 2016 used rather than the actual niraparib dosing from NOVA 2020	The ICER increases as the niraparib dose received is greater than modelled using the actual niraparib dose.	31,270

Abbreviations: non-gBRCAmut, non-germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; RS, routine surveillance; TOMT, time on maintenance treatment; TTD, time to treatment discontinuation

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Cancer Drugs Fund review

Cancer Drugs Fund review of technology appraisal 528 of niraparib as maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1644]

Response to clarification questions B3 and B6

June 2021

File name	Version	Contains confidential information	Date
[ID1644]_clarificationresponse_B3_B6_AIC_redacted	V1	Yes	14/06/21

Section B: Clarification on cost-effectiveness data

SACT data

B3. Please provide cost-effectiveness results for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups using SACT data. The ERG suggests the following approach if possible:

Niraparib arm:

- Extrapolation of SACT OS and TTD data;
- To estimate a “SACT” PFS curve, explore the following options as alternative scenarios:
    - SACT TTD as a surrogate for PFS;
    - Estimate a PFS:TTD ratio for niraparib from NOVA and apply it to the SACT TTD curve to estimate a niraparib PFS curve.

Routine surveillance arm

- For PFS, use the NOVA HR for PFS to generate the routine surveillance PFS curve;
- For OS, use a PFS:OS ratio of 1:1 as per the company base case (in the PSM model, this will be assuming the niraparib post-progression survival based on the SACT PFS and OS analysis is the same for routine surveillance).

The ERG acknowledges that the approach outlined above introduces several issues, however it is useful for the committee to see a “real world” base case using SACT data for niraparib. An alternative to the above approach which yields similar results would also be considered appropriate.

Response:

Niraparib OS

Overall survival (OS) summary statistics and Kaplan Meier (KM) data for the Systemic Anti-Cancer Therapy (SACT) dataset for the combined intention-to-treat (ITT), g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohorts were presented in Section A.6.2 and Appendix, Section A.19, of the company CDF review submission. As outlined in the CDF review submission, GSK was keen to further understand the differences between the NOVA and SACT populations. However, a proposed research study was not agreed to by NHS England and Improvement (NHSE&I) and SACT because the product is still in the CDF. It was therefore not possible to analyse the differences between the respective populations in further detail and consequently the assessment of the two patient populations is limited. Therefore, the niraparib SACT data were not used to inform the economic model as part of the submission basecase.

However, as requested, scenario analyses have been conducted using long-term extrapolations of OS from SACT to model niraparib OS for the combined ITT, g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohorts, respectively.

For the combined ITT cohort, the log-logistic curve was considered the most plausible curve based on statistical and visual fit (Table 1). Using the log-logistic distribution (Figure 1) niraparib mean OS was calculated as the area under the curve (AUC) using the trapezium rule as [redacted] years and [redacted] years after discounting. This was validated by an ovarian cancer (OC) clinical expert such that ~10% of patients alive at ~8 years, as shown in Figure 1, is deemed clinically plausible in the relapsed setting while on PARPi treatment.[1]

For the g*BRCA*mut 2L cohort, the log-logistic curve was considered the most plausible curve based on statistical and visual fit (Table 1). Using the log-logistic distribution (Figure 2), niraparib mean OS was calculated as the AUC using the trapezium rule as [redacted] years and [redacted] years after discounting. Using this best fitting log-logistic curve, [redacted] % of patients are alive at 5 years which is less than and more conservative than that extrapolated from NOVA (DCO October 2020) ([redacted] %) and observed for the olaparib arm of Study 19 (~35%).[2]

For the non-g*BRCA*mut 2L+ cohort, the generalised gamma and log-logistic curves had similar statistical fit (Table 1). Of these two curves, the log-logistic curve was considered the most plausible curve based on visual fit to the KM data and plausible long-term extrapolations. Using the log-logistic curve, [redacted] % of patients are alive at 5 years, which is conservative compared with extrapolations from NOVA (DCO October 2020) ([redacted] %) and observed data from the olaparib arm of Study 19 (~22%) at the 5 year mark.[2] The generalised gamma curve estimates that [redacted] % of patients are alive at 5 years; this is lower than ~10% of routine surveillance (RS) patients alive at 5 years reported by Lord et al. 2020,[3] and it is deemed too pessimistic to assume that the number of patients alive at 5 years would be lower in a PARPi treated population than in a routine surveillance population, and therefore was rejected. Using the log-logistic distribution (

Figure 3) niraparib mean OS was calculated as the AUC using the trapezium rule as [redacted] years and [redacted] years after discounting.

Table 1. Goodness of fit statistics for the SACT niraparib OS parametric distributions – combined ITT, gBRCAmut 2L and non-gBRCAmut 2L+

Curve	Combined ITT		gBRCAmut 2L		non-gBRCAmut 2L+	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; g*BRCA*mut, germline breast cancer susceptibility gene mutation; SACT, Systemic Anti-Cancer Therapy dataset.
Lower AIC/BIC indicates better fit. **Selected curve**

Figure 1. Log-logistic curve and KM for niraparib OS from SACT combined ITT


[redacted]

Abbreviations: ITT, intention-to-treat; KM, Kaplan-Meier; OS, overall survival; SACT, Systemic Anti-Cancer Therapy dataset.

Figure 2. Log-logistic curve and KM for niraparib OS from SACT gBRCAmut 2L

Abbreviations: g*BRCA*mut, germline breast cancer susceptibility gene mutation; KM, Kaplan-Meier; OS, overall survival; SACT, Systemic Anti-Cancer Therapy dataset.

Figure 3. Log-logistic curve and KM for niraparib OS from SACT non-gBRCAmut 2L+

Abbreviations: g*BRCA*mut, germline breast cancer susceptibility gene mutation; KM, Kaplan-Meier; OS, overall survival; SACT, Systemic Anti-Cancer Therapy dataset.

Niraparib TTD

In Section A.8.4 of the company CDF review submission and in response to B2 of the ERG questions, time to treatment discontinuation (TTD) data has been modelled via long-term extrapolations based on the SACT dataset for the combined ITT, g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohorts. Across all of these cohorts, the lognormal curve was considered the most plausible based on statistical and visual fit. Using the lognormal distribution, the mean TTD was calculated as the AUC using the trapezium rule for each cohort as shown in Table 2.

Table 2. Mean TTD for the SACT niraparib TTD lognormal distribution – combined ITT, gBRCAmut 2L and non-gBRCAmut 2L+

	ITT	gBRCAmut 2L	non-gBRCAmut 2L+
Niraparib mean undiscounted TTD (years)	[redacted]	[redacted]	[redacted]

Abbreviations: g*BRCA*mut, germline breast cancer susceptibility gene mutation; ITT, intention-to-treat; TTD, time to treatment discontinuation.

Niraparib PFS

No PFS data is reported in the SACT data. Therefore a proxy must be used to describe niraparib SACT PFS within the economic model.

As shown in Appendix, Section A.19, Table 17 of the company CDF review submission, in the combined ITT population of SACT, [redacted]% of patients stopped treatment due to progression of disease. For gBRCAmut 2L and non-gBRCAmut 2L+ this was reported as [redacted]% and [redacted]%, respectively. The remaining proportion of patients, [redacted]% and [redacted]% for gBRCAmut 2L and non-gBRCAmut 2L+ respectively, stopped treatment for reasons other than progression. On this basis, using TTD as a surrogate for progression-free survival (PFS) would not be appropriate.[4]

As proposed by the ERG, a niraparib PFS curve has been estimated using a PFS:TTD ratio for niraparib based on data from the NOVA trial and applying it to the SACT TTD curve. The PFS:TTD ratio was derived by dividing NOVA niraparib mean TTD by NOVA niraparib mean PFS from the model. This is presented in

Table 3 along with references for where these mean PFS and TTD values have been reported in the CDF review submission for each cohort.

Table 3. PFS:TTD ratio derived from NOVA – Combined ITT, gBRCAmut 2L and non-gBRCAmut 2L+

	Combined ITT	**gBRCAmut 2L**	**non-gBRCAmut 2L+**
Niraparib mean PFS	[redacted] Section A.8.2	3.63 Appendix, Section A.22.1	1.92 Appendix, Section A.22.1
Niraparib mean TTD	[redacted]* Section A.8.4	[redacted] Update of Appendix, Section A.22.3 due to TTD capped by PFS (as per B7 ERG question response)	[redacted]* Appendix, Section A.22.3
Niraparib mean PFS:TTD ratio	[redacted]	[redacted]	[redacted]

Abbreviations: g*BRCA*mut, germline breast cancer susceptibility gene mutation; ITT, intention-to-treat; PFS, progression-free survival; TTD, time to treatment discontinuation.
*Mean TTD has been corrected such that it is capped by the flexible PFS curve as identified in the ERG report.

The PFS:TTD ratios for niraparib shown in

Table 3 were applied to the SACT TTD curves to derive a niraparib PFS curve for each cohort. The 'Goal seek' function in Excel was used to determine the HR to apply to the SACT TTD curve such that niraparib mean PFS, calculated as the AUC using the trapezium rule, was equal to the niraparib mean TTD divided by the PFS:TTD ratio. On this basis, the niraparib mean PFS derived for each cohort is shown in Table 4. Comparing Table 4 with

Table 3 it can be observed that the niraparib mean PFS estimates derived from SACT TTD data are very conservative compared with estimates based on NOVA PFS data (DCO October 2020).

Table 4. Mean PFS for niraparib based on application of a PFS:TTD ratio – Combined ITT, gBRCAmut 2L and non-gBRCAmut 2L+

	Combined ITT	gBRCAmut 2L	non-gBRCAmut 2L+
Niraparib mean undiscounted PFS (years)	[redacted]	[redacted]	[redacted]

Abbreviations: g*BRCA*mut, germline breast cancer susceptibility gene mutation; ITT, intention-to-treat; TTD, time to treatment discontinuation.

Routine surveillance PFS

PFS summary statistics for the pooled ITT and non-g*BRCA*mut 2L+ cohort based on the NOVA data cut-off (DCO) June 2016 were presented in Section A.6.1 of the company CDF review submission and in the original submission (please refer to Document B of original Company submission, Section B.2.6.2, pp. page 56-60), respectively.

As per these previously presented summary statistics, along with analysis of the g*BRCA*mut 2L cohort, the NOVA HR for PFS for each cohort is shown in Table 5.

Table 5. NOVA HR for PFS – pooled ITT, gBRCAmut 2L and non-gBRCAmut 2L+

	Pooled ITT	gBRCAmut 2L	non-gBRCAmut 2L+
PFS HR	[redacted] (95% CI: [redacted] – [redacted])	[redacted] (95% CI: [redacted] – [redacted])	0.45 (95% CI: 0.34 – 0.61)

Abbreviations: CI, confidence interval; g*BRCA*mut, germline breast cancer susceptibility gene mutation; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.

As proposed by the ERG, the NOVA HR for PFS has been applied to the niraparib PFS curve (derived from the niraparib SACT TTD curve) to generate the RS PFS

curve. On this basis, the RS mean PFS, calculated as the AUC using the trapezium rule, derived for each cohort is shown in Table 6.

Table 6. Mean PFS for RS based on application of the NOVA HR for PFS – Combined ITT, gBRCAmut 2L and non-gBRCAmut 2L+

	Combined ITT	gBRCAmut 2L	non-gBRCAmut 2L+
RS mean undiscounted PFS (years)	[redacted]	[redacted]	[redacted]

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival; RS, routine surveillance; TTD, time to treatment discontinuation

Routine surveillance OS

As proposed and per the company base case, for RS OS a PFS:OS ratio of 1:1 was used. On this basis, the RS mean OS derived for each cohort is shown in **Error! Reference source not found.**.

Table 7. Mean OS for RS based on application of a PFS:OS ratio of 1:1 – Combined ITT, gBRCAmut 2L and non-gBRCAmut 2L+

	Combined ITT	gBRCAmut 2L	non-gBRCAmut 2L+
RS mean undiscounted OS (years)	[redacted]	[redacted]	[redacted]

Abbreviations: g*BRCA*mut, germline breast cancer susceptibility gene mutation; ITT, intention-to-treat; TTD, time to treatment discontinuation

Based on the methods presented, Table 8 presents the scenario analyses results using SACT data for the combined ITT, g*BRCA*mut 2L and non-g*BRCA*mut 2L+ cohorts, respectively. The respective ICERs are £28,285 per QALY gained for the combined ITT cohort, £17,930 for the g*BRCA*mut 2L cohort and £35,346 for the g*BRCA*mut 2L+ cohort. This scenario shows that although using real world data to inform the cost-effectiveness analysis leads to lower mean PFS, TTD and OS (except RS in the ITT cohort) values for niraparib and RS compared to the respective values derived from the NOVA clinical trial estimates, the cost-effectiveness estimates using real world data are similar to those estimated using clinical trial data. Differences range between a 7.93% reduction and 9.31% increase in the ICER per QALY gained compared with the base case (please note: this considers the base

case with TTD corrected in the model such that it is capped by the flexible PFS curve for the pooled ITT [base case ICER: £25,875 per QALY gained] and non-g*BRCA*mut 2L+ [base case ICER: £36,449] cohorts as identified in the ERG report). This scenario can be accessed via the switches in cell C21 (SACT niraparib TTD sensitivity analysis), C26 (SACT niraparib OS dataset), C31 (apply PFS:TTD ratio to obtain niraparib PFS) and C29 (apply PFS HR to RS PFS) on the Survival sheet of the economic model.

Table 8. Cost-effectiveness scenario results (deterministic) using SACT data applied to the company base case – [redacted]% PAS

Technologies	Total costs (£)	Total LYG (years)	Total QALYs	Incremental. costs (£)	Incremental LYG (years)	Incremental QALYs	Incremental ICER (£/QALY)
Combined ITT							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,285
g*BRCA*mut 2L							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,930
non-g*BRCA*mut 2L+							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	35,346

Abbreviations: g*BRCA*mut, germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life years; SACT, Systemic Anti-Cancer Therapy dataset; TTD, time to treatment discontinuation.

Alternative approach – Lord et al. 2020 ITT data used for routine surveillance PFS and OS

As per the ERG's suggestion that an alternative approach to the above would also be considered appropriate, an alternative approach which yields similar results using "real world" data for the RS arm, has been provided for the combined ITT cohort.

For this approach, niraparib OS, PFS and TTD have been modelled using the methods described above based on the SACT combined ITT data. RS has been modelled using real world evidence (RWE) from Lord et al. 2020 for OS and PFS.[3] Thus both arms are based on RWE.

Routine surveillance OS

In Section A.8.3 of the company CDF review submission, RS OS data has been modelled via long-term extrapolations based on the Lord et al. 2020 dataset for the combined ITT cohort. The lognormal curve was considered the most plausible based on statistical and visual fit. Using the lognormal distribution the RS mean OS was calculated at the AUC using the trapezium rule as 2.47 years and 2.36 years after discounting.

Routine surveillance PFS

Long-term extrapolations of PFS from Lord et al. 2020 were used to model RS PFS for the combined ITT cohort. The log-logistic curve was considered the most plausible curve based on statistical and visual fit (

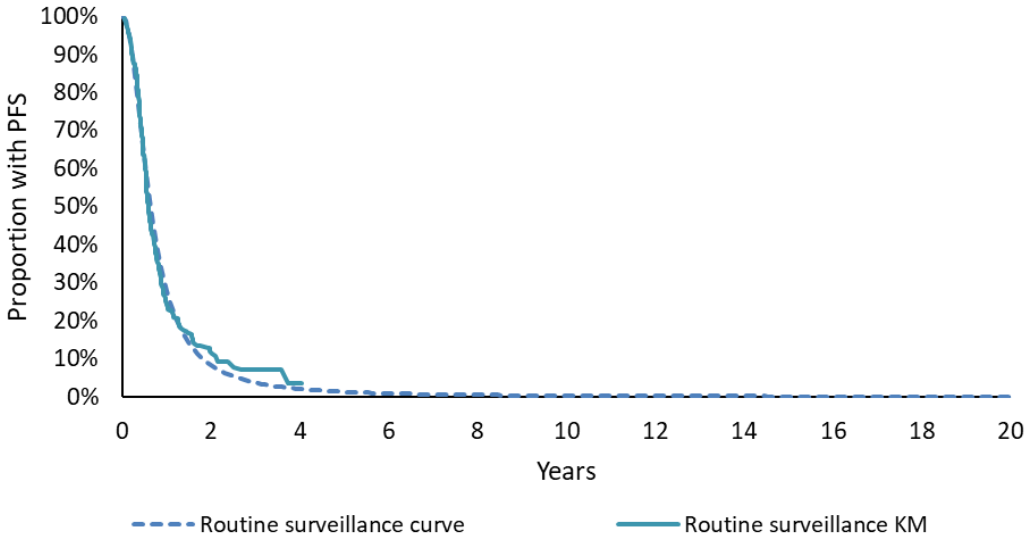
Table 9). Using the log-logistic distribution (Figure 4), applying a 20-year cap (patients could not be progression-free after 20 years) and ensuring PFS is less than OS, RS mean PFS was calculated as the AUC using the trapezium rule as 0.94 years and 0.93 years after discounting.

Table 9. Goodness of fit statistics for Lord et al. 2020 RS PFS parametric distributions – ITT

Curve	ITT	
	AIC	BIC
Exponential	1399.59	1403.04
Weibull	1390.38	1397.28
Gompertz	1401.14	1408.04
Log-logistic	**1338.53**	**1345.43**
Lognormal	1346.60	1353.50
Generalised gamma	1347.42	1357.78

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion, ITT, intention-to-treat; PFS, progression-free survival; RS, routine surveillance.
Lower AIC/BIC indicates better fit. **Selected curve**

Figure 4. Log-logistic curve and KM for RS PFS from Lord et al. ITT



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

Based on the methods presented, Table 8 presents the scenario analyses results using SACT and Lord et al. 2020 data for the combined ITT cohort. The resulting

ICER is £21,976 per QALY gained, demonstrating the cost effectiveness of niraparib in a real-world setting. This approach shows that using real world data to inform the cost-effectiveness analysis leads to mean PFS (except RS), TTD and OS values for niraparib and RS lower than the respective values derived from the NOVA trial. However the cost-effectiveness estimates improve, by £3899 (15.07%) per QALY gained compared with the company base case ICER from [£25,875 per QALY gained to £21,976].

Note that as the Lord et al data were not split into subgroups, it was not possible to calculate corresponding ICERs for the subgroups; gBRCAmut 2L and non-gBRCAmut 2L+.

This approach can be accessed using the extrapolated trial data (D10 on the Model Set up sheet) and via the switches in cell C16 (RS OS dataset), C17 (Lord PFS dataset), C26 (SACT niraparib OS dataset) and C31 (apply PFS:TTD ratio to obtain niraparib PFS) on the Survival sheet of the economic model.

Table 10. Cost-effectiveness scenario results (deterministic) using SACT and Lord et al. data applied to the company base case – [redacted]% PAS

Technologies	Total costs (£)	Total LYG (years)	Total QALYs	Incremental. costs (£)	Incremental LYG (years)	Incremental QALYs	Incremental ICER (£/QALY)
ITT							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,976

Abbreviations: g*BRCA*mut, germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life years; SACT, Systemic Anti-Cancer Therapy dataset; TTD, time to treatment discontinuation.

B6. Priority question: The extrapolation of niraparib overall survival (OS) based on Kaplan-Meier (KM) data from NOVA appears to overpredict survival for the gBRCAmut 2L subgroup. Please clarify why splines/other flexible approaches were not explored for the modelling of overall survival?

a) The ERG has explored the other standard parametric distributions for niraparib OS and found none fit the observed data well. Please explore flexible spline models in scenario analyses.

Response:

The extrapolation of niraparib OS based on KM data from NOVA, included in the economic model for validation purposes only, appeared to over predict survival for the g*BRCA*mut 2L subgroup due to incorrect KM data included in the model. The KM data included in the model was for a broad definition of 2L which includes g*BRCA*mut 2L niraparib patients who have any line of chemotherapy, including only two lines of platinum-based chemotherapy (n=79) (

Figure 5). This has now been corrected to be based on the specific definition of 2L which includes g*BRCA*mut 2L niraparib patients who have only had two lines of chemotherapy, both of which were platinum-based chemotherapy (n=70) (Figure 6). This update means that the KM data now matches with all other analyses performed in the model for the g*BRCA*mut 2L population. On this basis it can be observed that the lognormal curve fits the data well and does not overpredict. Nonetheless, as requested, flexible spline models have been explored.

The Company can confirm that within the economic model, the data which feeds into the results (survival coefficient data) is correct for the niraparib gBRCAmut 2L (n=70) cohort and aligns with Table 4 in the company response to ERG clarification letter. Therefore, the cost-effectiveness results, sensitivity and scenario analyse provided are correct for this subgroup.

Figure 5. Incorrect broad definition of gBRCAmut 2L niraparib KM data with extrapolated lognormal curve

Figure 6. Corrected specific definition of gBRCAmut 2L niraparib KM data with extrapolated lognormal curve

As a first step, to determine if flexible spline models would be appropriate the hazard function plot and log-cumulative plots are provided in Figure 7 and Figure 8, respectively. The hazard rate for niraparib initially increases and then decreases at approximately 63 months, indicating one turning point. As per Decision Support Unit (DSU) Technical Support Document (TSD) 14, the log curves are suitable parametric

distributions for modelling this type of curve.[5] In addition, the log-cumulative plot has reasonably straight lines which also indicates that the log distributions are suitable.

Figure 7. Hazard functions of OS from NOVA (DCO October 2020) for niraparib in the gBRCAmut 2L population

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; DCO, data cut-off; OS, overall survival

Figure 8. Log-cumulative hazard plot of OS from NOVA (DCO October 2020) for niraparib in the gBRCAmut 2L population

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation; DCO, data cut-off; OS, overall survival

Table 11 summarises the AIC and BIC scores for the flexible spline distributions for the g*BRCA*mut 2L population. The proportion of niraparib patients surviving at key time points are presented in Table 12.

The odds k=1, hazards k=0 and normal k=0 distributions, which are equivalent to the Weibull, log-logistic and lognormal curves, respectively, are statistically the best fitting curves when compared to the other flexible spline distributions. The statistical plausibility of these parametric distribution curves in relation to the other flexible spline distributions provides additional support for selecting the lognormal curve in the base case.

Table 13 summarises the mean OS for niraparib for the flexible distributions along with the estimated mean OS for RS (using the company base case PFS:OS ratio of 1:1). When compared with the mean OS value of 3.70 years for RS from long-term extrapolations of Study 19, of these statistically best fitting curves, the odds k=1 (equivalent to log-logistic) and normal k=0 (equivalent to lognormal) provide the most plausible estimates whilst ensuring niraparib OS remains conservative i.e. does not increase above the submitted base case OS estimate. However, in absence of this latter assumption, odds k=2 and normal k=3 also provide plausible estimates based on alignment with Study 19.

We maintain that the OS lognormal (equivalent to normal k=0) extrapolation is the most appropriate base case for niraparib for the g*BRCA*mut 2L population. However, Table 14 presents scenarios using the second-best fitting curve, log-logistic (equivalent to odds k=0), and other plausible curves (odds k=2 and normal k=3). In these scenarios there is minimal variation in the ICER from £19,475 (base case) to £19,454, £19,606 and £19,558 per QALY gained, respectively. This scenario can be accessed via the switch and input cells F51:53 on the Model setup sheet of the economic model.

Table 11: Goodness of fit statistics for flexible spline models for niraparib in the gBRCAmut 2L population

	Hazards k=0	Hazards k=1	Hazards k=2	Hazards k=3	Odds k=0	Odds k=1	Odds k=2	Odds k=3	Normal k=0	Normal k=1	Normal k=2	Normal k=3
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike Information Criterion; gBRCAmut, germline breast cancer susceptibility gene mutation; RS, routine surveillance

Table 12: Proportion surviving and progression-free at key timepoints for the lognormal and flexible spline models for niraparib in the gBRCAmut 2L population

Year	Company's base case (lognormal)	Hazards k=0	Hazards k=1	Hazards k=2	Hazards k=3	Odds k=0	Odds k=1	Odds k=2	Odds k=3	Normal k=0	Normal k=1	Normal k=2	Normal k=3
Niraparib													
5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
10	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
15	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
20	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Abbreviations: AIC, Akaike Information Criterion.

Table 13: Goodness of fit statistics for flexible spline models for niraparib in the gBRCAmut 2L population

	Hazards k=0	Hazards k=1	Hazards k=2	Hazards k=3	Odds k=0	Odds k=1	Odds k=2	Odds k=3	Normal k=0	Normal k=1	Normal k=2	Normal k=3
Niraparib mean OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RS OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike Information Criterion; g*BRCA*mut, germline breast cancer susceptibility gene mutation; RS, routine surveillance.

Table 14: Cost-effectiveness scenario results (deterministic) of the flexible odds k=0, odds k=2 and normal k=3 curve for niraparib OS applied to the revised company base case in the gBRCAmut 2L population – [redacted]% PAS

Technologies	Total costs (£)	Total LYG (years)	Total QALYs	Incremental. costs (£)	Incremental LYG (years)	Incremental QALYs	Incremental ICER (£/QALY)
Odds k=0 (log-logistic)							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,454
Odds k=2							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,606
Normal k=3							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,558

Abbreviations: g*BRCA*mut, germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; PAS, patient access scheme; PFS, progression-free survival.

References

1. GSK. Data on file. Clinical expert engagement. April 2021. 2021.
2. Friedlander M, Matulonis U, Gourley C, *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: 1075–1085.
3. Lord R, Rauniyar J, Morris T, *et al.* Real world outcomes in platinum sensitive relapsed ovarian, fallopian tube, or peritoneal cancer treated in routine clinical practice in the United Kingdom prior to poly-ADP ribose polymerase inhibitors. *Int J Gynecol Cancer* 2020. 30: 1026–1033.
4. Public Health England. Niraparib for treating ovarian cancer – data review. 2021.
5. Latimer NR. NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14. Survival Analysis for Economic Evaluations Alongside Clinical Trials—Extrapolation with Patient-Level Data: Inconsistencies, Limitations, and a Practical Guide. *Med Decis Making* 2013. 33: 743–754.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Cancer Drugs Fund review of technology appraisal 528 of niraparib as maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1644]

Thank you for agreeing to give us your organisation's 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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Gynaecological Cancer Society (BGCS)**

3. Job title or position	**Medical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	BGCS is a multidisciplinary group of health providers working and researching the area of gynaecological cancers. We represent trainees, nurses, unit leads, oncologists, pathologists and radiologists and as such can discuss and formulating policy on gynaecological cancer research and treatment. The society is made up of a membership who must be introduced to and approved by the council and who pay an annual membership fee.
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.]	GSK are one of a number of pharmaceutical companies who provide sponsorship for the BGCS annual educational meetings.

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**no**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	This is an oral maintenance treatment following response to platinum-base chemotherapy aiming to slow progression and delay the time to need further intravenous systemic anti-cancer treatment. This is not a curative intervention.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Increased progression-free survival and increased time to subsequent therapy while maintaining quality of life

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There are a number of unmet needs in advanced ovarian cancer but the delivery of oral maintenance PARPi in the platinum-sensitive population as per this indication is a significant advance in the treatment of relapsed disease
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Currently relapsed disease is treated with carboplatin-based chemotherapy and in those who respond oral PARP inhibitor treatment (Niraparib, Olaparib, Rucaparib) is offered – the choice of PARPi dependent on the BRCA status of the individual and consequent funding available
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	As per NICE: relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy in adults, only if they have a germline BRCA mutation and have had 2 courses of platinum-based chemotherapy or they do not have a germline BRCA mutation and have had 2 or more courses of platinum-based chemotherapy (NICE pathways – Managing Advanced Ovarian Cancer)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Pathway defined and in England it is limited by funding as above but choice of individual PARPi may vary from centre to centre with individual preference where funding may allow the option of more than one PARPi eg Rucaparib or Niraparib at 1st relapse.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	It has had a big impact on the pathway of care since introduced and as an oral therapy, during the COVID-19 pandemic, maintaining women on outpatient treatment with remote consultations and delaying the need for intravenous chemotherapy has been invaluable.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Already used as standard of care in NHS clinical practice
• How does healthcare resource use differ between the technology and current care?	n/a
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care within specialist outpatient clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Already running as standard

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	This provides clinically meaningful benefits compared with no maintenance treatment
• Do you expect the technology to increase length of life more than current care?	yes
• Do you expect the technology to increase health-related quality of life more than current care?	yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There is greater benefit with PARPi maintenance for those with a BRCA1 or BRCA2 mutation (germline or somatic) and for those with non-BRCA HRD (homologous recombination defects) but all patients who have responded to platinum-based therapy can benefit even those who have homologous recombination proficient disease (approx. 50%) albeit to a lesser extent.
The use of the technology	

13. 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.)	Already running . If not offering oral maintenance therapy as standard of care there is a requirement for monthly blood tests, blood pressure monitoring and clinical review which might otherwise have been approximately 3 monthly if receiving no maintenance therapy. However blood tests and blood pressure measurements can be performed in the community and medications sent to patients alongside virtual clinic appointments to minimise hospital attendances for patients.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment is continued until unacceptable toxicity or disease progression
15. 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?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	yes
• Is the technology a 'step-change' in the management of the condition?	yes
• Does the use of the technology address any particular unmet need of the patient population?	Improves outcomes for patients with relapsed disease responding to platinum-based chemotherapy

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	These medications are well -tolerated and side effects are rarely severe. They occur predominantly in the first few cycles of treatment and can be readily managed with dose adjustments and supportive medications and clinical trials have repeatedly confirm that they do not impact negatively on quality of life.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• 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 subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA528]?	J Clin Oncol 2019 Nov 10; 37(32):2968-2973 (NOVA trial results according to response to chemo) Gynaecol Oncol 2020 Nov;159(2):442-448 (Long term safety data for the NOVA trial) Lancet Oncol 2018 Aug;19(8):1117-1125 (Quality of life data for the NOVA trial) Annals of Oncology 2021 Apr:32(4):512-521 (NORA study of niraparib maintenance for platinum-sensitive recurrent ovarian cancer – individualised starting dose)
21. How do data on real-world experience compare with the trial data?	MONITOR-UK is a multicentre study recruiting retrospective and prospective patients receiving maintenance Niraparib as standard of care in the NHS and assessing toxicity and quality of life in the real world (recruitment ongoing currently)

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.	
Key messages	
23. In up to 5 bullet points, please summarise the key messages of your submission. • • • • •	

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Ovarian cancer (relapsed, platinum-sensitive) - niraparib (maintenance) (CDF Review of TA528) [ID1644]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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- 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 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 10 full-time members of staff and 2 part-time; there is also 1 full-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.]	£300 from Clovis Oncology for video interview of cancer patient discussing impact of treatment £300 from Clovis Oncology for speaking engagement: By Victoria Clare, CEO - talk: 'What Do Patients Need?' 11 June 2020 £100 from Adelphi for speaking engagement by Victoria Clare £1,500 from GlaxoSmithKline for the first 25 hours' work on an awareness project. £240 from GlaxoSmithKline for Review of Zejula patient information booklet £10,000 from MSD for Survivors Teaching Students programme £10,000 from Pfizer for our Staying Connected programme of support £3,500 from Abbvie, £7,000 from Clovis Oncology, £7,000 from AstraZeneca, £3,500 from BMS and £10,500 from Roche for salaries for our Staying Connected programme of support*

If so, please state the name of manufacturer, amount, and purpose of funding.	*This income did not come to us directly but from a partnership with Ovarian Cancer Action (OCA).The funding was given to OCA and they then gave us funds towards our partnership project
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 there is no PARP inhibitor routinely available second line (second line PARP inhibitors are only available through the Cancer Drugs Fund). There is considerable benefit of having a maintenance therapy available where none existed before, regardless of BRCA or HRD status. The NOVA trial has proven Niraparib's efficacy in extending progression free survival for women with and without germline BRCA mutations and that health-related quality-of-life scores were similar between the niraparib and control arms. Our members tell us that PARP inhibitors are an easily managed treatment that they can take orally without the need to travel to hospital and enables them to have a good quality of life with tolerable side effects. 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?	Five of our members said: "I consider myself blessed that this treatment has been available for me. My quality of life is excellent, and, every day, I feel grateful for Niraparib, the NHS & Oncology Department." "… thanks to Niraparib I am a lot happier with my lot. I have a blood test every 8 weeks which is quite stressful until I see those figures, but apart from that I can mostly 'forget' the cancer. I also think it's about attitude to it too, I worked through 3 lots of chemo and am still working now. It's made me appreciate time off more and I won't say no to anything as life really is too short anyway without this. I love my Niraparib ❤️ I sometimes stress over how long it will work or will be funded for, but it is working and being funded for now so what's the point of worrying." "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

14. 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 NOVA trial has proven Niraparib's efficacy in extending progression free survival for women with and without germline 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

Cancer Drugs Fund review of technology appraisal 528 of niraparib as maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1644]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- 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 10 pages.

About you	
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 We are the only national charity fighting ovarian cancer on all three of these fronts, across all four nations of the UK. We are the authority on ovarian cancer. We work with women, family members, and health professionals to ensure we target the areas that matter most for those living and working with Target Ovarian Cancer is funded through voluntary donations and in the last 12 months we have been in receipt from two grants from manufacturers which are outlined below
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** May 2020 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, January 2021 £120 honorarium for a speaking engagement **AstraZeneca** August 2020 a £20,000 grant. The grant for the running of Target Ovarian Cancer's nurse-led support line and online support to women 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?	• Anecdotal feedback from patients and their families. • Patient survey on access to cancer drugs. • Calls to the Target Ovarian Cancer support line, questions submitted to our Ask the Experts forum and questions/comments posted on social media.
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?	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 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 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?	*"The latest drugs offer hope and the chance that women with progressive disease can enjoy a better quality of life and longer survival. If new drugs are not made available, the current survival rates will continue to be dire in comparison with other cancers and this has to change. Women with ovarian cancer should be given the same right to life as those with other, more widely supported, cancers."* Woman with ovarian cancer Platinum-based chemotherapy is effective in maintaining stable disease, and helping alleviate the impact of ovarian cancer symptoms. However, platinum-based chemotherapy will cause some side effects which women find difficult to manage, including tiredness and fatigue, hair loss, nausea and vomiting, and tingling and numbness in the fingers and toes. In order to maximise the benefits of platinum-based chemotherapy it is crucial to increase the time intervals between chemotherapy cycles, this works to reduce the risk of the ovarian cancer developing platinum-resistance and the individual developing an allergic reaction. If sensitivity to platinum chemotherapy is maintained women can expect to be effectively treated with this regimen for multiple

	recurrences, however, most women will eventually become platinum-resistant. This is why progression free survival (PFS) is hugely important to women who have had a recurrence *Very limited options, with limited success new treatments are urgently needed*" Woman with ovarian cancer
8. Is there an unmet need for patients with this condition?	Platinum-based chemotherapy is the primary treatment for recurrent platinum-sensitive ovarian cancer. However, the risk of developing platinum resistance is high. Treatment for platinum-resistant disease is extremely limited. Maintenance treatments like niraparib give patients and clinicians a valuable opportunity to extend the progression free survival period and therefore the interval between chemotherapy treatment. This can prolong the efficacy of standard platinum-based chemotherapy; delaying the onset of platinum drug resistance. There are currently no maintenance treatments available in routine commissioning for women who do not have a BRCA mutation.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	**Choice** – niraparib gives clinicians and women another option for extending progression free survival (PFS). Many women welcome the opportunity to be involved in making decisions about their care and treatments they receive, and feel they are able to take some control at what is typically a very uncertain time. There are also no maintenance treatments available in routine commissioning for women who do not have a BRCA mutation. *'Women with ovarian cancer usually have very little time to live. My mum would have liked six months to put her affairs in order and say goodbye to people. If a drug can do this, she should have been able to access it.'* Family member of a woman with ovarian cancer

	'(it was) a relief to have an alternative other than having to waiting for the another round of chemo. It has given me hope in extending my life. My quality of life has been great . I'm swimming three or four times a week, doing exercise classes and can walk up to five or six miles a day. The real advantage is the mental health effects. I can relax a little and not be constantly worrying that my cancer is growing or not stable' Woman who had taken niraparib **Best possible care** – often women are aware of the poor outcomes associated with ovarian cancer. By accessing niraparib as part of their treatment plan, they may feel they are giving themselves the best possible chance of prolonging the disease free interval. *'I felt optimistic and that my future seemed much brighter, and full of possibilities. I was pleased I would be monitored regularly and have been taking it now for 18 months and so far so good.'* Woman who had taken niraparib *'Niraparib has given me the chance to lead a useful, active and fulfilling life, with manageable side effects'* Woman who had taken 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 **Physical wellbeing** - once a woman has recurrent ovarian cancer she will inevitably go through further treatment cycles for subsequent recurrences. Niraparib offers women the opportunity to extend their PFS and therefore the interval between chemotherapy, this benefit is likely for many to outweigh the possible side effects associated with niraparib. A longer PFS may be beneficial in terms of supporting a better physical recovery from chemotherapy, enabling the individual to successfully undergo subsequent

	treatment. It is thought that prolonging the interval between treatments is likely to make subsequent treatment more effective. **Emotional/mental health** – once a woman has been diagnosed with recurrent ovarian cancer, further recurrence will be expected as the cancer runs its course. For many, receiving the news that their cancer has returned can be more devastating than the initial ovarian cancer diagnosis. Improvement in PFS offered by niraparib will allow give women valuable time to recover from the mental impact of recurrence and treatment, allowing them to resume normality, and live their lives as fully as possible. *'My quality of life has been great . I'm swimming three or four times a week, doing exercise classes and can walk up to five or six miles a day. The real advantage is the mental health effects. I can relax a little and not be constantly worrying that my cancer is growing or not stable'* Woman who had taken niraparib *'Niraparib has given me the chance to lead a useful, active and fulfilling life, with manageable side effects and has enabled me to be around too welcome 2 grandsons into the family, something I didn't think I'd live to see – I don't regret starting it for a single minute. I wanted it to carry on working for ever, though even now, it doesn't appear to have stopped working entirely, and I'm so thankful I got the opportunity to have the drug'* Woman who had taken niraparib **Mode of delivery** – niraparib is administered orally which is well tolerated.

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. *'I felt anxious when I first started taking Niraparib because of the long list of side effects (like chemo). My oncologist assured me that I would probably be ok on the drug as had minimal side effects from chemo. I've been very lucky and had relative few effects. I felt quiet confident in taking the drug, knowing how thorough the research was behind the drug'* 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 *'Stared at 300mg,then 200mg now 100mg doing ok lots of side effects but better than chemo" Woman who had taken niraparib'* 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	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- 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.
- Women diagnosed with ovarian cancer are likely to experience multiple recurrences. Extending PFS is beneficial in supporting a woman's physical and emotional recovery between chemotherapy treatment.

- Multiple rounds of platinum-based chemotherapy are associated with cumulative toxicities eg peripheral neuropathy, and an increased likelihood of developing drug resistance. Maintenance therapies like niraparib which extend the time between platinum-based chemotherapy may reduce toxic effects and prolong tumour response to chemotherapy.
- Niraparib is available to women regardless of BRCA mutation which means more women will be able to access the treatment. There are currently no maintenance treatments available in routine commissioning for women who do not have a BRCA mutation.

Thank you for your time.

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Public Health England

Protecting and improving the nation's health

Niraparib for treating ovarian cancer – data review

Commissioned by NHS England and NHS Improvement

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Public Health England exists to protect and improve the nation's health and wellbeing and reduce health inequalities. We do this through world-leading science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health and Social Care, and a distinct delivery organisation with operational autonomy. We provide government, local government, the NHS, Parliament, industry and the public with evidence-based professional, scientific and delivery expertise and support.

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Contents

Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of niraparib for the maintenance treatment of patients diagnosed with ovarian cancer. The appraisal committee highlighted clinical uncertainty around estimates of treatment duration and overall survival (OS) in the evidence submission. As a result, they recommended commissioning of niraparib through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned Public Health England (PHE) to evaluate the real-world treatment effectiveness of niraparib in the CDF population during the managed access period. This report presents the results of the use of niraparib, in clinical practice, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and PHE partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 94% of patients and 85% of patient outcomes reported in the SACT dataset. PHE and NHS England and NHS Improvement are committed to providing world first high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for niraparib for ovarian cancer in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE's routinely collected SACT data to provide SACT treatment history.

Between 01 June 2018 and 30 November 2019, 1,175 applications for niraparib were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 1,016 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

1,016 (95%) unique patients with CDF applications were reported in the SACT dataset.

Median treatment duration for the **germline BRCA mutation** analysis cohort was 12.2 months[a](371 days). 71% [95% CI: 63%,77%] of patients were receiving treatment at 6 months and 51% [95% CI: 42%, 60%] of patients were receiving treatment at 12 months.

Median treatment duration for the **no germline BRCA mutation** analysis cohort was 6.4 months (194 days) [95% CI: 6.0,7.1]. 54% [95% CI: 50%,57%] of patients were receiving treatment at 6 months and 28% [95% CI: 24%, 32%] of patients were receiving treatment at 12 months.

At data cut off for the **germline BRCA mutation** cohort, 43% (N=68) of patients were identified as no longer being on treatment; 56% (N=38) of patients stopped treatment due to progression, 18% (N=12) of patients stopped treatment due to acute toxicity, 6% (N=4) of patients chose to end their treatment, 7% (N=5) of patients died not on treatment and 13% (N=9) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

At data cut off for the **no germline BRCA mutation** cohort, 59% (N=509) of patients were identified as no longer being on treatment; 64% (N=325) of patients stopped treatment due to progression, 12% (N=61) of patients stopped treatment due to acute toxicity, 4% (N=21) of patients chose to end their treatment, 10% (N=53) of patients died not on treatment, 1% (N=6) of patients died on treatment and 8% (N=43) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

The median overall survival for the germline BRCA mutation cohort was not reached. OS at 6 months was 96% [95% CI: 96%, 98%], OS at 12 months was 89% [95% CI: 89%, 93%].

The median overall survival for the no germline BRCA mutation cohort was not reached. OS at 6 months was 94% [95% CI: 92%, 96%], OS at 12 months was 78% [95% CI: 75%, 84%].

A sensitivity analysis was conducted for a cohort with at least 6 months data follow-up in the SACT dataset. Results for treatment duration and survival were consistent with the full analysis cohort. Any differences were not significant.

Conclusion

This report analyses SACT real world data for patients treated with niraparib for ovarian cancer in the CDF. It evaluates treatment duration, overall survival and treatment outcomes for all patients treated with niraparib for this indication.

[a] Confidence intervals for treatment duration could not be produced for the germline BRCA mutation cohort as there was an insufficient number of events at the time this report was produced

Introduction

Ovarian cancers are rare cancers and account for 4% of all cancer diagnoses amongst women. In 2017, 5,676 women were diagnosed with ovarian cancer[2].

Niraparib is recommended for use within the Cancer Drugs Fund as an option for treating relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy in adults[3], only if:

- they have a germline BRCA mutation and have had 2 courses of platinum-based chemotherapy or
- they do not have a germline BRCA mutation and have had 2 or more courses of platinum-based chemotherapy and
- the conditions in the managed access agreement for niraparib are followed.

Background to this report

The Public Health England and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England and NHS Improvement and Public Health England's (PHE's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by PHE. This includes NHS England and NHS Improvement commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England[4]. From the 29th July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical and cost effectiveness. During this period of managed access, ongoing data collection is used to answer the uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

PHE will analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of PHE.

NICE Appraisal Committee review of niraparib for treating ovarian cancer [TA528].

The NICE Appraisal Committee reviewed the evidence for the clinical and cost effectiveness of niraparib in treating ovarian cancer [TA528] and published guidance for this indication in July 2018[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended commissioning of niraparib through the CDF for a period of 24 months, from June 2018 to June 2020.

During the CDF funding period, results from an ongoing clinical trial evaluating niraparib in the licensed indication is likely to answer the main clinical uncertainties raised by the NICE committee. The ongoing trial to support the evaluation of niraparib is ENGOT-OV16/NOVA[7]. Data collected from the ENGOT-OV16/NOVA clinical trial would be the primary source of data collection.

Analysis of the SACT dataset would provide information on real-world treatment patterns and outcomes for niraparib for ovarian cancer in England, during the CDF funding period. This would act as a secondary source of information alongside the results of the ENGOT-OV16/NOVA clinical trial[7].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- **Treatment duration** for the use of niraparib
- **Overall survival** from the start of a patient's first treatment with niraparib

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, PHE and the company (GSK) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of niraparib. It also detailed the eligibility criteria for patient access to niraparib through the CDF and CDF entry and exit dates.

This report includes patients with approved CDF applications for niraparib, approved through Blueteq® and followed-up in the SACT dataset collected by PHE.

Methods

CDF applications - identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. PHE has access to the Blueteq database and key data items such as NHS numbers, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the EU General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). The processing of special categories of personal data is also covered under article 9(2)(h) of EU GDPR (processing is necessary for the purposes of preventive or occupational medicine). As NHS E & I do not have an exemption to the Common Law Duty of Confidentiality, NHS E & I cannot access the identifiable data directly. PHE, through the National Cancer Registration and Analysis Service have permission to process confidential patient information though Regulation 2 of The Health Service (Control of Patient Information) Regulations 2002.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Niraparib clinical treatment criteria

- Clinician is aware of the likely toxicities of niraparib, the associated monitoring required and the reasons why 48% of patients in the ENGOT-OV16/NOVA trial had dose interruptions in the 1st cycle and 47% commenced their 2nd cycle at a reduced niraparib dosage
- Patient has a confirmed histological diagnosis of predominantly high grade serous epithelial ovarian, fallopian tube or primary peritoneal carcinoma
- <12 weeks since the patient completed 2nd line chemotherapy
- Patient has not previously received any PARP inhibitor
- Patient has an ECOG performance status of either 0 or 1. A patient with a performance status of 2 or more is not eligible for niraparib
- Niraparib will be continued until disease progression or unacceptable toxicity or patient choice to stop treatment
- A formal medical review will be conducted by at least by the start of the second cycle of treatment. This review will discuss whether maintenance treatment with niraparib should continue or not and the dose which should be used
- Niraparib will be used as monotherapy
- No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed. Treatment breaks of <6 weeks are permitted to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve
- Niraparib is otherwise to be used as set out in its Summary of Product Characteristics

Key patient eligibility criteria for the use of niraparib in the Cancer Drugs Fund in adults with a germline BRCA mutation who have received 2 courses of platinum-based chemotherapy include:

- Patient has had a germline BRCA test and a documented germline BRCA mutation
- Patient has relapsed following 1st line chemotherapy (i.e. the penultimate line of treatment) and had platinum-sensitive disease at this relapse. Platinum sensitivity is defined by a complete or partial remission which lasted for more than 6 months following completion of 1st line platinum-based chemotherapy (whether given pre- and/or post-operatively or if the patient did not have surgery)
- Patient is in a complete or partial response following completion of 2nd line platinum-based chemotherapy (i.e. the most recent chemotherapy) and that the serum CA125 is either normal or has demonstrated a >90% decrease from before the initiation of 2nd line chemotherapy and is stable

Key patient eligibility criteria for the use of niraparib in the Cancer Drugs Fund in adults without a germline BRCA mutation who have received 2 or more courses of platinum-based chemotherapy include:

- Patient has had a germline BRCA test and does not have a documented germline BRCA mutation.
- Patient relapsed following penultimate line of chemotherapy (i.e. the line of treatment preceding the most recent line of chemotherapy) and had platinum-sensitive disease at this relapse. Platinum sensitivity is defined by a complete or partial remission which lasted for more than 6 months following completion of penultimate line of platinum-based chemotherapy (whether given pre-and/or post-operatively or if the patient did not have surgery)

- Patient is in a complete or partial response following completion of the most recent line platinum-based chemotherapy which must be at least second line treatment and that the serum CA125 is either normal or has demonstrated a >90% decrease from before the initiation of 2nd line chemotherapy and is stable

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

- If two trusts apply for niraparib for the treatment of ovarian cancer for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

- If two trusts apply for niraparib for the treatment of ovarian cancer for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

- If two applications are submitted for niraparib for the treatment of ovarian cancer and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

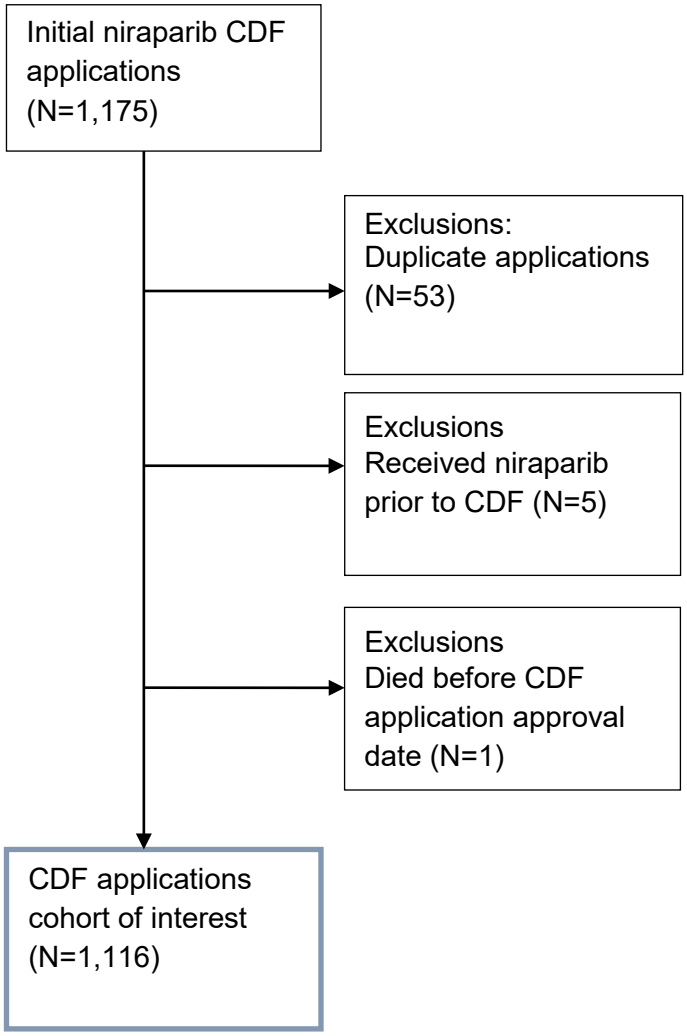
The analysis cohort is limited to the date niraparib entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the pharmaceutical company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 01 June 2018 to 30 November 2019. A snapshot of SACT data was taken on 4 April 2020 and made available for analysis on the 14 April 2020. The snapshot includes SACT activity up to the 31 December 2019. Tracing the patients' vital status was carried out on 22 May 2020 using the personal demographics service (PDS)[1].

There were 1,175 applications for CDF funding for niraparib for ovarian cancer between 01 June 2018 and 30 November 2019 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 1,122 unique patients.

Five patients were excluded from these analyses as they appeared to have received niraparib prior to the drug being available through the CDF and one patient was excluded as they died before the blueteq approval date.

Figure 1: Derivation of the cohort of interest from the initial CDF applications made for niraparib for ovarian cancer between 1 June 2018 and 30 November 2019.



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for niraparib in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[8] used to determine a patient's earliest treatment date are:

- Start date of regimen – SACT data item #22
- Start date of cycle – SACT data item #27
- Administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)[8] are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen
A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle
A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date
An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length' which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Niraparib is administered orally, treatment is generally prescribed in a healthcare facility and healthcare professionals are able to confirm that the prescribing of treatment has taken place on a specified date. A duration of 28-days has been added to final treatment date for all patients; this represents the duration from a patient's last cycle to their next[9]. Niraparib is a 28-day cycle consisting of one administration.

Treatment duration is calculated for each patient as:
Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days).

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died.
- the outcome summary (SACT data item #41) detailing the reason for stopping treatment has been completed.
- there is no further SACT records for the patient following a three-month period.

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead/alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) – treatment start date

The patient is flagged as either:

Dead (event):
At the date of death recorded on the PDS.

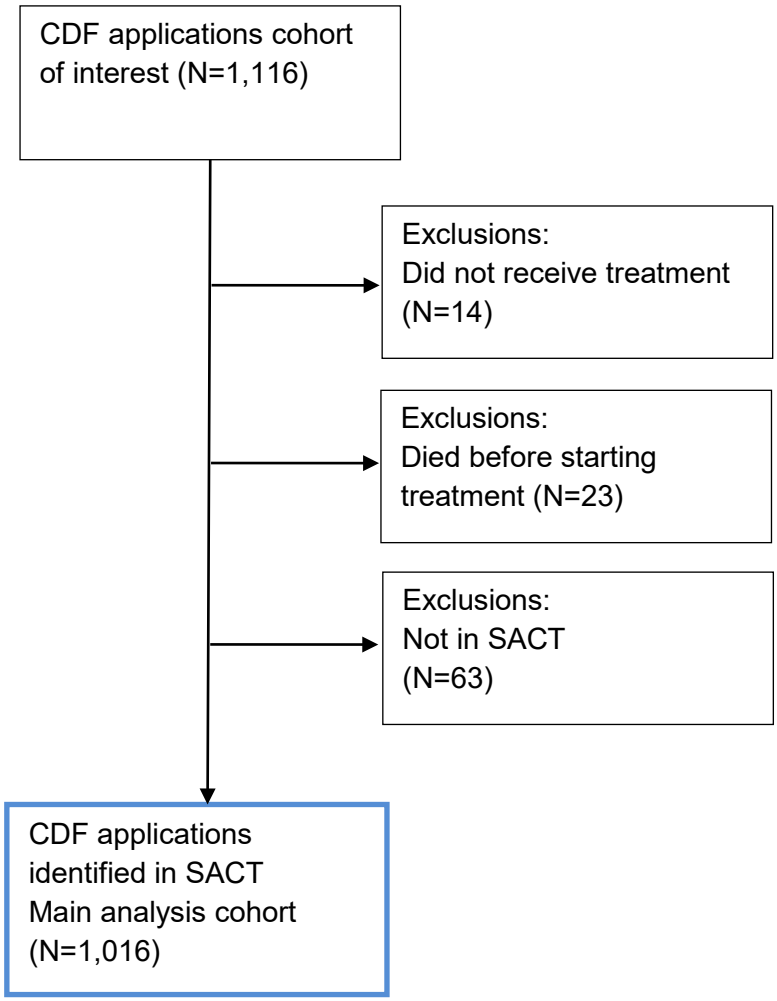
Alive (censored):
At the date patients were traced for their vital status as patients are confirmed as alive on this date.

Results

Cohort of interest

Of the 1,116 new applications for CDF funding for niraparib for ovarian cancer, 14 patients did not receive treatment, of which, one patient went on to receive urgent chemotherapy treatment instead, 23 patients died before treatment and 63 patients were missing from SACT [b] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for niraparib for ovarian cancer between 1 June 2018 and 30 November 2019



[b] Of the 14 patients that did not receive treatment, 13 were confirmed with the relevant trusts by the PHE data liaison team and one patient started a different therapy within a month of their CDF application form. Of the 23 patients that died before treatment, 16 were confirmed with the relevant trusts by the PHE data liaison team.

A maximum of 1,079 niraparib records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 94% (1,016/1,079) of these applicants for CDF funding have a treatment record in SACT.

Blueteq application forms

Table 1 presents a breakdown of mutation status, as recorded on the Blueteq application, for CDF patients.

Table 1: Breakdown of germline BRCA mutation (N=1,016)

Variable	N	(%)
Germline BRCA mutation	157	15%
No germline BRCA mutation	859	85%
Total	**1,016**	**100%**

Completeness of SACT key variables

Table 2 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 84% complete for the germline BRCA mutation cohort and 85% complete for the no germline BRCA mutation cohort.

Table 2: Completeness of key SACT data items for the niraparib cohort (N=1,016)

Variable	Germline BRCA mutation Completeness (%)	No germline BRCA mutation Completeness (%)
Primary diagnosis	100%	100%
Date of birth (used to calculate age)	100%	100%
Sex	100%	100%
Start date of regimen	100%	100%
Start date of cycle	100%	100%
Administration date	100%	100%
Performance status at start of regimen	84%	85%

Table 3 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with niraparib in at least three months. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 577 patients (68 germline BRCA mutation, 509 no

germline BRCA mutation). Of these, 489 (85%) have an outcome summary recorded in the SACT dataset.

Table 3: Completeness of outcome summary for patients that have ended treatment (N=577)

Variable	Germline BRCA mutation Completeness (%)	No germline BRCA mutation negative Completeness (%)
Outcome summary of why treatment was stopped	82%	85%

Patient characteristics

The median age amongst women who had the germline BRCA mutation and who are receiving niraparib for ovarian cancer was 60 years. The median age amongst women who did not have the germline BRCA mutation was 68.

Table 4: Germline BRCA mutation patient characteristics (N=157)

Patient characteristics[c]			
		Frequency (N)	Percentage (%)
Sex	Female	157	100%
Age	<40	3	2%
	40-49	21	13%
	50-59	52	33%
	60-69	46	29%
	70-79	29	18%
	80+	6	4%
Performance status	0	76	48%
	1	56	36%
	2	0	0%
	3	0	0%
	4	0	0%
	Missing/unknown	25	16%

[c] Figures may not sum to 100% due to rounding.

Table 5: No germline BRCA mutation negative patient characteristics (N=859)

Patient characteristics[d]			
		Frequency (N)	**Percentage (%)**
Sex	Female	859	100%
Age	<40	4	<1%
	40-49	27	3%
	50-59	169	20%
	60-69	283	33%
	70-79	324	38%
	80+	52	6%
Performance status	0	339	39%
	1	378	44%
	2	10	1%
	3	0	0%
	4	0	0%
	Missing/unknown	132	15%

[d] Figures may not sum to 100% due to rounding.

Time to subsequent treatments in SACT - germline BRCA mutation

36/157 (23%) unique patients treated with niraparib in the CDF have subsequent therapies recorded in the SACT dataset, received after the patient's last niraparib cycle. Table 6 reports regimens prescribed after niraparib, as recorded in the SACT dataset, some patients have more than one subsequent therapy.

The median time from a patient's last niraparib cycle in SACT to their next treatment was 53 days[e].

The median time from a patient's first niraparib cycle in SACT to their next treatment was 206 days.

Table 6: Distribution of subsequent treatments (N=36)[f,g]

Regimen	Total
Carboplatin + liposomal dox	9
Gemcarbo	8
Paclitaxel	6
Carboplatin	5
Liposomal doxorubicin	5
Cisplatin	2
Cisplatin + gemcitabine	2
Olaparib	2
Trial	2
Cisplatin + etoposide	1
Cyclophosphamide	1
Etoposide	1
Gemcitabine	1
Nab-paclitaxel	1
Total	**46**

[e] If a patient has > 1 subsequent regimen recorded in SACT, time to next treatment only includes regimen immediately after niraparib.
[f] Some patients will have received more than one subsequent therapy. Table 6 lists all subsequent therapies including those prescribed immediately after niraparib and in a subsequent treatment line.
[g] These data have not been validated/confirmed with trusts or by the SACT DLO team.

Time to subsequent treatments in SACT – no germline BRCA mutation

310/859 (36%) unique patients treated with niraparib in the CDF have subsequent therapies recorded in the SACT dataset, received after the patient's last niraparib cycle. Table 7 reports regimens prescribed after niraparib, as recorded in the SACT dataset, some patients have more than one subsequent therapy.

The median time from a patient's last niraparib cycle in SACT to their next treatment was 56 days[h].

The median time from a patient's first niraparib cycle in SACT to their next treatment was 164.5 days.

Table 7: Distribution of subsequent treatments (N=310) [i,j]

Regimen	Total
Paclitaxel	115
Gemcarbo	74
Liposomal doxorubicin	48
Carboplatin + liposomal dox	49
Carboplatin	31
Trial	18
Cisplatin + etoposide	11
Cyclophosphamide	9
Etoposide	9
Dice trial	7
Carboplatin + paclitaxel	7
Cisplatin + gemcitabine	5
Gemcitabine	5
Cisplatin + liposomal doxorubicin	3
Cisplatin + paclitaxel	3
Cisplatin	2
Topotecan	2
Carboplatin + docetaxel	1
Chlorambucil	1
Total	**400**

[h] If a patient has > 1 subsequent regimen recorded in SACT, time to next treatment only includes regimen immediately after niraparib.

[i] Some patients will have received more than one subsequent therapy. Table 7 lists all subsequent therapies including those prescribed immediately after niraparib and in a subsequent treatment line.

[j] These data have not been validated/confirmed with trusts or by the SACT DLO team.

Treatment duration - germline BRCA mutation

Of the 157 patients with CDF applications, 68 (43%) were identified as having completed treatment by 31 December 2019 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with niraparib in at least 3 months (see Table 8). The median follow-up time in SACT was 6.8 months (206 days).

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 19 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides the maximum follow-up period of 20 months. SACT follow-up ends 31 December 2019.

Table 8: Breakdown by patients' treatment status[k,l,m]

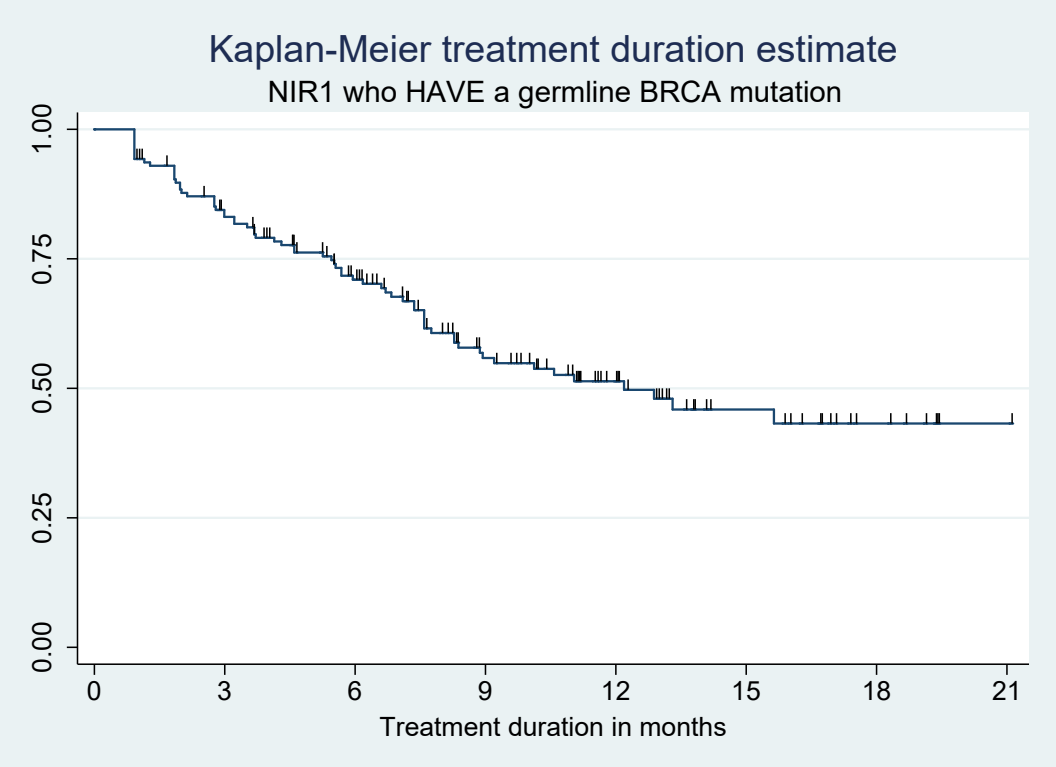
Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	27	17%
Treatment stopped	41	26%
Treatment ongoing	89	57%
Total	**157**	**100%**

[k] Figures may not sum to 100% due to rounding.
[l] Table 11 presents the outcome summary data reported by trusts. This includes patients from Table 8 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[m] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/

The Kaplan-Meier curve for ongoing treatment is shown in figure 3. The median treatment duration for all patients was 12.2 months[n] (371 days) (N=157).

71% of patients were still receiving treatment at 6 months [95% CI: 63%,77%], 51% of patients were still receiving treatment at 12 months [95% CI: 42%, 60%].

Figure 3: Kaplan-Meier treatment duration (N=157)



Tables 9 and 10 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 19 months (577 days).

Table 9: Number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0 - 21	3 - 21	6 - 21	9 - 21	12 - 21	15-21	18-21	21
Number at risk	157	124	89	56	31	17	7	1

[n] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced

Table 10 shows that for all patients who received treatment, 89 were still on treatment (censored) at the date of follow-up and 68 had ended treatment (events).

Table 10: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	0 - 21	3 - 21	6 - 21	9 - 21	12 - 21	15-21	18-21	21
Censored	89	82	64	48	27	16	7	1
Events	68	42	25	8	4	1	0	0

Table 11 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 82% (N=68) of patients had ended treatment at 31 December 2019.

Table 11: Treatment outcomes for patients that have ended treatment (N=68)[o,p]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	38	56%
Stopped treatment – acute chemotherapy toxicity	12	18%
Stopped treatment – patient choice	4	6%
Stopped treatment – died not on treatment[q]	5	7%
Stopped treatment – no treatment in at least 3 months	9	13%
Total	**68**	**100%**

[o] Figures may not sum to 100% due to rounding.
[p] Table 11 presents the outcome summary data reported by trusts. This includes patients from Table 8 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[q] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/

Table 12: Treatment outcomes and treatment status for patients that have ended treatment (N=68)

Outcome[r]	Patient died[s] not on treatment	Treatment stopped
Stopped treatment – progression of disease	16	22
Stopped treatment – acute chemotherapy toxicity	6	6
Stopped treatment – patient choice		4
Stopped treatment – died not on treatment	5	
Stopped treatment – no treatment in at least 3 months		9
Total	**27**	**41**

[r] Relates to outcomes submitted by the trust in table 11.

[s] Relates to treatment status in table 8 for those that have ended treatment.

Treatment duration – no germline BRCA mutation

Of the 859 patients with CDF applications, 509 (85%) were identified as having completed treatment by 31 December 2019 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with niraparib in at least 3 months (see Table 7). The median follow-up time in SACT was 4.6 months (139 days).

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 19 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides the maximum follow-up period of 20 months. SACT follow-up ends 31 December 2019.

Table 13: Breakdown by patients' treatment status[t,u,v]

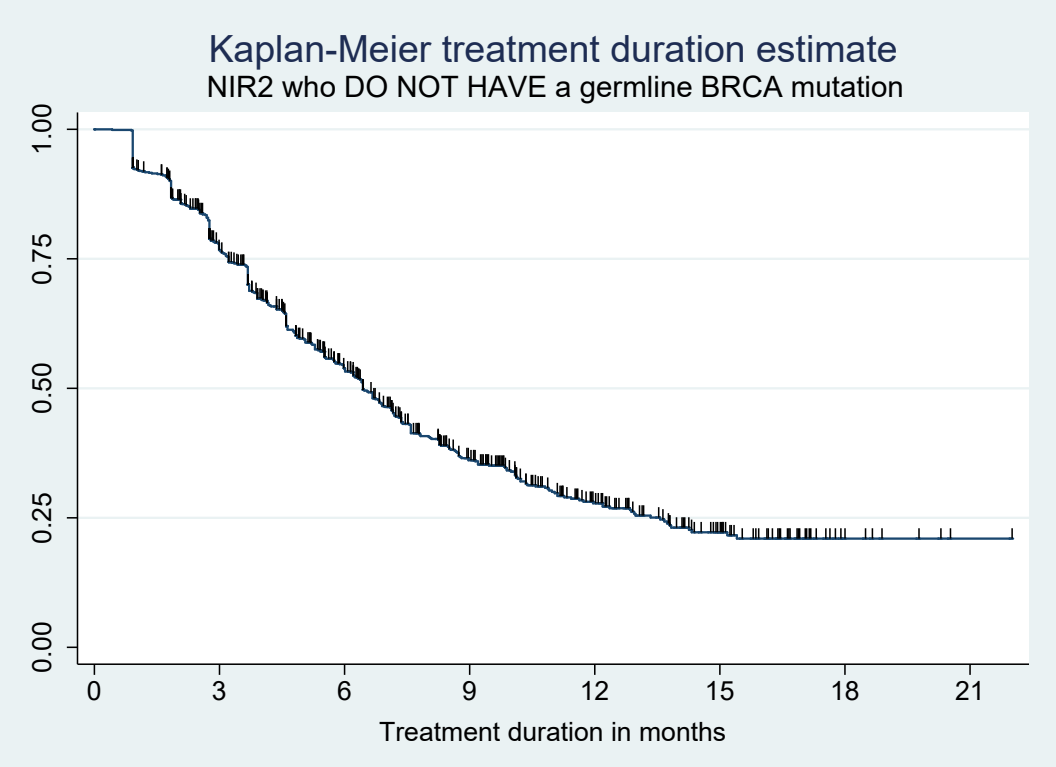
Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	230	27%
Patient died – on treatment	6	1%
Treatment stopped	273	32%
Treatment ongoing	350	41%
Total	**859**	**100%**

[t] Figures may not sum to 100% due to rounding.
[u] Table 16 presents the outcome summary data reported by trusts. This includes patients from Table 13 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[v] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/

The Kaplan-Meier curve for ongoing treatment is shown in figure 4. The median treatment duration for all patients was 6.4 months [95% CI: 6.0, 7.1] (194 days) (N=859).

54% of patients were still receiving treatment at 6 months [95% CI: 50%,57%], 28% of patients were still receiving treatment at 12 months [95% CI: 24%, 32%].

Figure 4: Kaplan-Meier treatment duration (N=859)



Tables 14 and 15 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 19 months (577 days).

Table 14: Number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0 - 21	3 - 21	6 - 21	9 - 21	12 - 21	15-21	18-21	21
Number at risk	859	593	346	176	91	39	7	1

Table 15 shows that for all patients who received treatment, 350 were still on treatment (censored) at the date of follow-up and 509 had ended treatment (events).

Table 15: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	0 - 21	3 - 21	6 - 21	9 - 21	12 - 21	15-21	18-21	21
Censored	350	276	193	125	74	37	7	1
Events	509	317	153	51	17	2	0	0

Table 16 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 59% (N=509) of patients had ended treatment at 31 December 2019.

Table 16: Treatment outcomes for patients that have ended treatment (N=509)[w,x]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	325	64%
Stopped treatment – acute chemotherapy toxicity	61	12%
Stopped treatment – patient choice	21	4%
Stopped treatment – died not on treatment[y]	53	10%
Stopped treatment – died on treatment	6	1%
Stopped treatment – no treatment in at least 3 months	43	8%
Total	**509**	**100%**

[w] Figures may not sum to 100% due to rounding.
[x] Table 16 presents the outcome summary data reported by trusts. This includes patients from Table 13 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[y] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/

Table 17: Treatment outcomes and treatment status for patients that have ended treatment (N=509)

Outcome[z]	Patient died [aa] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – progression of disease	152	173	
Stopped treatment – acute chemotherapy toxicity	21	40	
Stopped treatment – patient choice	4	17	
Stopped treatment – died not on treatment	53		
Stopped treatment – died on treatment			6
Stopped treatment – no treatment in at least 3 months		43	
Total	**230**	**273**	**6**

[z] Relates to outcomes submitted by the trust in table 16.

[aa] Relates to treatment status in table 13 for those that have ended treatment.

Overall survival - germline BRCA mutation

Of the 157 patients with a treatment record in SACT, the minimum follow-up was 5.7 months (173 days) from the last CDF application. Patients were traced for their vital status on 22 May 2020. This date was used as the follow-up date (censored date) if a patient is still alive.

The median follow-up time in SACT was 13.7 months (416 days). Figure 5 provides the Kaplan-Meier curve for overall survival, censored at 22 May 2020. The median survival was not reached. Survival at 6 months was 96% [95% CI: 96%, 98%], 12 months survival was 89% [95% CI: 89%, 93%].

Figure 5: Kaplan-Meier survival plot (N=157)

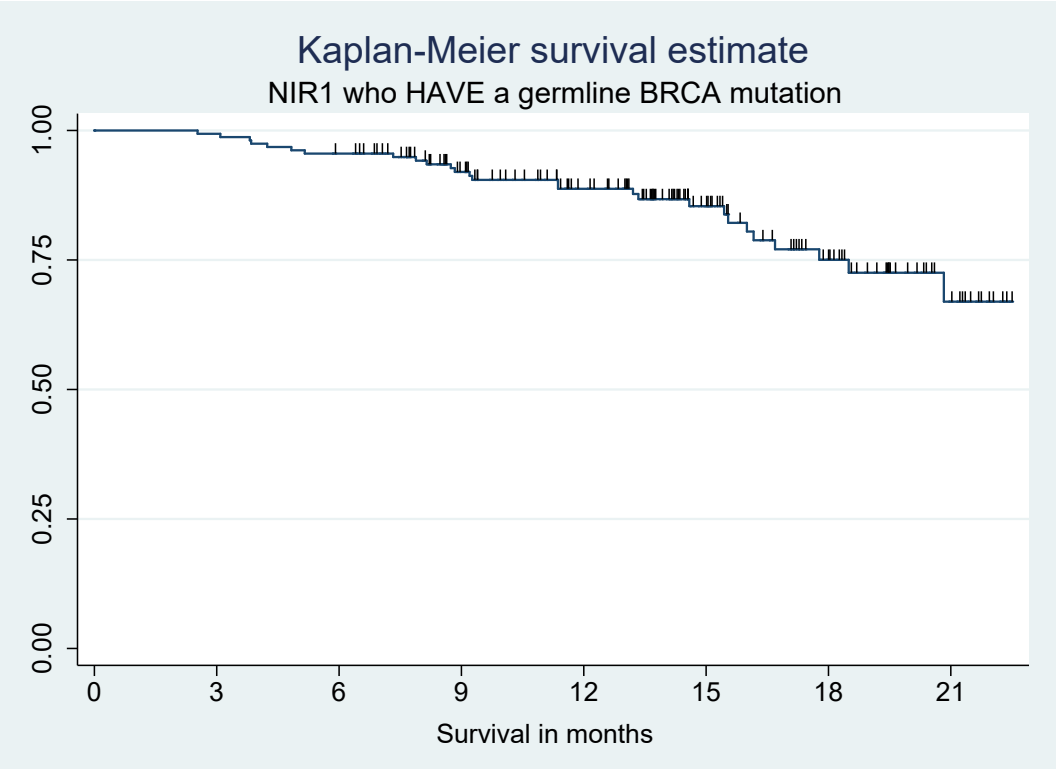


Table 18 and 19 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 23.7 months (721 days), all patients were traced on 22 May 2020.

Table 18: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Number at risk	157	156	149	123	98	59	34	11

Table 19 shows that for all patients who received treatment, 130 were still alive (censored) at the date of follow-up and 27 had died (events).

Table 19: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Censored	130	130	129	108	87	51	32	11
Events	27	26	20	15	11	8	2	0

Overall survival – no germline BRCA mutation

Of the 859 patients with a treatment record in SACT, the minimum follow-up was 5.7 months (173 days) from the last CDF application. Patients were traced for their vital status on 22 May 2020. This date was used as the follow-up date (censored date) if a patient is still alive.

The median follow-up time in SACT was 12 months (365 days). Figure 6 provides the Kaplan-Meier curve for overall survival, censored at 22 May 2020. The median survival was not reached. Survival at 6 months was 94% [95% CI: 92%, 96%], 12 months survival was 78% [95% CI: 75%, 81%].

Figure 6: Kaplan-Meier survival plot (N=859)

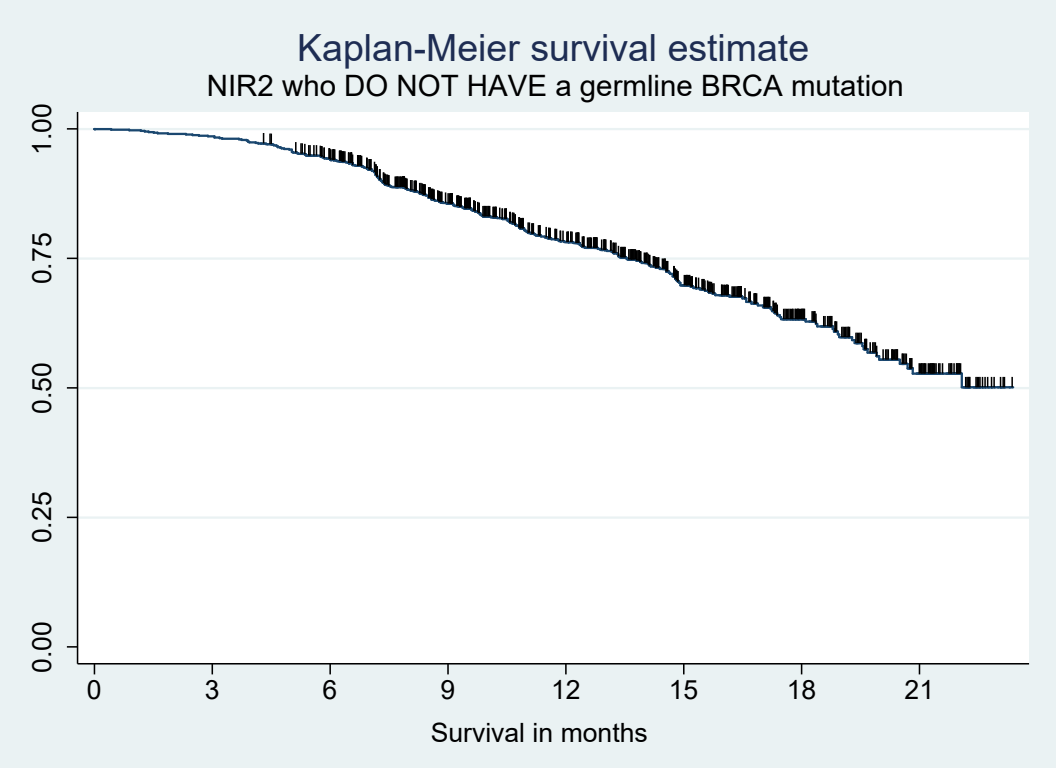


Table 20 and 21 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 23.7 months (721 days), all patients were traced on 22 May 2020.

Table 19: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Number at risk	859	847	789	587	429	276	143	46

Table 21 shows that for all patients who received treatment, 623 were still alive (censored) at the date of follow-up and 236 had died (events).

Table 21: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Censored	623	623	602	466	353	238	125	45
Events	236	224	187	121	76	38	18	1

Sensitivity analyses

Cohort 1: 6-month SACT follow up

Treatment duration

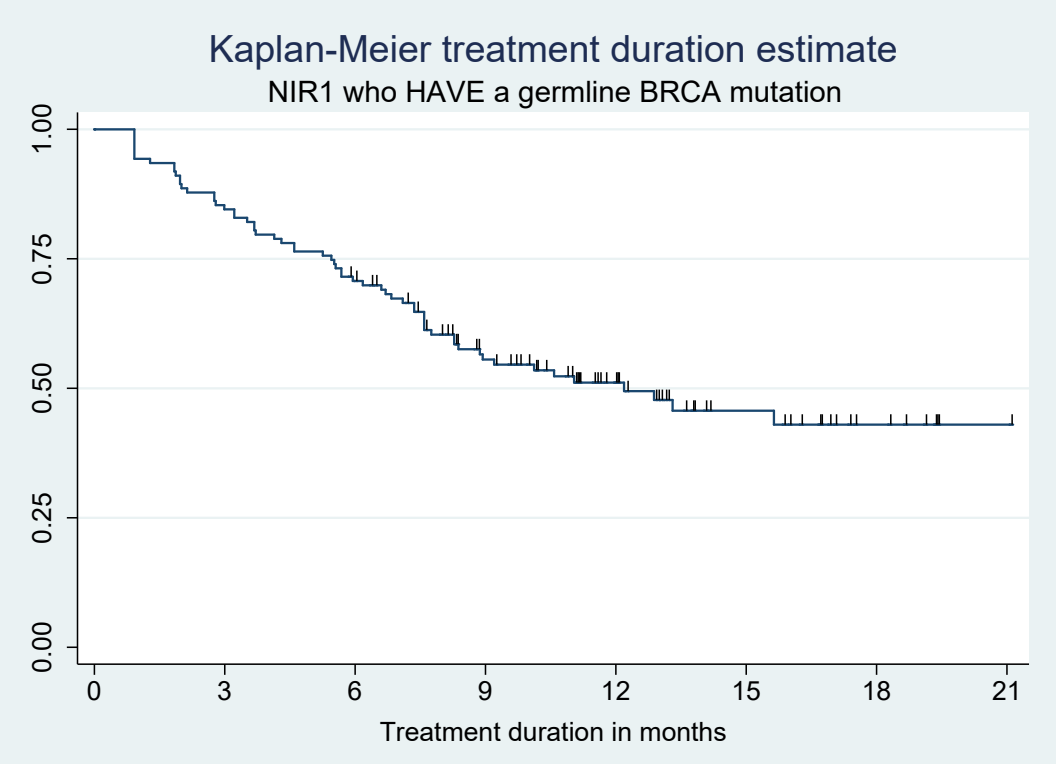
Sensitivity analyses was carried out on a cohort with at least 6 months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 01 June 2018 to 31 June 2019 and SACT activity was followed up to 31 December 2019.

Germline BRCA mutation

Following the exclusions above, 123 patients (78%) were included in these analyses. The median follow-up time in SACT was 8.3 months (252 days)

The Kaplan-Meier curve for ongoing treatment is shown in figure 7. The median treatment duration for patients in this cohort was 12.2 months[bb] (371 days) (N=123).

Figure 7: Kaplan-Meier treatment duration plot (N=123)



[bb] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced

Tables 22 and 23 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 19 months (577 days).

Table 22: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Number at risk	123	104	85	56	31	17	7	1

Table 23 shows that for all patients who received treatment, 62 were still on treatment (censored) at the date of follow-up and 61 had ended treatment (events).

Table 23: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

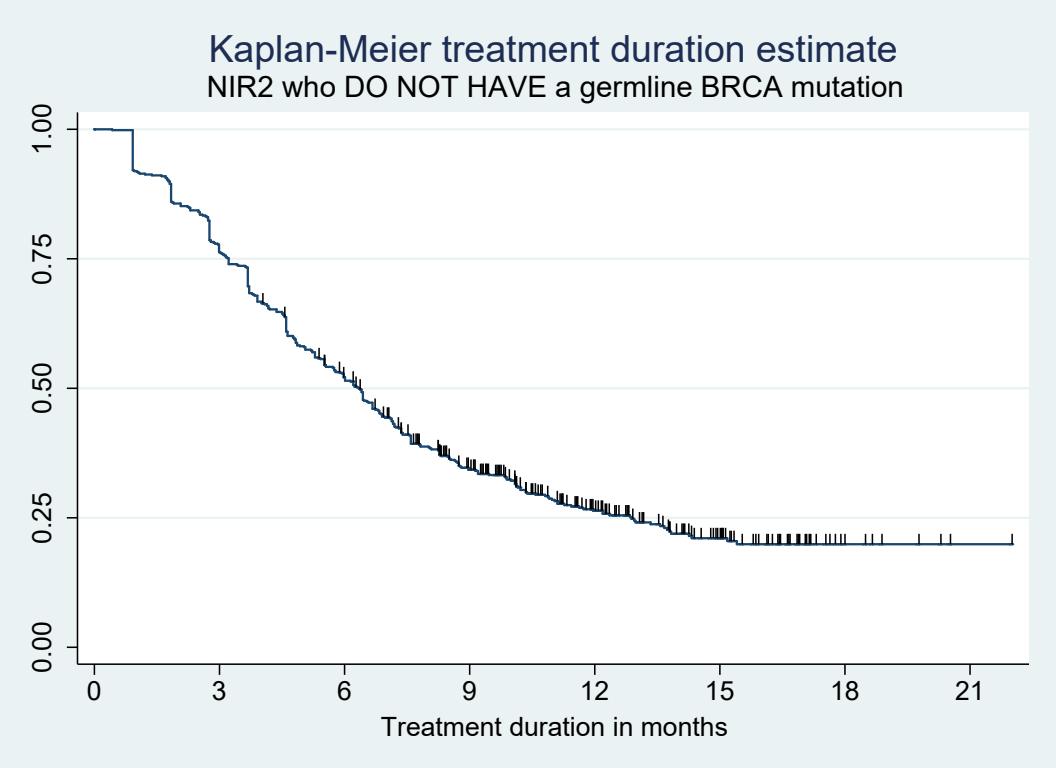
Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Censored	62	62	60	48	27	16	7	1
Events	61	42	25	8	4	1	0	0

No germline BRCA mutation

Following the exclusions above, 607 patients (71%) were included in these analyses. The median follow-up time in SACT was 6.2 months (188 days)

The Kaplan-Meier curve for ongoing treatment is shown in figure 8. The median treatment duration for patients in this cohort was 6.3 months [95% CI: 5.7, 6.7] (191 days) (N=607).

Figure 8: Kaplan-Meier treatment duration plot (N=607)



Tables 24 and 25 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 19 months (577 days).

Table 25: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Number at risk	607	463	310	174	91	39	7	1

Table 25 shows that for all patients who received treatment, 164 were still alive (censored) at the date of follow-up and 443 had died (events).

Table 25: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Censored	164	164	157	123	74	37	7	1
Events	443	299	153	51	17	2	0	0

Overall survival

Sensitivity analyses was also carried out for overall survival on a cohort with at least 6 months follow-up in SACT. To identify the cohort, CDF applications were limited from 01 June 2018 to 22 November 2019.

Germline BRCA mutation

Overall survival was not re-calculated for the germline BRCA mutation cohort as the last CDF application date for this indication was 12 November 2020.

No germline BRCA mutation

Following the exclusions above, 850 patients (99%) were included in these analyses. The median follow-up time in SACT was 12.1 months (368 days)

Figure 9 provides the Kaplan-Meier curve for overall survival, censored at 22 May 2020. The median survival was not reached.

Figure 9: Kaplan-Meier survival plot (N=850)

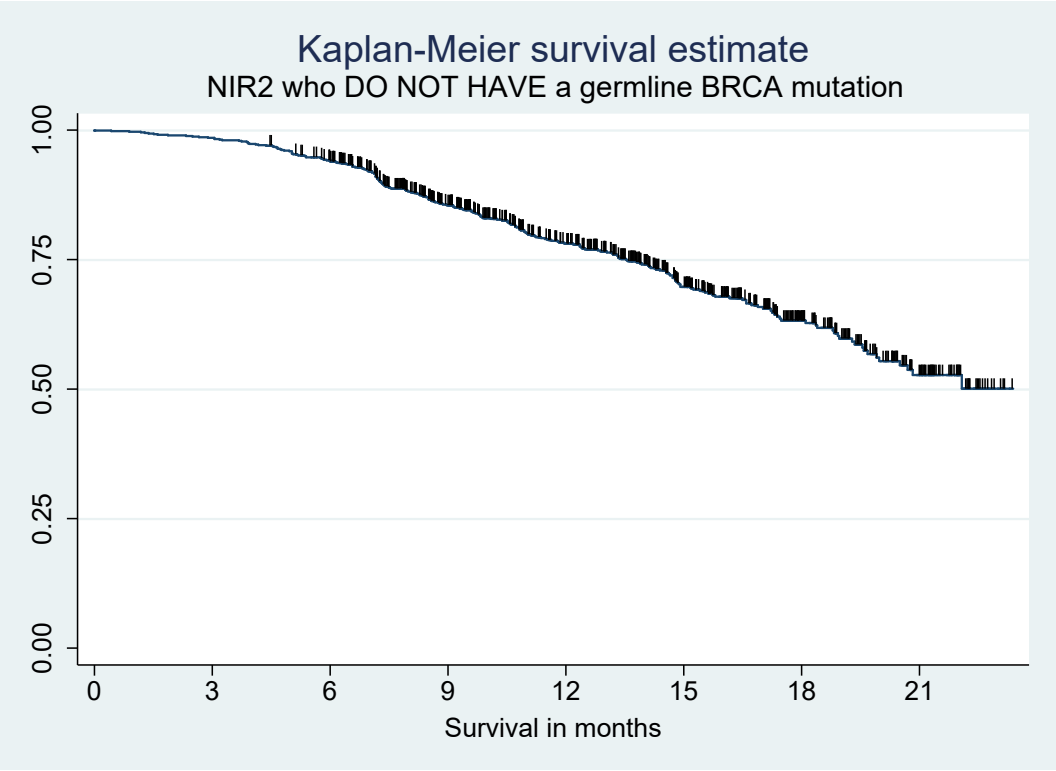


Table 26 and 27 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 23.7 months (721 days), all patients were traced on 22 May 2020.

Table 26: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Number at risk	850	838	789	587	429	276	143	46

Table 27 shows that for all patients who received treatment, 614 were still alive (censored) at the date of follow-up and 236 had died (events).

Table 27: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Censored	614	614	602	466	353	238	125	45
Events	236	224	187	121	76	38	18	1

Table 28: Median treatment duration and overall survival, full cohort and sensitivity analysis – germline BRCA mutation[cc].

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort: treatment duration	Sensitivity analysis: 6 months follow-up cohort: OS
N	157	123	157
Median treatment duration	12.2 months (371 days)	12.2 months (371 days)	
Median OS	Not reached		Not reached

Table 29: Median treatment duration and overall survival, full cohort and sensitivity analysis – no germline BRCA mutation.

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort: treatment duration	Sensitivity analysis: 6 months follow-up cohort: OS
N	859	607	850
Median treatment duration	6.4 months (194 days) [95% CI: 6.0, 7.1]	6.3 months (191 days) [95% CI: 5.7, 6.7]	
Median OS	Not reached		Not reached

[cc] Confidence intervals for treatment duration could not be produced for the germline BRCA mutation cohort as there was an insufficient number of events at the time this report was produced

Conclusions

1,080 patients received niraparib for the treatment of ovarian cancer [TA528] through the CDF in the reporting period (1 June 2018 and 30 November 2019). 1,016 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 95%. An additional 36 patients with a CDF application did not receive treatment or died before treatment. This was confirmed with the trust responsible for the CDF application by the team at PHE.

Patient characteristics amongst the germline BRCA mutation cohort, from the SACT dataset, show most of the cohort was aged between 50 and 69 years (62%, N=98) and 84% (N=132) of patients had a performance status between 0 and 1 at the start of their regimen.

Patient characteristics amongst the no germline BRCA mutation cohort, from the SACT dataset, show most of the cohort was aged between 50 and 79 years (90%, N=776) and 83% (N=718) of patients had a performance status between 0 and 1 at the start of their regimen.

At data cut off for the **germline BRCA mutation** cohort, 43% (N=68) of patients were identified as no longer being on treatment; 56% (N=38) of patients stopped treatment due to progression, 18% (N=12) of patients stopped treatment due to acute toxicity, 6% (N=4) of patients chose to end their treatment, 7% (N=5) of patients died not on treatment and 13% (N=9) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

At data cut off for the **no germline BRCA mutation** cohort, 59% (N=509) of patients were identified as no longer being on treatment; 64% (N=325) of patients stopped treatment due to progression, 12% (N=61) of patients stopped treatment due to acute toxicity, 4% (N=21) of patients chose to end their treatment, 10% (N=53) of patients died not on treatment, 1% (N=6) of patients died on treatment and 8% (N=43) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

Median treatment duration for the **germline BRCA mutation** analysis cohort was 12.2 months (371 days). 71% [95% CI: 63%,77%] of patients were receiving treatment at 6 months and 51% [95% CI: 42%, 60%] of patients were receiving treatment at 12 months.

Median treatment duration for the **no germline BRCA mutation** analysis cohort was 6.4 months (194 days) [95% CI: 6.0,7.1]. 54% [95% CI: 50%,57%] of patients were receiving treatment at 6 months and 28% [95% CI: 24%, 32%] of patients were receiving treatment at 12 months.

The median overall survival was not reached. The minimum follow-up was 5.7 months (173 days), the maximum follow-up was 25 months (760 days).

Sensitivity analyses were carried out to evaluate a cohort for which all patients had a minimum follow-up of six months. Results for these cohorts were consistent with the full analysis cohorts for both the germline BRCA mutation cohort and the no germline BRCA mutation cohort. Treatment duration for the germline BRCA mutation cohort (full cohort = 12.2 months; sensitivity analysis cohort = 12.2 months). Treatment duration for the no germline BRCA mutation cohort (full cohort = 6.4 months; sensitivity analysis cohort = 6.3 months) and overall survival for the full cohort and the sensitivity analysis cohort was not reached. Differences in treatment duration was not statistically significant.

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Public Health England

Niraparib for treating ovarian cancer (TA528)

Niraparib overall survival (OS) refresh (patient trace on 3 February 2021)

Commissioned by NHS England and NHS Improvement

1,016 applications (157 germline BRCA mutation, 859 no germline BRCA mutation) to the CDF were identified in the NHS England and NHS Improvement's Blueteq system and SACT as receiving niraparib for ovarian cancer (TA528) in England between 1 June 2018 and 30 November 2019. Tracing the patients' vital status was carried out on 3 February 2021 using the personal demographics service (PDS)[1].

OS - germline BRCA mutation

Of the 157 patients with a treatment record in SACT, the minimum follow-up was 14.2 months (432 days) from the last CDF application. Patients were traced for their vital status on 3 February 2021. This date was used as the follow-up date (censored date) if a patient is still alive.

The median follow-up time in SACT was 20.3 months (617 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Figure 1 provides the Kaplan-Meier curve for OS, censored at 3 February 2021. The median survival was not reached. Table 1 provides survival at 6, 12, 18 and 24 months.

Table 1: OS at 6, 12, 18 and 24 months.

Survival (months)	OS
6 months	96% [95% CI: 91%, 98%]
12 months	87% [95% CI: 81%, 92%]
18 months	77% [95% CI: 69%, 83%]
24 months	64% [95% CI: 55%, 72%]

Figure 1: Kaplan-Meier survival plot (N=157)

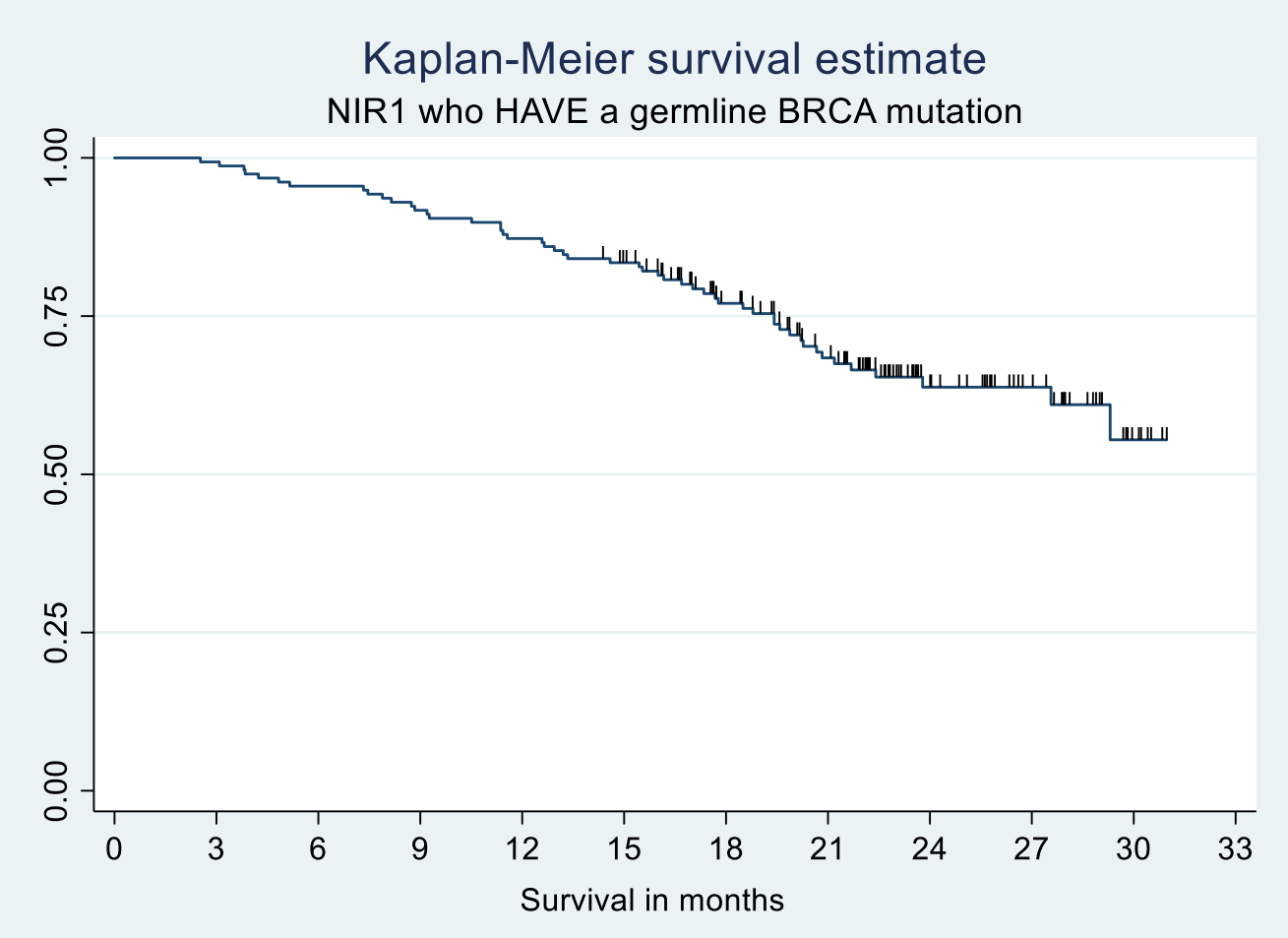

Table 2 and 3 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 32 months (974 days), all patients were traced on 3 February 2021.

Table 2: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	**0-30**	**3-30**	**6-30**	**9-30**	**12-30**	**15-30**	**18-30**	**21-30**	**24-30**	**27-30**	**30-33**
Number at risk	157	156	150	144	137	127	98	74	38	24	6

Table 3 shows that for all patients who received treatment, 106 were still alive (censored) at the date of follow-up and 51 had died (events).

Table 3: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	**0-30**	**3-30**	**6-30**	**9-30**	**12-30**	**15-30**	**18-30**	**21-30**	**24-30**	**27-30**	**30-33**
Censored	106	106	106	106	106	102	82	68	36	22	6
Events	51	50	44	38	31	25	16	6	2	2	0

OS – no germline BRCA mutation

Of the 859 patients with a treatment record in SACT, the minimum follow-up was 14.2 months (432 days) from the last CDF application. Patients were traced for their vital status on 3 February 2021. This date was used as the follow-up date (censored date) if a patient is still alive.

The median follow-up time in SACT was 17.5 months (532 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Figure 2 provides the Kaplan-Meier curve for OS, censored at 3 February 2021. The median survival was 22.6 months [95% CI: 21.3%, 24.7%] (687 days). Table 4 provides survival at 6, 12, 18 and 24 months.

Table 4: OS at 6, 12, 18 and 24 months

Survival (months)	OS
6 months	94% [95% CI: 92%, 96%]
12 months	78% [95% CI: 75%, 80%]
18 months	63% [95% CI: 60%, 66%]
24 months	47% [95% CI: 43%, 51%]

Figure 2: Kaplan-Meier survival plot (N=859)

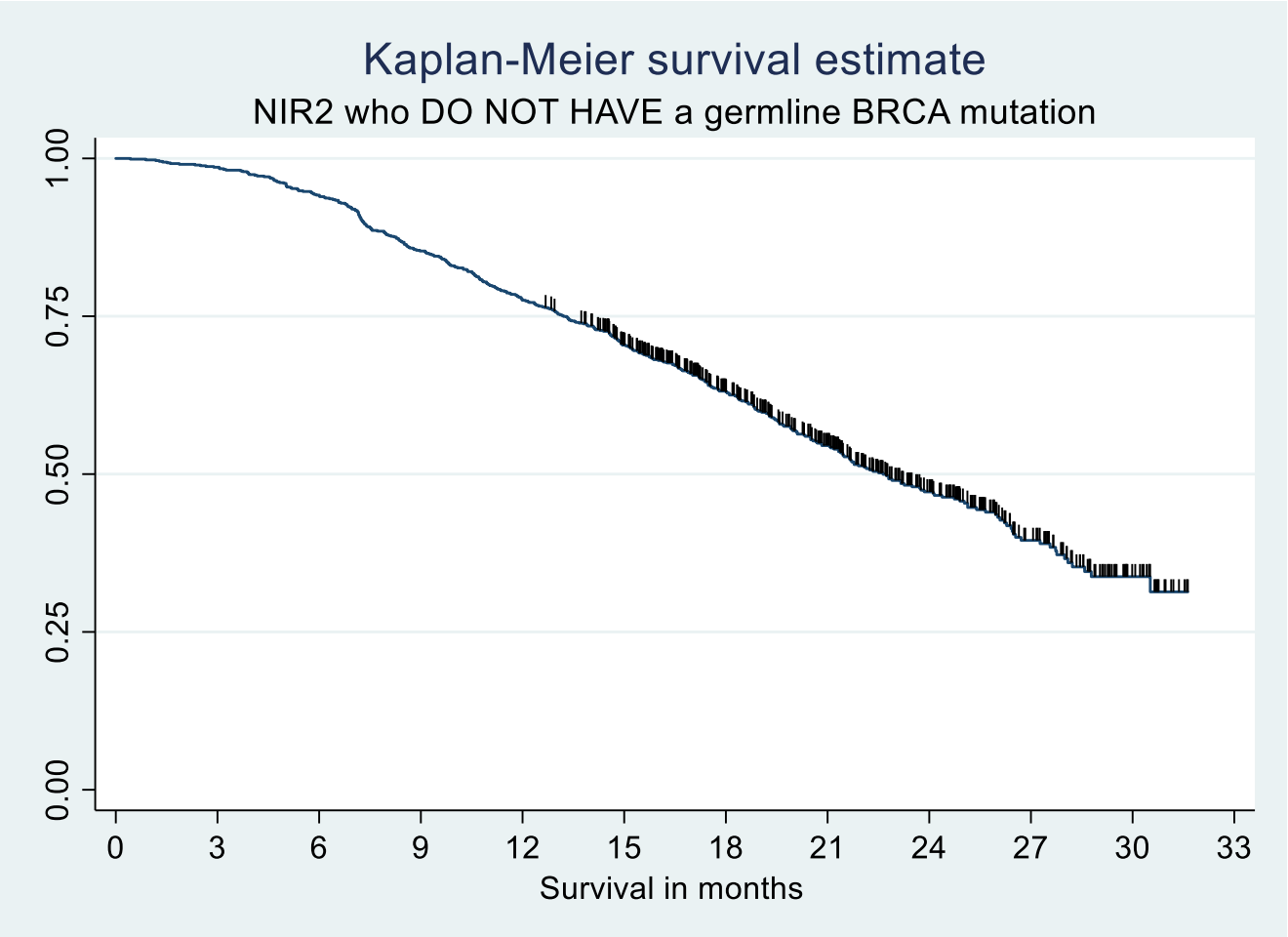

Table 5 and 6 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 32 months (974 days), all patients were traced on 3 February 2021.

Table 5: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	**0-30**	**3-30**	**6-30**	**9-30**	**12-30**	**15-30**	**18-30**	**21-30**	**24-30**	**27-30**	**30-33**
Number at risk	859	847	809	733	666	565	409	287	172	79	21

Table 6 shows that for all patients who received treatment, 439 were still alive (censored) at the date of follow-up and 420 had died (events).

Table 6: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	**0-30**	**3-30**	**6-30**	**9-30**	**12-30**	**15-30**	**18-30**	**21-30**	**24-30**	**27-30**	**30-33**
Censored	439	439	439	439	439	398	295	224	142	69	20
Events	420	408	370	294	227	167	114	63	30	10	1

References

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BMJ TAG

Niraparib for maintenance treatment of platinum-sensitive ovarian cancer after second response to chemotherapy (CDF review of TA528)

Cancer Drugs Fund review

Source of funding

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Report reference:	Edwards SJ, Karner C, Jhita T, Wakefield V. Niraparib for maintenance treatment of platinum-sensitive ovarian cancer after second response to chemotherapy. A Cancer Drugs Fund Review of TA528. BMJ-TAG, 2021.

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; and drafted the summary, background and clinical results sections
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence
Tracey Jhita	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

All authors read and commented on draft versions of the ERG report.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACD	Appraisal committee document
AE	Adverse events
AIC	Akaike information criterion
AUC	Area under the curve
BIC	Bayesian information criterion
BRCA	Breast cancer susceptibility cancer
BRCAwt	Breast cancer susceptibility cancer wildtype
CDF	Cancer Drug Fund
CI	Confidence interval
CS	Company submission
CSR	Clinical study report
DNA	Deoxyribonucleic acid
DSU	NICE Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EQ-5D-3L	European Quality of Life scale 5 dimensions 3 level
EQ-5D-5L	European Quality of Life scale 5 dimensions 5 level
ERG	Evidence Review Group
FAD	Final appraisal determination
gBRCAmut	Germline breast cancer susceptibility gene mutation
gBRCAmut 2L	Germline breast cancer susceptibility gene mutation second line
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRQoL	Health related quality of life
HSUV	Health state utility values
HTA	Health technology assessment
IA	Investigator assessed

ICER	Incremental cost-effectiveness
IRC	Independent review committee
ITT	Intention-to-treat
KM	Kaplan-Meier curve
LYG	Life-years gained
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
Non-gBRCAmut	Non germline breast cancer susceptibility gene mutation
OS	Overall survival
OWSA	One-way sensitivity analyses
PARP	Poly ADP (adenosine diphosphate) ribose polymerase
PAS	Patient access scheme
PD	Progressive disease
PFD	Progression free disease
PFS	Progression free survival
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life years
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
RCT	Randomised control trial
RS	Routine surveillance
SACT	Systemic anti-cancer therapy
SE	Standard error
STA	Single technology appraisal
TA	Technology appraisal
TAG	Technology assessment group
ToE	Terms of Engagement

TSD	Technical support document
TTD	Time to treatment discontinuation

1 Executive summary

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides a critique of the adherence to committee's preferred assumptions from the Terms of Engagement (ToE) in the company's submission. Section 1.2 provides an overview of the key issues. Section 1.3 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.4 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of the National Institute of Health and Care Excellence (NICE).

1.1 Critique of the adherence to committees preferred assumptions from the Terms of Engagement in the company's submission

In general, the ERG considers that the company has adhered to the committee's preferred assumptions from the ToE. The company has partially departed from the following of the committee's preferred assumptions:

- Population – The company has focused their submission on the intention-to-treat (ITT) population but also provide separate scenario analyses for the gBRCAmut 2L subgroup and the non-gBRCAmut 2L+ cohort, which are the relevant populations for the CDF review.
- Progression-free survival (PFS) – No updated PFS data have been presented as independent review committee assessed PFS was the primary endpoint in the NOVA trial and this endpoint was met in data cut-off in May 2016. The company's modelling of PFS is, therefore, unchanged since the original appraisal.
- Overall survival (OS) – The company presented updated OS data for NOVA but OS for the placebo arm did not inform the company's base case as the trial suffered from a large amount of missing survival data in both trial arms and a substantial amount of subsequent PARP inhibitor use primarily confounding OS of the placebo arm. Instead, the company relied on a PFS:OS ratio for their base case, and scenario analyses where routine surveillance was informed by the placebo arm of Study 19 or a retrospective cohort study by Lord *et al.* 2020.

- End of life – Niraparib was not considered to meet the end-of-life criteria but the company has put forward evidence for end-of-life to be assessed separately for the non-gBRCAmut 2L+ and the gBRCAmut 2L populations.

1.2 Overview of the ERG's key issues

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	Model structure accepted for decision making in TA528	4.1.3
2	Extrapolation of PFS	4.1.4.1
3	Investigator assessed versus independent review committee PFS	3.1.1 and 4.1.4.1
4	OS for routine surveillance	3.1.2, 3.3, and 4.1.4.2
5	Treatment specific utilities	4.1.6
6	Dose data for niraparib	4.1.7
7	OS extrapolation for SACT	**Error! Reference source not found.**

Abbreviations: OS, overall survival; PFS, progression-free survival.

1.3 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained. All cost-effectiveness analyses presented in this report are inclusive of the company's patient access scheme (PAS) simple discount of [redacted].

Overall, the technology is modelled to affect QALYs by:

- Increasing OS and PFS compared with patients on routine surveillance.

Overall, the technology is modelled to affect costs by:

- its higher unit price compared with monitoring alone.

The modelling assumptions that have the greatest effect on the ICER are:

- size of the PFS benefit, as it is linked to OS using the PFS:OS ratio;
- modelling OS for routine surveillance using Study 19 data (thus removing the PFS:OS link);

- applying utility values based on progression status rather than using treatment specific utility values;
- using prescribed dose data for niraparib instead of actual dose received; and
- extrapolation of time to treatment discontinuation (TTD) (non-gBRCAmut subgroup only).

1.4 The clinical and cost effectiveness evidence: summary of the ERG's key issues

Table 2 to Table 7 present the ERG's key issues of the company's clinical effectiveness evidence and updated cost-effectiveness.

Table 2. Issue 1: Model structure for decision making

Report section	4.1.3
Description of issue and why the ERG has identified it as important	In TA528, the company's means-based model structure was accepted as adequate for decision-making and was listed in the CDF ToE to be used for the CDF review. However, the committee's decision was based on a statement made by the company during the committee meeting that the ICER difference between the means-based model and a partitioned survival model was only around £1,000 per QALY. However, the company's partitioned survival model was not presented to the ERG to verify the claim and was not be supplied during the clarification stage of the CDF review. The ERG considers that the unverified partitioned survival model results quoted by the company in TA528 had an undue influence on the committee's decision to accept the means-based model structure and considers it likely that the model doesn't exist. Therefore, the ERG recommends the committee should reconsider its decision to accept the means-based model structure as it potentially sets a dangerous precedent where companies can introduce unverified new evidence during a committee meeting, which influences committee decision making, but is never subsequently assessed.
What alternative approach has the ERG suggested?	The ToE states that the company should fully investigate the most appropriate PFS and OS modelling using updated clinical trial data. The ERG considers that as more mature OS data are now available from NOVA (which was a limitation in TA528), the company should explore a partitioned survival model structure or provide the model referred to in TA528 (with updated data from NOVA) to validate the results from their means-based model.
What is the expected effect on the cost-effectiveness estimates?	It is unknown what the impact on the cost-effectiveness estimates would be as a result of using a partitioned survival model structure and the company's claim that is it is only £1,000 per QALY is unverified.
What additional evidence or analyses might help to resolve this key issue?	During the clarification stage, the ERG requested the company to supply the partitioned survival model quoted in TA528 but this was not supplied. The ERG considers that a partitioned survival model would be important to validate the results of the means-based model as well as remove the need for the PFS:OS ratio, thus reducing the uncertainty around the cost-effectiveness results.

Abbreviations: CDF, Cancer Drugs Fund; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; ToE, Terms of Engagement

Table 3. Issue 2: Extrapolation of PFS

Report section	4.1.4.1
Description of issue and why the ERG has identified it as important	As part of the ToE, the committee requested the company to fully investigate the most appropriate PFS modelling using updated clinical trial data. For the CDF submission, the company resubmitted their preferred extrapolation for PFS for the gBRCAmut 2L subgroup from their original submission (lognormal) and the best fitting spline model for the non-gBRCAmut 2L+ subgroup from their ACD response (normal k=1 spline). The company justified maintaining their approach as their PFS extrapolations as the estimates were similar to published long-term on-treatment data for olaparib from Study 19. However, the ERG notes that in Study 19 patients could be treated beyond progression if deemed appropriate by the investigator. As such, on-treatment data from Study 19 may not be a reliable measure of long-term progression-free survival for niraparib.
What alternative approach has the ERG suggested?	The ERG acknowledges the committee's consideration that the ERG preferred PFS approach from TA528 may be pessimistic and that the committee considered a flexible modelling approach maybe more appropriate. As such, the ERG explored the company's flexible spline analysis and considers that the hazard k=1 spline provides a less pessimistic, but clinically plausible long-term extrapolation.
What is the expected effect on the cost-effectiveness estimates?	Implementing the hazard k=1 spline for the gBRCAmut 2L subgroup increased the ICER from £19,475 to £21,838. For the non-gBRCAmut 2L+ subgroup, the corrected company ICER increased from £36,449 to £39,990.
What additional evidence or analyses might help to resolve this key issue?	Expert clinical input to the committee around plausible long-term PFS may help to resolve the uncertainty.

Abbreviations: CDF, Cancer Drugs Fund; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; ToE, Terms of Engagement

Table 4. Issue 3: Investigator assessed versus independent review committee PFS

Report section	3.1.1 and 4.1.4.1
Description of issue and why the ERG has identified it as important	The company used IRC assessed PFS, which was the primary outcome of NOVA. In contrast, treatment discontinuation, and therefore TTD, was determined by the investigators. Sensitivity analysis in NOVA shows a large difference, especially for the gBRCAmut cohort, in median PFS for niraparib depending on the assessment (IA or IRC). This difference is likely to be driven by informative censoring. The ERG, therefore, considers that using IA data for TTD and IRC data for PFS is fundamentally flawed as this leads to a disconnect between PFS and TTD.
What alternative approach has the ERG suggested?	As the committee has accepted that TTD from NOVA was appropriate for use in the economic model, the ERG considers that a scenario exploring extrapolated IA PFS is appropriate to align costs and benefits in the economic model.
What is the expected effect on the cost-effectiveness estimates?	In TA528, the ERG explored scenarios that focussed on using equivalence of IRC PFS to estimate TTD and IA TTD (preferred by the committee) to estimate IA PFS, in lieu of the company supplying IA PFS. Both scenarios substantially increased the company ICERs in TA528.
What additional evidence or analyses might help to resolve this key issue?	The ERG requested a scenario using IA PFS at the clarification stage for this CDF review, but the company maintained their position from TA528 and declined to provide the analysis, stating that the committee did not consider assessment of PFS as an uncertainty. Nonetheless, the ERG considers that exploring the discrepancy between IA and IRC PFS estimates is a resolvable issue but relies on the company providing analysis using IA PFS.

Abbreviations: CDF, Cancer Drugs Fund; ERG, Evidence Review Group; IA, investigator assessed; ICER, incremental cost-effectiveness ratio; IRC, independent review committee; PFS, progression-free survival; ToE, Terms of Engagement.

Table 5. Issue 4: Overall survival for routine surveillance

Report section	3.1.2, 3.3, and 4.1.4.2
Description of issue and why the ERG has identified it as important	While niraparib was in the CDF, longer-term OS data from the NOVA study was collected, which was a key limitation in TA528. The more mature OS for niraparib has been used in the economic model. However, the NOVA trial suffered from a large amount of missing survival data in both trial arms and a substantial amount of subsequent PARP inhibitor use which confounded OS data primarily in the placebo arm. Thus, the company used a PFS:OS ratio of 1:1 to estimate OS for routine surveillance as a way to "bypass" the confounded OS data from the placebo arm in NOVA. The ERG fundamentally disagrees with the use of a PFS:OS ratio as there is a lack of consistent evidence around the relationship between PFS to OS in advanced or metastatic cancer, making it an unreliable and uncertain measure. Furthermore, this approach intrinsically links changes to PFS to OS benefits.
What alternative approach has the ERG suggested?	The ERG considers that using randomised control trial OS data from both NOVA and Study 19, maintains a "like for like" comparison in the model (i.e. RCT data compared with RCT data). Thus, the ERG prefers the use of OS data from Study 19 for the routine surveillance arm, as per the approach in TA528. In addition, using Study 19 OS data for routine surveillance, reinforces the suitability a partitioned survival model structure. However, the ERG highlights that this analysis is based on a naïve comparison with no adjustments made for differences between the relevant subgroups in NOVA and Study 19. The comparison of niraparib and placebo in the gBRCAmut 2L and BRCAmut subgroups of NOVA and Study 19, respectively, is likely to provide a conservative estimate, whereas, the comparison in the non-gBRCAmut 2L+ and BRCAwt subgroups may potentially overestimate the difference between niraparib and placebo.
What is the expected effect on the cost-effectiveness estimates?	Implementing Study 19 OS for routine surveillance increases the ICER from £19,475 to £22,205. For the non-gBRCAmut 2L+ subgroup, the corrected company ICER increased from £36,449 to £39,608.
What additional evidence or analyses might help to resolve this key issue?	The company supplied the relevant Study 19 OS scenarios for routine surveillance in their CDF submission. However, the ERG considers that using Study 19 OS placebo data in a partitioned survival model structure is more appropriate and robust.

Abbreviations: CDF, Cancer Drugs Fund; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; ToE, Terms of Engagement.

Table 6. Issue 5: Treatment specific utility values

Report section	4.1.6
Description of issue and why the ERG has identified it as important	In TA528, the company implemented treatment-specific utilities based on data from NOVA. For the CDF review, the company has maintained their approach, but updated the utility analysis with the latest data cut from NOVA. In TA528, the ERG considered it was debatable that niraparib would be associated with higher HRQoL when the adverse event rate was also higher compared with placebo. Furthermore, no statistical tests were performed by the company, or results supplied to determine if the difference in utility values between niraparib and placebo were statistically significant.
What alternative approach has the ERG suggested?	The ERG maintains its position that utility values based on progression status alone are the most appropriate for the cost-effectiveness analysis and this position is supported by the ERG's clinical experts. During the clarification stage, the company supplied a scenario using utilities based on progression status from NOVA.
What is the expected effect on the cost-effectiveness estimates?	During the clarification stage, the company supplied a scenario using utilities based on progression status from NOVA. For the gBRCAmut 2L subgroup, the ICER increase from £19,475 to £20,527. For the non-gBRCAmut 2L+ subgroup, the corrected company ICER increased from £36,449 to £40,662.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence is required.

Abbreviations: CDF, Cancer Drugs Fund; ERG, Evidence Review Group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio.

Table 7. Issue 6: Updated niraparib dose data

Report section	4.1.7
Description of issue and why the ERG has identified it as important	In the company's updated base case for the CDF review, dosing data for niraparib has been changed to be based on actual dose received (defined as dispensed dose minus returned dose) as opposed to the prescribed dose data used in TA528. The ERG considers that in UK clinical practice, niraparib doses prescribed are unlikely to be returned to the NHS and reused.
What alternative approach has the ERG suggested?	The ERG prefers the company's original approach of using the prescribed dose data reflects that natural wastage that will occur in clinical practice.
What is the expected effect on the cost-effectiveness estimates?	During the clarification stage, the company supplied a scenario using prescribed dose data from TA528. For the gBRCAmut 2L subgroup, the ICER increase from £19,475 to £20,507. For the non-gBRCAmut 2L+ subgroup, the corrected company ICER increased from £36,449 to £39,202.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence is required.

Abbreviations: CDF, Cancer Drugs Fund; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio.

Table 8. Issue 7: SACT scenario analysis

Report section	**Error! Reference source not found.**
Description of issue and why the ERG has identified it as important	The trajectory of the observed SACT KM data for the non-gBRCAmut 2L+ subgroup reflects a constant steep decline. The rapid decline in observed overall survival may be clinically plausible when considering the baseline characteristics of the SACT non-gBRCAmut 2L+ patients reflect an older and sicker population compared with the NOVA cohort and could be driven by short post-progression survival. The ERG's clinical expert advised that for the SACT non-gBRCAmut 2L+ cohort, survival beyond 6 or 7 years is unlikely. As such, the ERG considers the company's log-logistic extrapolation to be optimistic. For the SACT gBRCAmut 2L subgroup, the ERG's clinical expert advised that within the cohort, there may be a subset of patients who are "super beneficiaries" but considered that the company's extrapolation may also be too optimistic.
What alternative approach has the ERG suggested?	The ERG considers the Weibull distribution represents a more clinically plausible extrapolation for the SACT non-gBRCAmut 2L+ subgroup analysis, with a similar statistical and visual fit to the observed data compared with the company's selection of the log-logistic distribution. Based on the ERG's clinical expert opinion, the ERG considers the generalised gamma distribution for the SACT gBRCAmut 2L subgroup captures the "super beneficiaries" but also reflects the conservative prognosis of the SACT cohort.
What is the expected effect on the cost-effectiveness estimates?	For the SACT non-gBRCAmut 2L+ subgroup, the ICER increased from £35,346 to £37,986. For the gBRCA 2L subgroup, the ICER increased from £17,930 to £18,312
What additional evidence or analyses might help to resolve this key issue?	Expert clinical input to the committee around plausible long-term OS may help to reduce the uncertainty.

Abbreviations: CDF, Cancer Drugs Fund; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; SACT, systemic anti-cancer therapy.

1.5 Summary of ERG's preferred assumptions and resulting ICER

Table 9 and Table 10 presents the ERG's preferred assumptions for the cost-effectiveness of niraparib for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups. Table 11 and Table 12 presents the detailed deterministic and probabilistic ERG base case results.

Table 9. ERG preferred assumptions – gBRCAmut 2L subgroup

Scenario	Incremental costs	Incremental QALYs	ICER (change from company base case
Company base case	[redacted]	[redacted]	19,475

Hazard k=1 spline for PFS + ERG TTD correction	[redacted]	[redacted]	21,838
OS based on Study 19 for routine surveillance	[redacted]	[redacted]	22,205
Utility values based on progression status + removal of disutility for AEs	[redacted]	[redacted]	20,527
Prescribed dose data from TA528	[redacted]	[redacted]	22,507
ERG's preferred base case [combination of all scenarios]	[redacted]	[redacted]	**27,399**

Abbreviations: AE, adverse event; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; TTD, time to maintenance treatment discontinuation.

Table 10. ERG preferred assumptions – non-gBRCAmut 2L+ subgroup

Scenario	Incremental costs	Incremental QALYs	ICER (change from company base case
Company base case	[redacted]	[redacted]	28,942
Corrected company base case	[redacted]	[redacted]	36,449
Hazard k=1 spline for PFS	[redacted]	[redacted]	39,990
OS based on Study 19 for routine surveillance	[redacted]	[redacted]	39,608
Gompertz distribution for TTD	[redacted]	[redacted]	40,518
Utility values based on progression status + removal of disutility for AEs	[redacted]	[redacted]	40,662
Prescribed dose data from TA528	[redacted]	[redacted]	39,202
ERG's preferred base case [combination of all scenarios]	[redacted]	[redacted]	**51,684**

Abbreviations: AE, adverse event; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; TTD, time to maintenance treatment discontinuation.

Table 11. ERG's deterministic base case results – gBRCAmut 2L subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,399

Probabilistic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,348
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.							

Table 12. ERG's deterministic base case results – non-gBRCAmut 2L+ subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,684
Probabilistic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,328
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.							

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,684
Probabilistic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,328

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Table 13 and Table 14 presents the ERG's preferred assumptions for the SACT cost-effectiveness scenarios for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups. Table 15 and Table 16 presents the detailed deterministic and probabilistic ERG base case results.

Table 13. ERG's preferred model assumptions – SACT gBRCAmut 2L subgroup

Preferred assumption	Section in ERG report	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Cumulative ICER (£/QALY)
Company base case	5.1.1	[redacted]	[redacted]	17,930	-
Generalised gamma distribution for OS	**Error! Reference source not found.**	[redacted]	[redacted]	18,312	18,312
Utility values based on progression status + removal of disutility for AEs	4.1.6	[redacted]	[redacted]	18,464	18,783
Prescribed dose data from TA528	4.1.7	[redacted]	[redacted]	20,695	21,683
ERG preferred SACT base case	-	[redacted]	[redacted]	**21,683**	-

Abbreviations: AE, adverse event; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; TTD, time to maintenance treatment discontinuation.

Table 14. ERG's preferred model assumptions - SACT non-gBRCAmut 2L+ subgroup

Preferred assumption	Section in ERG report	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Cumulative ICER (£/QALY)
Company base case	5.1.1	[redacted]	[redacted]	35,346	-
Weibull distribution for OS	**Error! Reference source not found.**	[redacted]	[redacted]	37,986	37,986
Utility values based on progression status + removal of disutility for AEs	4.1.6	[redacted]	[redacted]	39,798	41,695
Prescribed dose data from TA528	4.1.7	[redacted]	[redacted]	38,343	45,265
ERG preferred SACT base case	-	[redacted]	[redacted]	**45,265**	-

Abbreviations: AE, adverse event; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; TTD, time to maintenance treatment discontinuation.

Table 15. ERG's SACT results – gBRCAmut 2L subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,683
Probabilistic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,961

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Table 16. ERG's SACT results – non-gBRCAmut 2L+ subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,265
Probabilistic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,454

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Modelling errors identified and corrected by the ERG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the ERG, see Section 6.2 and Section 6.3.

2 Introduction and background

2.1 Introduction

This review is of niraparib (brand name Zejula©) as a maintenance treatment of relapsed, platinum-sensitive, high-grade serous ovarian cancer. Ovarian cancer encompasses a range of cancers that originate in the ovary, fallopian tube and primary peritoneum, and high-grade serous cancer is the most common histological subtype of ovarian tumours. Platinum-sensitive ovarian cancers are those that progress more than 6 months after platinum-based chemotherapy. Patients with platinum-sensitive ovarian cancer have a better prognosis and more treatment options, including maintenance therapy with poly ADP (adenosine diphosphate) ribose polymerase (PARP) inhibitors such as niraparib, than patients with platinum resistant cancer.

Niraparib was granted marketing authorisation in November 2017 and has been approved for use in England and Wales since July 2018 through the Cancer Drugs Fund (CDF) as a maintenance treatment for ovarian cancer that has responded to the most recent course of platinum-based chemotherapy in adults that:

- have a germline BRCA mutation and have had 2 prior lines of platinum-based chemotherapy (gBRCAmut 2L) or
- do not have a germline BRCA mutation and have had 2 or more prior lines of platinum-based chemotherapy (non-gBRCAmut 2L+).

Around 20% of patients with high-grade serous ovarian cancer carry a germline BRCA mutation. Patients with a BRCA mutation have deficiencies in their DNA repair pathways, which makes them more susceptible to treatment with PARP inhibitors, which block DNA base excision repair and thereby utilise this deficiency to promote tumour cell death.[1]

The clinical effectiveness evidence for niraparib in the original company submission (CS) for TA528 were derived from one randomised controlled trial (RCT), NOVA. This report comprises a review of the latest clinical and cost-effectiveness evidence on niraparib based on updated data from NOVA and real-world data collected within the CDF by Public Health England.

2.2 Background

Maintenance therapy for ovarian cancer is a treatment taken between different lines of chemotherapy to help maintain progression-free survival (PFS) and sustain platinum sensitivity. In England and Wales the only currently available maintenance therapy recommended by NICE for use

in routine clinical practice is olaparib, a PARP inhibitor which is approved for high-grade serous ovarian cancer patients who are platinum-sensitive, have a BRCA mutation, and have received three or more lines of platinum-based chemotherapy. Several PARP inhibitors are also available as maintenance therapy after first-line and second-line chemotherapy through the CDF but not through routine commissioning.

The company proposes that niraparib should be provided as maintenance therapy for all patients with recurrent platinum-sensitive, high-grade serous ovarian cancer, who show a complete or partial response to platinum-based chemotherapy, irrespective of BRCA mutation status. The population in the NOVA trial is consistent with the company's proposed positioning of niraparib in clinical practice. However, at the initial appraisal of niraparib, the committee noted that niraparib could not be considered plausibly cost-effective compared with olaparib in people with BRCA mutation who have had three or more courses of chemotherapy, and the company has presented separate scenario analyses for the gBRCAmut 2L and the non-gBRCAmut 2L+ populations, the two populations for which niraparib was recommended in the CDF.

Key uncertainties during the original appraisal were around the most appropriate method for extrapolating PFS and overall survival (OS) estimates, which were immature at the time. However, issues with the updated OS data from NOVA has meant that the company has had to explore other sources to inform the OS of the comparator arm (placebo/routine surveillance) in the economic model. This report provides a critique of the updated evidence and of the analyses the company has provided to relieve these uncertainties.

2.3 Critique of company's adherence to committees preferred assumptions from the Terms of Engagement

In general, the ERG considers that the company has adhered to the committee's preferred assumptions from the Terms of Engagement.[2] The ERG's critique of the company's adherence to the committee's preferred assumptions from the Terms of Engagement is provided in Table 17.

Table 17. Preferred assumptions from Terms of Engagement

Assumption subject	Committee preferred assumptions Terms of Engagement	Adherence or departing form assumption by the company	Justification if different	ERG comment
Population	The committee noted that niraparib could not be considered plausibly cost-effective compared with olaparib in people with BRCA mutation who have had 3 or more courses of chemotherapy. The relevant populations for the CDF review are, therefore, patients with and without BRCA mutation after 2 courses of platinum-based chemotherapy	**Partially departing from assumption**. The company focus their submission on the ITT population, that is, pooled data for the two randomised patient cohorts of the NOVA trial: gBRCAmut 2L+ and non-gBRCAmut 2L+. The company does, however, provide scenario analyses separately for the gBRCAmut 2L subgroup and the non-gBRCAmut 2L+ cohort.	The company highlights that the pooled ITT population is aligned with the marketing authorisation for niraparib and states that it reflects the current use in UK clinical practice. Furthermore, the presentation of a pooled ITT population allows OS outcomes of patients treated with niraparib to be compared to published, UK-based, real world evidence (RWE) OS outcomes of patients on routine surveillance.	The ERG does not consider the ITT population of NOVA relevant to this appraisal as the committee has concluded that niraparib could not be considered plausibly cost-effective compared with olaparib in people with BRCA mutation who have had 3 or more courses of chemotherapy. The efficacy of niraparib versus routine surveillance is likely to be overestimated in the ITT population which includes a proportion of patients with BRCA mutation who have had 3 or more courses of chemotherapy, who would be eligible for olaparib.
HRD positive tumour subgroup	Evidence according to HRD subgroup status is not expected to be considered	**Adhering to assumption**	NA	NA

Progression-free survival	The company should fully investigate the most appropriate PFS modelling using updated clinical trial data.	**Partially departing from assumption**. The PFS data are unchanged since the original appraisal but the company has provided updated modelling of PFS.	IRC PFS was the primary endpoint in the NOVA trial and this endpoint was met in data cut-off in May 2016. Therefore, no additional PFS data have been collected.	To resolve the disparity between outcomes assessed based on investigator assessment (IA) and independent review committee (IRC), the ERG considers that the economic assessment should be based on IA PFS rather than IRC PFS as TTD is IA. Furthermore, as survival analysis has been used to extrapolate PFS, a partitioned survival model structure would be more robust than a means-based model to estimate costs and QALYs.
Overall survival	The company should fully investigate the most appropriate OS modelling using updated clinical trial data.	**Partially departing from assumption.** For the niraparib arm the company use OS data from the latest available data cut from NOVA (Oct 2020). OS for the placebo arm of NOVA did not inform the company's base case. Instead, the company relied on a PFS:OS ratio of 1:1 for their base case, and scenario analyses where routine surveillance was informed by the placebo arm of Study 19 or a retrospective cohort study by Lord *et al* 2020.	The NOVA trial suffered from a large amount of missing survival data in both trial arms and a substantial amount of subsequent PARP inhibitor use primarily in the placebo arm.	The ERG considers Study 19 to provide the most robust data to inform the comparison of OS between niraparib and routine surveillance but highlights that the analysis is based on a naïve comparison with no adjustments made for differences between the relevant subgroups in NOVA and Study 19. Furthermore, using randomised control trial OS data from both NOVA and Study 19 maintains a "like for like" comparison in the model and reinforces the suitability a partitioned survival model structure.
Time to treatment discontinuation	The time to treatment discontinuation, as measured in the NOVA trial, should be used to within the economic model.	**Adhering to assumption** The company use time to treatment discontinuation data from the latest available data cut (Oct 2020) for NOVA.	NA	The ERG agrees with the use of TTD, which was determined by the trial investigators (IA) from NOVA in the economic model, but in order to keep consistency between outcomes the ERG prefers the use of IA PFS over IRC PFS.

End of life	Niraparib does not meet the end-of-life criteria	**Partially departing from assumption.** The company has put forward evidence for end-of-life to be assessed for the non-gBRCAmut 2L+ populations.	The company proposes that the non-gBRCAmut 2L+ population meets the end-of-life criteria, but that the gBRCAmut 2L population does not.	The ERG does not consider either population to fulfil both criteria for end-of-life when looking at either the outputs of the model or RWE. The data for end-of-life are presented in Section 7.

Abbreviations: 2L, two prior lines of platinum-based chemotherapy; 2L+, two or more prior lines of platinum-based chemotherapy; BRCA, breast cancer susceptibility gene; ERG, Evidence Review Group; gBRCAmut, germline BRCA mutation; IA, investigator assessed, IRC, independent review committee; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; RWE, real-world evidence, TTD, time to treatment discontinuation

3 Clinical effectiveness

In accordance with the data collection agreement, the company provided the following data and updated analyses:

- Further follow-up from NOVA provided for overall survival (OS) and time to treatment discontinuation (TTD), from the final data cut-off (October 2020);
- Systemic Anti-Cancer Therapy (SACT) dataset - real-world evidence (RWE) collected within the Cancer Drugs Fund (CDF) by Public Health England, providing evidence of the TTD and OS for patients who received niraparib in clinical practice;
- Alternative data sources for OS on routine surveillance based on Study 19 and Lord *et al* 2020.

3.1 The NOVA trial

3.1.1 Progression-free survival

In the original submission, data for NOVA were presented based on the primary PFS analysis with a data cut-off in May 2016. PFS was not assessed after the primary analysis and therefore these data are unchanged for the CDF submission.

In the original appraisal, the company used PFS assessed by an Independent Review Committee (IRC), which was the primary outcome of NOVA. In contrast, treatment discontinuation, and therefore TTD, was determined by the investigators. As highlighted in the original appraisal, the ERG maintains that using IA data for TTD and IRC data for PFS is fundamentally flawed as this leads to a disconnect between PFS and TTD in the economic model (see Section 4.1.4.1).

Sensitivity analysis in NOVA show a longer median PFS for patients treated with niraparib when assessed by the IRC compared with IA PFS, primarily in the gBRCAmut cohort but a small difference also in the non-gBRCAmut cohort (Table 18). In NOVA, IRC assessment was done retrospectively, meaning patients would be censored in the IRC analysis if the date of progression assessed by the investigator was earlier than assessed by the IRC. This would be informative censoring as IRC assessed progression could only be the same or earlier than the IA progression. Informative censoring may, therefore, be one of the main drivers for the difference between IA and IRC PFS in NOVA.

In the FAD for the original niraparib appraisal,[3] the committee stated that modelling of TTD should be based on IA data from the NOVA trial. To accommodate the committee's preference and at the same time avoid the disconnect between the outcomes, the ERG considers it most appropriate to use IA PFS and IA TTD in the model. In the original appraisal, the company did not provide IA PFS as it was not considered subject to robust data collection in the NOVA trial. The ERG acknowledge that IRC PFS was the primary outcome of the trial, and although IRC in general is of lower risk of bias than investigator assessment, as it was done retrospectively in NOVA, it is likely to be confounded by informative censoring.

At the clarification stage of the current CDF review, the company was requested to provide a scenario analysis using IA PFS. The company did not provide this analysis, referencing the FAD and the Terms of Engagement which state the committee's preference for using TTD from NOVA as this would more closely reflect TTD in clinical practice than IRC PFS. The company also states that IA PFS is not considered appropriate as it was not a primary or a secondary outcome in NOVA. The ERG notes that neither IA PFS nor TTD were listed as primary or secondary outcome and considers it important for the committee to see the impact of having a consistent assessment for TTD and PFS. This is discussed further in Section 4.1.4.1.

Table 18. Results of the Sensitivity Analyses for Progression-free Survival in the gBRCAmut and non-gBRCAmut Cohorts of NOVA (adapted from CSR Table 27 and Table 32)

	Median PFS (months (95% CI)		Hazard ratio (95% CI)	p-value
	Niraparib (N=138)	**Placebo (N=65)**		
gBRCAmut				
Central radiological (RECIST) review only	[redacted]	[redacted]	[redacted]	[redacted]
Investigator assessment	14.8 (12.0 to 16.6)	5.5 (4.9 to 7.2)	0.27 (0.182 to 0.401)	<0.0001
non-gBRCAmut				
Central radiological (RECIST) review only	[redacted]	[redacted]	[redacted]	[redacted]

Investigator assessment	8.7 (7.3 to 10.0)	4.3 (3.7 to 5.5)	0.53 (0.405 to 0.683)	<0.0001

Abbreviations: BRCA, breast cancer susceptibility gene; CI, confidence interval; gBRCAmut, germline BRCA mutation; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours

3.1.2 Overall survival and time to treatment discontinuation

OS and TTD data are presented for the final data cut-off in October 2020. The company highlights that, at the final data cut, discontinuation from the trial was greater than 80% in both the niraparib and placebo arms of the gBRCAmut 2L+ and non-gBRCAmut 2L+ cohorts. Of these, the majority of patients had died but a large proportion of patients withdrew from the study for other reasons. According to the trial protocol, all patients were to be followed every 90 days for subsequent anti-cancer therapy and the assessment of survival status following disease progression. However, it was also specified in the protocol that investigators were required to discontinue patients from the study if the patient was unblinded to the study treatment. Patients were unblinded in emergency situations, such as for the treatment of a study drug-related adverse event (AE), but patients who had discontinued treatment due to disease progression and wanted to enrol in another study of a PARP inhibitor were also allowed to be unblinded and informed of their treatment assignment. The premature study discontinuation, highlighted by the company, limited the collection of long-term follow-up data such as post-progression therapy and survival status.

The company reports that a protocol amendment allowed data entry of last known survival update or death based on public records. Due to this protocol amendment, there was a smaller but still considerable amount of missing survival data in both trial arms of the gBRCAmut 2L+ and non-gBRCAmut 2L+ cohorts at the final data cut-off (Table 19).

Table 19. Missing survival data

Survival data not determined	Placebo	Niraparib
gBRCAmut 2L+		
Events n/N (%)	9/65 (14)	19/138 (14)
non-gBRCAmut 2L+		
Events n/N (%)	15/116 (13)	33/234 (14)

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene mutation

Crossover from placebo to niraparib was not allowed in the trial but patients could receive PARP inhibitor therapy post-progression. Based on the available data on subsequent PARP inhibitor use, a substantial proportion of patients, especially in the placebo arm, received subsequent PARP inhibitor therapy (Table 20). However, these proportions could be substantially different considering the missing data (Table 20).

Table 20. Proportion of patients in the NOVA trial in the gBRCAmut 2L and non-gBRCAmut 2L+ cohorts who received subsequent PARPi therapy (reproduced from the response to clarification question A2, Table 1)

	gBRCAmut 2L (n = 100)		Non-gBRCAmut 2L+ (n = 350)	
	Niraparib n = 70 (%)	**Placebo n = 30 (%)**	**Niraparib n = 234 (%)**	**Placebo n = 116 (%)**
Number of patients who received subsequent PARPi n (%)	[redacted]	[redacted]	15 (6.4)	15 (12.9)
Missing information n (%)	[redacted]	[redacted]	51 (21.8)	31 (26.7)
Number of patients who received subsequent PARPi n (% of patients for whom subsequent PARPi therapy information was available)	[redacted]	[redacted]	15 (8.2)	15 (17.6)

Abbreviation: 2L, second-line; g*BRCA*mut, germline breast cancer susceptibility gene mutation; PARPi, poly (ADP-ribose) polymerase inhibitor

Due to the high rate of post-progression PARP inhibitor use in the control arm of NOVA, and missing data on post-progression PARP inhibitor in both trial arms, the ERG agrees with the company that the OS results are likely to be confounded and conservative. Although there are several methods for adjusting for treatment switching and for imputing missing data, the combination of relatively large amounts of missing data and treatment switching make it difficult to reliably adjust for both. The company, therefore, used the final OS data for niraparib but not for placebo in the economic model (see section 4.1.4.2).

To estimate the OS of patients on routine surveillance in the economic model, the company used an assumption of a PFS:OS relationship for their base case, similar to the original submission. However, instead of using the PFS:OS ratio to estimate OS for niraparib, as was done in the original

submission, the company has used the updated niraparib OS data from NOVA and estimates OS for the placebo arm using a PFS to OS benefit ratio of 1:1. This is discussed in section 4.1.4.2. The company also present scenario analyses that rely on alternative data sources to inform OS for patients on RS: placebo data from the olaparib RCT, Study 19, and routine surveillance data from UK RWE published by Lord *et al.* 2020. A summary and critique of Study 19 and Lord *et al.* 2020 are presented in Section 3.2.

The company has focused their submission on the pooled intention-to-treat (ITT) population, that is, the combined data for the gBRCAmut 2L+ and non-gBRCAmut 2L+ cohorts of the NOVA trial. The company highlights that the pooled ITT population is aligned with the marketing authorisation for niraparib and that it allows OS outcomes of patients treated with niraparib to be compared with the UK-based, RWE OS outcomes of patients treated with routine surveillance published by Lord *et al.* 2020. The ERG does not consider the comparison of niraparib and routine surveillance in the ITT population of NOVA relevant to this CDF review. The efficacy of niraparib versus routine surveillance is likely to be overestimated in the ITT population, which includes a proportion of patients with BRCA mutation who have had 3 or more courses of chemotherapy. The relevant comparator to niraparib in this subgroup is olaparib, which the committee has concluded is likely to remain the cost-effective option when compared with niraparib.[3]

The updated data for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups are presented in Table 21, and results for the pooled ITT population can be found in the CS. There were some discrepancies in the OS and TTD data presented for the gBRCAmut 2L subgroup in the appendix of the company submission. At the clarification stage the company explained that it was due to the gBRCAmut 2L population being analysed in two different ways:

- A broad definition of 2L which includes patients who have had any number of lines of chemotherapy but including only two lines of platinum-based chemotherapy (n=116).
- A specific definition of 2L which includes patients who have only had two lines of chemotherapy, both of which were platinum-based (n=100)

The company confirmed that the more specific definition was used for PFS and OS in the original submission and for the updated TTD and OS data presented in Table 21. At the time of the final OS analysis (data cut-off October 2020) of NOVA, median OS on niraparib was [redacted] months for the gBRCAmut 2L subgroup and 31.11 months for the non-gBRCAmut 2L+ cohort Table 21). The OS

Kaplan-Meier (KM) curves for these populations (Figure 1 and Figure 2) show that there is no statistically significant difference between niraparib and placebo. As described above, this comparison is confounded by post-progression PARP inhibitor therapy, primarily in the placebo arm, and substantial uncertainty due to the large amount of missing survival data in both arms.

Data from the October 2020 data cut-off, at which time [redacted]% of patients had discontinued treatment, confirms the analyses at the primary PFS analysis (data cut-off May 2016), showing that TTD was longer with niraparib than with placebo in both the gBRCAmut 2L subgroup and the non-gBRCAmut 2L+ cohort (

Figure 3 and Figure 4). For the gBRCAmut 2L subgroup, median TTD was [redacted] months with niraparib compared with [redacted] months with placebo, and for the non-gBRCAmut 2L+ cohort median TTD was [redacted] and [redacted] months with niraparib and placebo, respectively (Table 21).

Table 21. Key efficacy outcomes from NOVA - data cut-off October 2020 (adapted from the response to clarification question A3, Table 4)

Endpoint	Placebo	Niraparib
Overall survival – gBRCAmut 2L cohort[a]		
Number of patients	30	70
Events (%)	[redacted]	[redacted]
Median (95% CI) (months)	[redacted]	[redacted]
HR (95% CI), *p-value*	[redacted]	
Overall survival – non-gBRCAmut 2L+ cohort[a,b]		
Number of patients	116	234

Events (%)	[redacted]	[redacted]
Median (95% CI) (months)	36.47 [redacted]	31.11 [redacted]
HR (95% CI), *p-value*	1.10 (0.83 to 1.46), *p* =NR	
Time to treatment discontinuation – gBRCAmut 2L cohort[a]		
Number of patients	30	70
Events (%)	[redacted]	[redacted]
Median (95% CI) (months)	[redacted]	[redacted]
HR (95% CI), *p-value*	[redacted]	
Time to treatment discontinuation – non-gBRCAmut 2L+ cohort[a]		
Number of patients	116	234
Events (%)	[redacted]	[redacted]
Median (95% CI) (months)	[redacted]	[redacted]
HR (95% CI), *p-value*	[redacted]	

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; HR, hazard ratio; NE, non-evaluable; NR, not reported; OS, overall survival; TTD, time to treatment discontinuation.

[a] NOVA PLD analysis[8] analysis, simple cox model.

[b] Matulonis 2021[9]

Figure 1. OS KM for niraparib and placebo, NOVA gBRCAmut 2L cohort, data cut-off October 2020 (reproduced from the CS Appendix, Figure 12)

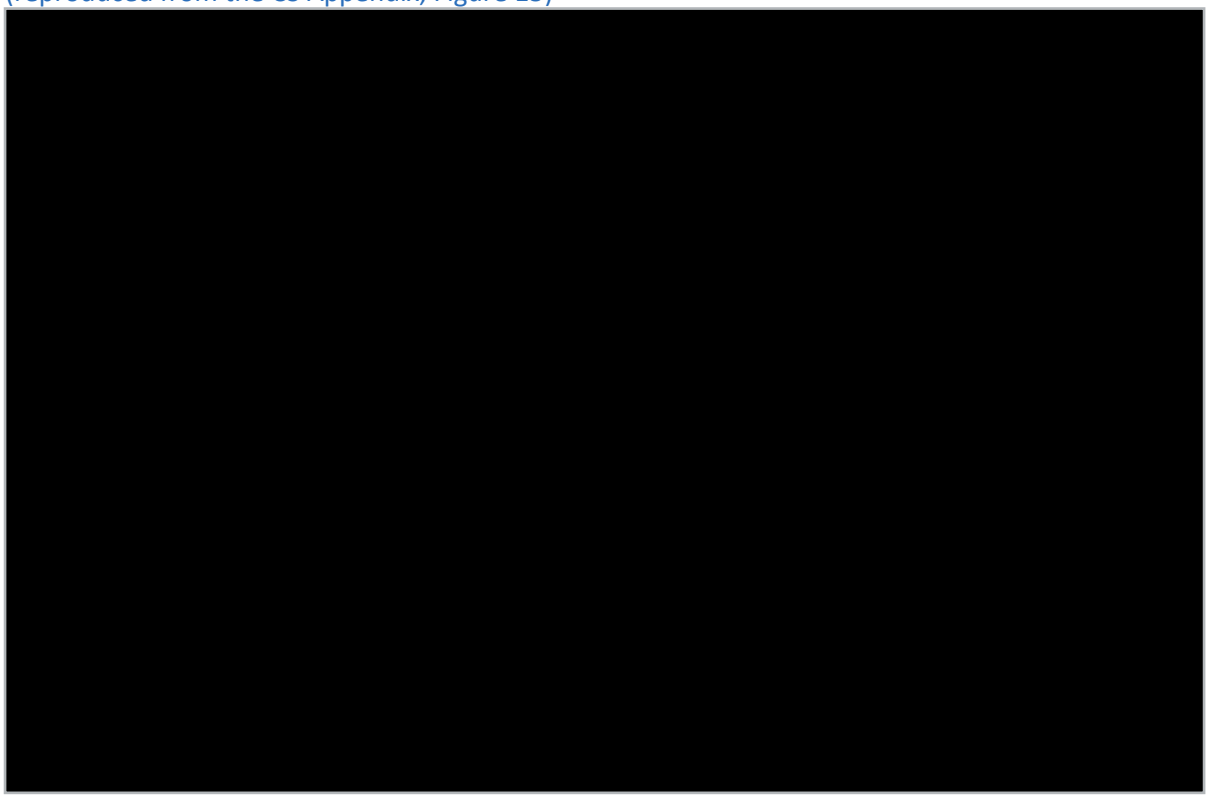

[redacted]

Abbreviations: non-gBRCAmut, non-germline breast cancer susceptibility gene; KM, Kaplan-Meier; PLD, patient level data; OS, overall survival. Source. NOVA PLD analysis[8]

Figure 2. OS KM for niraparib and placebo, NOVA non-gBRCAmut 2L+ cohort, data cut-off October 2020 (reproduced from the CS Appendix, Figure 13)

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene; KM, Kaplan-Meier; PLD, patient level data; OS, overall survival. Source. NOVA PLD analysis[8]

Figure 3. TTD KM for niraparib and placebo, NOVA gBRCAmut 2L cohort, data cut-off October 2020 (reproduced from the CS Appendix, Figure 15)



Abbreviations: non-gBRCAmut, non-germline breast cancer susceptibility gene; KM, Kaplan-Meier; PLD, patient level data; TTD, time to treatment discontinuation. Source. NOVA PLD analysis[8]

Figure 4. TTD KM for niraparib and placebo, NOVA non-gBRCAmut 2L+ cohort, data cut-off October 2020 (reproduced from the CS Appendix, Figure 16)

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene; KM, Kaplan-Meier; PLD, patient level data; TTD, time to treatment discontinuation. Source. NOVA PLD analysis[8]

3.2 Systemic Anti-Cancer Therapy data

Between 1 June 2018 and 30 November 2019, 157 patients with a gBRCA mutation who had had 2 prior lines of platinum-based chemotherapy (gBRCAmut 2L), and 859 patients without a gBRCA mutation and 2 or more prior lines of platinum-based chemotherapy (non-gBRCAmut 2L+) were enrolled to receive treatment with niraparib through the Systemic Anti-Cancer Therapy (SACT) framework. The company presents data for these two populations separately as well as for the ITT population (n=647). For the two relevant subgroups, TTD data are available with a data cut-off of December 2019 and OS data with a data cut-off of February 2021, whereas data for the ITT population are based on an interim report with a data cut-off in June 2019, at which time patients were still being enrolled. As the ITT population is of limited relevance to this CDF review and the data for the ITT population are based on an earlier data cut with shorter follow up and fewer patients, it is not discussed further in this report but can be found in the CS (Section A.6) and in the NHSE report.[4]

By the December 2019 data cut 43% (N=68) of gBRCAmut 2L patients and 59% (N=509) of non-gBRCAmut 2L+ patients had completed treatment, that is, patients had stopped treatment due to either progression, acute toxicity, patient choice, the patient died, or the patient did not have a treatment record in SACT in at least three months. Median follow-up for OS was 20.3 months and 17.5 months for the gBRCAmut 2L and non-gBRCAmut 2L+ cohorts, respectively. Median OS was not reached for the gBRCAmut 2L cohort, but the survival rates show that 87% were alive at 12 months, which decreased to 64% at 24 months (Table 23). For the non-gBRCAmut 2L+ cohort median OS was 22.6 months.

The OS outcomes of patients in the non-gBRCAmut 2L+ SACT cohort are worse than for the equivalent cohort in NOVA (median OS 31.11 months). Although median OS is not yet reached for the gBRCAmut 2L cohort in SACT, it is likely to be shorter than the median OS observed for this population in NOVA. Similarly, median duration of treatment with niraparib was shorter in the SACT cohorts with 12.2 months for gBRCAmut 2L and 6.4 months for non-gBRCAmut 2L+ based on the SACT data, compared with 14.72 and 7.16 months, respectively, in NOVA (Table 23).

The observed differences between the SACT cohorts and the NOVA cohorts are likely to be due in part to differences between the patient populations. A summary of the baseline characteristics reported for patients treated with niraparib in the gBRCAmut 2L and non-gBRCAmut 2L+ cohorts of the SACT datasets compared with the same characteristics for patients enrolled in the equivalent subgroups of NOVA, is presented in Table 22. The SACT cohorts constitute slightly older and more frail (lower proportion of patients with performance status 0) populations than those of NOVA, as can be expected when comparing a controlled clinical trial and real-world evidence (RWE). The absolute outcomes of patients in the SACT cohorts are, therefore, likely to be slightly worse than what is observed in NOVA. Although there are clear differences in the absolute results between the SACT cohorts and the equivalent subgroups in NOVA, it is unclear if the differences between the patient cohorts and settings will have an effect on the relative efficacy between niraparib and routine surveillance. The NOVA trial data remains the most mature and robust niraparib data but the ERG highlights that there is a degree of uncertainty around the generalisability of the NOVA data as it may not be fully reflective of clinical practice.

The company did not use the OS SACT data to inform the economic model. However, in response to a clarification request the company is exploring the possibility of providing a RWE scenario using SACT OS and TTD data for niraparib (see Section **Error! Reference source not found.**).

Table 22. Comparison of patient characteristics from SACT cohort and niraparib NOVA cohort (reproduced from the CS Appendix A.17, Table 14)

Patient characteristics	SACT cohort[a]		Niraparib NOVA cohort[b]	
	gBRCAmut 2L	Non-gBRCAmut 2L+	gBRCAmut 2L+	Non-gBRCAmut 2L+
N	157	859	138	234
Median age (range)	60 (NR)	68 (NR)	57 (36 to 83)	63 (33 to 84)
Performance status (%)				
0	76 (48)	339 (39)	91 (66)	160 (68)
1	56 (36)	378 (44)	47 (34)	74 (32)
2	0	10 (1)	0	0
3	0	0	0	0
4	0	0	0	0
Missing/unknown	25 (16)	132 (15)	0	0

Abbreviations: BRCA, breast cancer susceptibility gene; gBRCAmut, germline BRCA mutation; non-gBRCAmut, non-germline BRCA mutation; NR, not reported; SACT, Systematic Anti-Cancer Therapy

a. Source: Niraparib for treating ovarian cancer – data review.[6] b. Mirza et al. 2016[7]

Table 23. Key efficacy outcomes from SACT dataset – niraparib (adapted from the CS Appendix A.19, Table 16)

Endpoint	gBRCAmut cohort	non-gBRCAmut cohort
N	157	859
Overall survival[a]		
Events (%)	51 (32.48)	420 (48.89)
Median follow-up time (95% CI) (months)	20.3	17.5
Median (95% CI) (months)	Not reached	22.6 (21.3 to 24.7)
Survival rate % (95% CI) at		
6 months	96 (91 to 98)	94 (92 to 96)
12 months	87 (81 to 92)	78 (75 to 80)
18 months	77 (69 to 83)	63 (60 to 66)

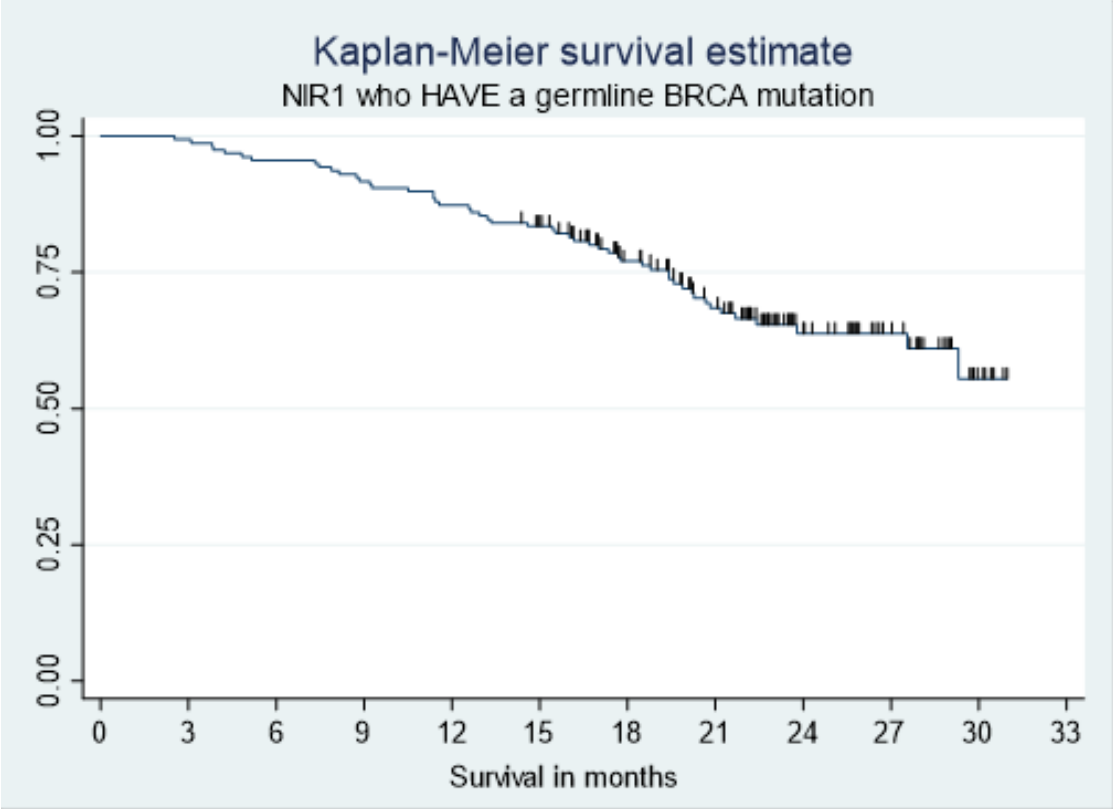
24 months	64 (55 to 72)	47 (43 to 51)
Time to treatment discontinuation[b]		
Events (%)	68 (43.31)	509 (59.25)
Median follow-up time (95% CI) (months)	6.8	4.6
Median (95% CI) (months)	12.2	6.4

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; OS, overall survival; SACT, Subsequent Anti-Cancer Therapy; TTD, time to treatment discontinuation.

a. Source: Niraparib overall survival (OS) refresh (patient trace 3rd February 2021)[11]

b. Niraparib for treating ovarian cancer – data review[6]

Figure 18. OS KM for niraparib SACT gBRCAmut 2L cohort

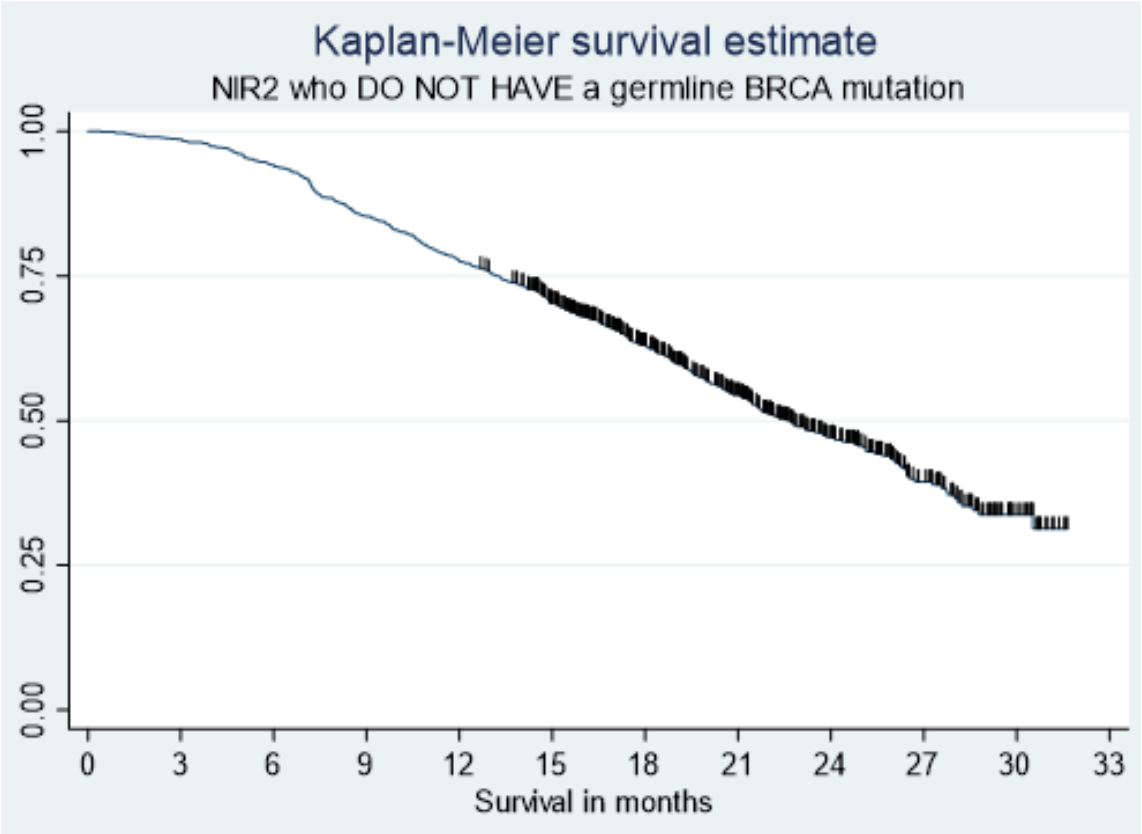


Time intervals (months)	0-30	3-30	6-30	9-30	12-30	15-30	18-30	21-30	24-30	27-30	30-33
Number at risk	157	156	150	144	137	127	98	74	38	24	6
Censored	106	106	106	106	106	102	82	68	36	22	6
Events	51	50	44	38	31	25	16	6	2	2	0

Abbreviations: gBRCAmut, germline breast cancer susceptibility gene; KM, Kaplan-Meier; OS, overall survival.

Source: Niraparib overall survival (OS) refresh (patient trace 3rd February 2021)[10]

Figure 19. OS KM for niraparib SACT non-gBRCAmut 2L+ cohort



Time intervals (months)	0-30	3-30	6-30	9-30	12-30	15-30	18-30	21-30	24-30	27-30	30-33
Number at risk	859	847	809	733	666	565	409	287	172	79	21
Censored	439	439	439	439	439	398	295	224	142	69	20
Events	420	408	370	294	227	167	114	63	30	10	1

Abbreviations: non-gBRCAmut, germline breast cancer susceptibility gene; KM, Kaplan-Meier; OS, overall survival.
Source: Niraparib overall survival (OS) refresh (patient trace 3rd February 2021)[10]

3.3 Alternative data sources for overall survival on routine surveillance

The company presents scenario analyses, whereby OS with routine surveillance is based on long-term extrapolations from the placebo arm of Study 19 or from Lord *et al.* 2020. The relevance of each of these data sources as a comparator niraparib for OS, are discussed in the following sections.

3.3.1 Study 19

Study 19, which in the original appraisal was used to inform OS for niraparib, is a double-blind, placebo-controlled, international multicentre phase II RCT designed to assess the safety and efficacy of olaparib in patients with platinum-sensitive recurrent ovarian or fallopian tube cancer or primary peritoneal cancer with high grade serous features or a serous component. In this CDF review, the company has used Study 19 to inform OS for patients on routine surveillance compared with OS for niraparib from NOVA, in a scenario analysis.

Study 19 enrolled patients who had received two or more courses of platinum-based chemotherapy and had responded to their latest regimen. Of the 129 patients randomised to placebo, 62 patients had either a germline or somatic BRCA mutation or both (BRCAmut subgroup), and 61 patients had wildtype BRCA (BRCAwt subgroup), that is, no BRCA mutation. The BRCAwt subgroup of Study 19 is likely to have a worse prognosis than the non-gBRCAmut subgroup of NOVA as the latter group includes some patients with a somatic BRCA mutation.

As mentioned earlier, the company has focused their submission on the ITT population of NOVA, as well as the ITT population of Study 19. In order to assess the comparability of the subgroups relevant to this CDF review, the ERG presents the baseline characteristics based on BRCA mutation status of patients randomised to placebo in Study 19 and to niraparib in NOVA. These are presented in Table 24. The ERG highlights that for the gBRCAmut 2L subgroup these characteristics, which were presented in the original appraisal of niraparib, are for the broader definition of 2L described in section 3.1.2. The baseline characteristics of the population for which data are presented in section 3.1.2 and which is informing the economic model are therefore likely to be somewhat different.

The median age of patients in the subgroups of Study 19 was similar to that of patients in NOVA, with a slightly higher age in the BRCAwt and non-gBRCAmut subgroups compared with the BRCAmut and gBRCAmut subgroups (Table 24). In both subgroups of Study 19, patients had a slightly better performance status, with a larger proportion of patients with ECOG 0, than the equivalent subgroup

in NOVA. Primary tumour site and histology were relatively similar between the NOVA and Study 19 subgroups.

A larger proportion of patients had a complete response to their most recent platinum-based therapy in the non-gBRCAmut group given niraparib (50%) in NOVA than in the BRCAwt group given placebo in Study 19 (41%). This is likely to benefit niraparib in this comparison. Response to the most recent therapy wasn't reported for the gBRCAmut 2L group in NOVA but for the full gBRCAmut cohort the proportion with a complete response was similar (51.4%) to the proportion in the BRCAmut subgroup in Study 19 (55%).

Prior bevacizumab use was not reported for the subgroups but comparing the full placebo arm of Study 19 with the niraparib arm in NOVA, a larger proportion of patients had received prior bevacizumab in the niraparib arm of NOVA (25.5%) than in the placebo arm of Study 19 (11.6%).

Similar to NOVA, crossover to PARP inhibitor therapy was not permitted in Study 19 but some patients went on to receive PARP inhibitor therapy after disease progression. In the BRCAmut and gBRCAmut 2L subgroups of Study 19 and NOVA, respectively, [redacted] received subsequent PARP inhibitor therapy (Table 24). The subsequent PARP inhibitor use is likely to have a larger impact on the survival of patients in the placebo arm, which have no prior exposure to this treatment class. Ignoring all other differences between the niraparib arm of the gBRCAmut 2L subgroup in NOVA and the placebo arm of the BRCAmut subgroup in Study 19, this is likely to give a conservative estimate of OS on niraparib compared with placebo.

Subsequent PARP inhibitor use was [redacted] the niraparib arm of the non-gBRCAmut 2L subgroup in NOVA [redacted] the placebo arm of the BRCAwt subgroup of Study 19 (Table 24). However, the proportion of patients who received post-progression PARP inhibitor therapy in this subgroup of NOVA is likely to be an underestimate considering the number of patients for whom subsequent PARP inhibitor therapy information was unavailable.

These differences in patient characteristics between the subgroups in NOVA and Study 19 play an important role as the company, as a scenario analysis, provides naïve comparisons of niraparib from NOVA and placebo from Study 19, for these subgroups. The comparison of niraparib and placebo in the gBRCAmut 2L and BRCAmut subgroups of NOVA and Study 19, respectively, is likely to provide a

conservative estimate, whereas, the comparison in the non-gBRCAmut 2L+ and BRCAwt subgroups may potentially overestimate the difference between niraparib and placebo.

Table 24. Baseline characteristics from placebo or routine surveillance arms of NOVA and Study 19 in the BRCAwt/non-gBRCAmut and gBRCAmut subgroups

Characteristic	Study 19[a] BRCAmut placebo (n= 62)	NOVA[b] gBRCAmut 2L niraparib (n=79)	Study 19[a] BRCAwt placebo (n= 61)	NOVA[c] Non-gBRCAmut 2L+ niraparib (n=234)
Median age, years (range)	55 (33–84)	56.6 (37, 83)	63 (49–79)	63 (33–84)
Age (years), n (%)				
<50	16 (26)		1 (2)	
≥50 to <65	35 (56)		37 (61)	
18–64		62 (78.5)		130 (55.6)
65–74		14 (17.7)		85 (36.3)
≥65	11 (18)	17 (21.5)	23 (38)	104 (44.4)
≥75		3 (3.8)		19 (8.1)
Eastern Cooperative Oncology Group performance status, n (%)				
0	45 (73)	56 (70.9)	45 (74)	160 (68.4)
1	15 (24)	23 (29.1)	14 (23)	74 (31.6)
2	1 (2)	NA	1 (2)	NA
Unknown	1 (2)	NA	1 (2)	NA
Primary tumour site, n (%)†				
Ovary	54 (87)	72 (91.1)	49 (80)	192 (82.1)
Primary peritoneum		3 (3.8)		24 (10.3)
Fallopian tube		4 (5.1)		18 (7.7)
Fallopian tube or primary peritoneal	8 (13)		12 (20)	

Histologic subtype, n (%)[a]				
Serous	(100)*	69 (90.8)	(100)*	215 (96.4)
Endometrioid		2 (2.6)		1 (0.4)
Mucinous		0		0
Others		7 (9.2)		11 (4.9)
Time to progression after penultimate platinum therapy, n (%)				
6 to <12 months	26 (42)	9 (11.4)**	24 (39)	90 (38.5)
≥12 months	36 (58)	1 (1.3)**	37 (61)	144 (61.5)
Best response to most recent platinum therapy, n (%)				
Complete	34 (55)		25 (41)	117 (50.0)
Partial	28 (45)		36 (59)	117 (50.0)
Germline BRCA mutation, n (%)¶				
BRCA1	44 (71)	40 (50.6)		
BRCA2	17 (27)	17 (21.5)		
BRCA1, BRCA2 rearrangement, or both	1 (2)	6 (7.6)		
Number of patients who received subsequent PARPi				
n/N (%)	14/62 (22.6)	[redacted]	3/61 (4.9)	[redacted][#]

Abbreviations: BMI, body mass index; BRCA, breast cancer susceptibility gene; gBRCAmut, germline BRCA mutation; SD, standard deviation.

* serous features or a serous component

[a] Ledermann 2016[5]

[b] Company submission TA528, clarification response A10

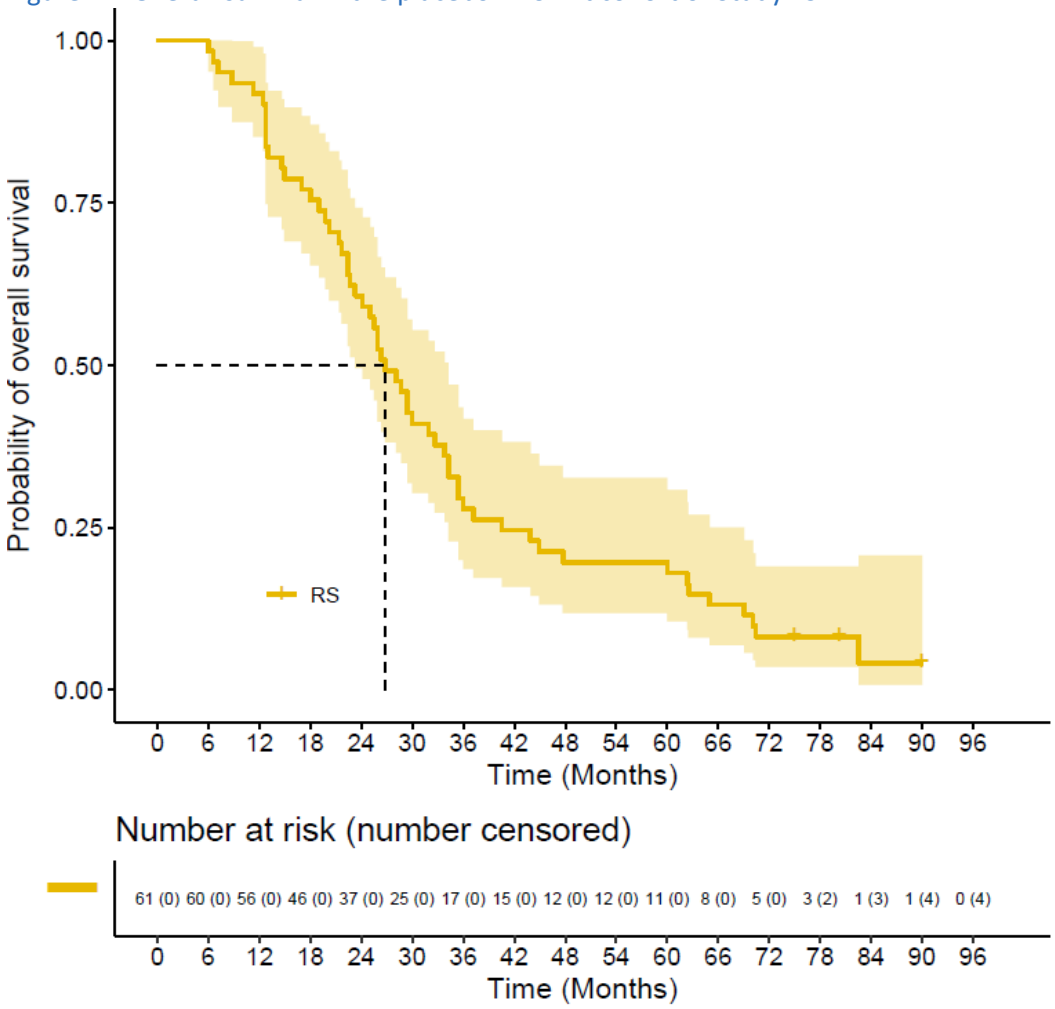
[c] Company submission TA528, Table 5 and Table 10

** Reported as "Months of penultimate platinum-based therapy" rather than "Time to progression after penultimate platinum therapy"

[#] Based on the response to clarification question A2. Note that data on subsequent therapy was missing for ≥20% of patients in NOVA

In the BRCAwt cohort of Study 19, median OS was 26.6 months for the placebo arm and 93.4% (57/61) of patients had died at final data cut-off May 2016. In comparison, median OS was 31.11 months for patients in the non-gBRCAmut 2L+ subgroup treated with niraparib on NOVA.

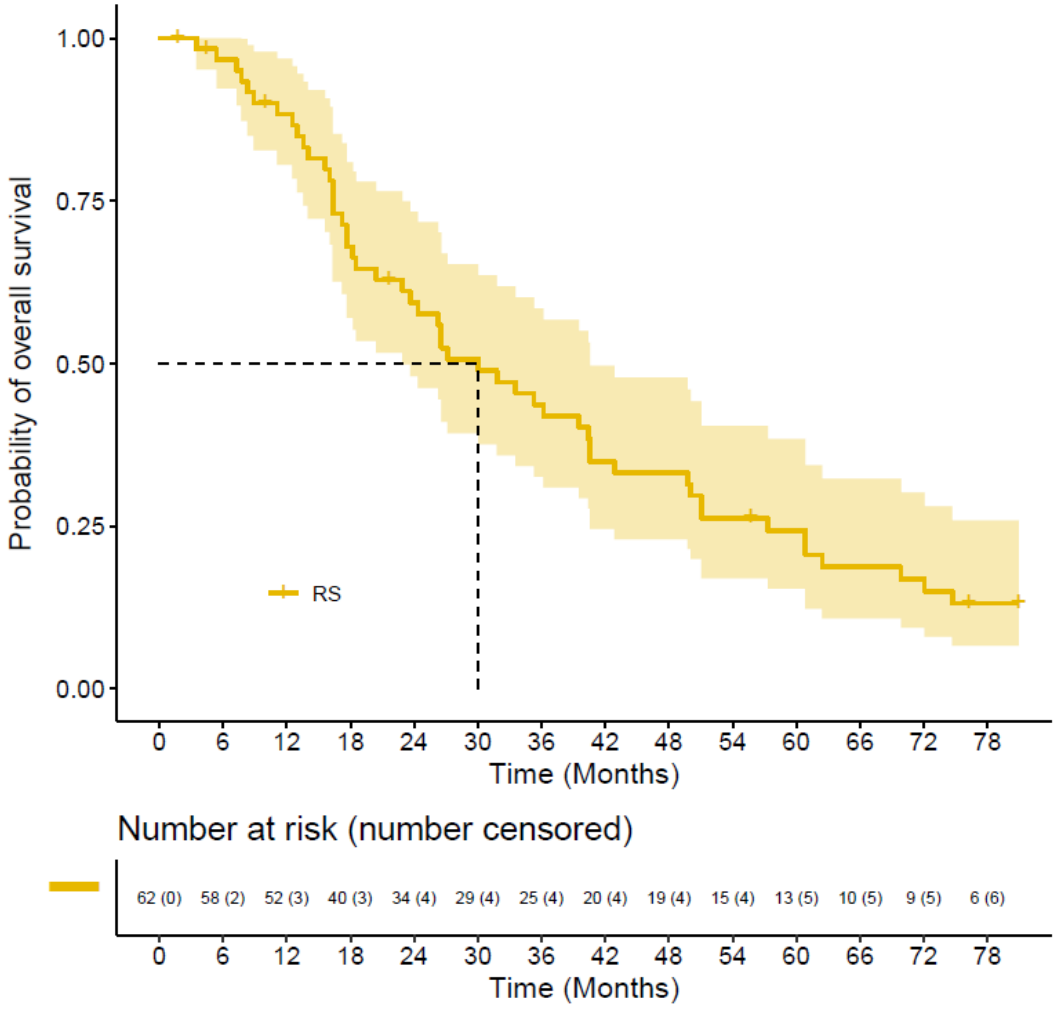
Figure 22: Overall survival in the placebo BRCAwt cohort of Study 19



RS, routine surveillance
Source: Digitised from Friedlander et al. (2018)[15]

In the BRCAmut cohort of Study 19, median OS was 30.2 for the placebo arm and 80.6% (50/62) of patients had died at final data cut-off May 2016. In comparison median OS was 51.58 months for patients treated with niraparib in the gBRCAmut 2L subgroup of NOVA.

Figure 23: Overall survival in the placebo BRCAmut cohort of Study 19



RS, routine surveillance

Source: Digitised from Friedlander et al. (2018)[15]

3.3.2 Lord et al. 2020

Lord *et al.* 2020 is an observational, retrospective chart review investigating survival outcomes for standard of care (routine surveillance) across 13 NHS Trusts in the UK. It includes 233 patients with advanced ovarian cancer treated between January 2007 and December 2014. The study included patients who had completed two lines of platinum-based chemotherapy with evidence of an objective response (complete or partial response), similar to patients enrolled in NOVA. BRCA status was unknown for the majority of patients (84.5%) and the results were only presented for the full cohort and not available by BRCA status.

As highlighted by the company, differences in baseline characteristics, such as age and performance status, are expected when comparing patients in real-life cohorts with patients enrolled in clinical trials. The ERG, therefore, considers the trial Study 19 to be a more relevant source for comparator data than the RWE from Lord *et al.* 2020. In addition, as the populations of interest to this CDF review are patients with and without BRCA mutation, which are not available for Lord *et al.* 2020, the ERG does not provide further description or critique of Lord *et al.* 2020 in this report.

3.4 Conclusions of the clinical effectiveness section

The company has generally taken on board the committees preferred assumptions as stated in the Terms of Engagement. The key uncertainties identified at the original appraisal were around the survival evidence, which was immature, and the most appropriate method for modelling PFS and OS.

The company has focused their submission on the ITT population of the NOVA trial, that is, pooled data for the two randomised patient cohorts of the trial: gBRCAmut 2L+ and non-gBRCAmut 2L+. The company does, however, provide scenario analyses separately for the gBRCAmut 2L subgroup and the non-gBRCAmut 2L+ cohort, which are the populations specified as of relevance to this CDF review in the Terms of Engagement.

The PFS data are unchanged since the original appraisal, where the company used PFS assessed by an Independent Review Committee (IRC), which was the primary outcome of NOVA. This endpoint was met at the primary analysis in May 2016 and, therefore, no additional PFS data were collected. The committee has, in the FAD for the original appraisal, stated that modelling of TTD should be based on TTD as determined by the investigator and captured in the NOVA trial. To accommodate the committee's preference for TTD and at the same time resolve the disparity between outcomes assessed based on IA and IRC, the ERG considers that the economic assessment should be based on IA PFS rather than IRC PFS as TTD is IA. However, these data were not provided by the company.

The company has presented more mature OS and TTD data from NOVA, based on the final data cut-off in October 2020. This decreases the uncertainty around OS for patients treated with niraparib compared with the original data cut. The company has used the updated OS data for the niraparib arm but OS for the placebo arm of NOVA did not inform the company's base case because the trial suffered from a large amount of missing data in both trial arms and a substantial amount of subsequent PARP inhibitor use primarily in the placebo arm, confounded the data. Instead, the company relied on a PFS:OS ratio of 1:1 for their base case, and scenario analyses, where routine

surveillance was informed by the placebo arm of Study 19 or a retrospective cohort study by Lord *et al* 2020. The ERG considers Study 19 to provide the most robust data to inform the comparison of OS between niraparib and routine surveillance but highlights that the analysis is based on a naïve comparison with no adjustments made for differences between the relevant subgroups in NOVA and Study 19.

For the gBRCAmut 2L subgroup in NOVA and the BRCAmut subgroup in Study 19, the results of the naïve comparison of OS may be conservative. This is mainly because a large proportion in both groups received post-progression PARP inhibitor therapy and that this is likely to benefit the placebo group from Study 19 more than the niraparib group from NOVA. The comparison of the non-gBRCAmut 2L+ subgroup on NOVA with the BRCAwt group in Study 19, on the other hand, may provide an overestimate of the benefit of niraparib over placebo as the non-gBRCAmut subgroup includes some patients with a somatic BRCA mutation, whereas patients in the BRCAwt subgroup does not. There are, of course, other both observed and likely unobserved differences between these populations which will have an impact on the direction and magnitude of the relative effectiveness of niraparib and placebo. So, although a lot of the uncertainty around the OS for patients treated with niraparib has been resolved, there is still uncertainty around the relative efficacy of niraparib compared with routine surveillance for OS.

SACT data has been collected for 157 gBRCAmut 2L patients and 859 non-gBRCAmut 2L+ who have received niraparib treatment through the CDF. Median follow-up for OS was 20.3 months and 17.5 months for the gBRCAmut 2L and non-gBRCAmut 2L+ cohorts, respectively. Median OS was not reached for the gBRCAmut 2L cohort, but the survival rates show that 87% were alive at 12 months, which decreased to 64% at 24 months. For the non-gBRCAmut 2L+ cohort median OS was 22.6 months. The OS outcomes of patients in the non-gBRCAmut 2L+ SACT cohort are worse than for the equivalent cohort in NOVA (median OS 31.11 months). Although median OS is not yet reached for the gBRCAmut 2L cohort in SACT, it is likely to be shorter than the median OS observed for this population in NOVA. The SACT dataset provides important RWE of the efficacy of niraparib in UK clinical practice, but the company has not incorporated the SACT OS data in the updated economic model for this CDF review. However, in response to a clarification request the company provided a RWE scenario using SACT OS and TTD data for niraparib.

4 Cost effectiveness

The company's submission (CS) for the cancer drugs fund (CDF) review of niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer was mostly unchanged from the approach implemented in the original Single Technology Appraisal 528 (TA528).[6] The key updates made by the company for the CDF submission were as follows:

- Increase in the patient access scheme (PAS) discount from [redacted] to [redacted].
- Overall survival (OS) data from NOVA from data cut off October 2020 implemented in the economic model for niraparib only.
- PFS:OS ratio of 1:1 used in the economic model to estimate OS for the routine surveillance arm.
- Modelling of progression-free survival (PFS) for the subgroup of patients without a germline BRCA mutation (non-gBRCAmut 2L+ subgroup) based on a flexible spline curve (normal k=1).
- Time to maintenance treatment discontinuation (TTD), treatment specific utilities and dosing data updated in the economic model using the 2020 data cut from NOVA.

As part of their CDF submission, the company presented new analyses for a *post-hoc* pooled intention-to-treat (ITT) population from the NOVA trial. The pooled ITT population is comprised of the randomised gBRCAmut 2L+ and non-gBRCAmut 2L+ population. The ERG notes that the pooled ITT analysis is not restricted to gBRCAmut patients who have only had two lines of platinum-based chemotherapy, as per the committee's preferred assumptions from the Terms of Engagement (ToE). As such, the ERG considers that the pooled analysis is outside the scope of the CDF review and will not be discussed any further for the remainder of this report.

Table 25 and Table 26 presents the company's final base case results from TA528 (original and updated PAS) alongside the company's updated CDF base case for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups.

Table 25. Deterministic cost-effectiveness results for the gBRCAmut 2L subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Final base case results from TA528 ([redacted] PAS)[6]							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-

Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,694
Final base case results from TA528 ([redacted] PAS)							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,153
Updated base case results (post clarification)							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,475

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; PAS, patient access scheme; QALY, quality-adjusted life-year.

Table 26. Deterministic cost-effectiveness results for the non-gBRCAmut 2L+ subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Final base case results from TA528 ([redacted] PAS)[6]							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,795
Final base case results from TA528 ([redacted] PAS)							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,585
Updated base case results (post clarification)							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,942

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; PAS, patient access scheme; QALY, quality-adjusted life-year.

4.1 Summary and critique of the company's submitted economic evaluation by the ERG

4.1.1 Population

The patient population considered by the company for the cost-effectiveness analysis is based on the NOVA trial population which included adult patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube or primary peritoneal cancer who have previously received at least two platinum-based regimens and were responsive (partial or complete) to their last platinum-based chemotherapy. Two separate cohorts were prespecified and randomised in the trial and included; patients with a deleterious germline BRCA mutation or genetic variant, or a suspected deleterious mutation (gBRCAmut cohort) and patients without the hereditary germline BRCA mutation (non-gBRCAmut cohort). The cost-effectiveness analysis for the non-gBRCAmut cohort is focused on the population who have had 2 lines or more of platinum-based chemotherapy (non-gBRCAmut 2L+). For the gBRCAmut cohort, the analysis is for patients who have had only two lines of platinum-based chemotherapy (gBRCAmut 2L). The population remains unchanged from that accepted by the committee for TA528.[6]

4.1.2 Interventions and comparators

The intervention and comparators considered in the economic analysis were niraparib (intervention) and routine surveillance and remains unchanged from TA528.[6]

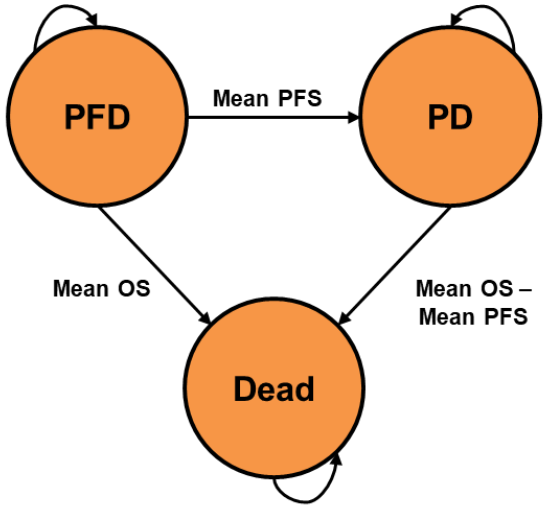
The treatment regimen for niraparib is three 100mg capsules taken orally once daily, equivalent to a total daily dose of 300mg. However, the company noted that data from NOVA indicated that on average in clinical practice, the full dose of niraparib may not be consumed by patients and instead used data on prescribed dose received to calculate a mean daily dose per treatment cycle (28 days) to inform the model for TA528. In the first treatment cycle, patients received the full dose of 300mg and were subsequently down titrated each cycle until reaching a plateau by cycle 5. The company's approach to using a mean daily dose based on treatment cycles 1 to 5+ from NOVA remains unchanged for the CDF submission. However, the data from NOVA informing the company's CDF analysis has been updated to use actual dose consumed (dispensed dose minus returned dose) using a later data-cut from 2020. The change in dose data used in the economic model has resulted in a reduction in the mean dose per treatment cycle and as a result a reduction in treatment costs implemented in the model. This issue is discussed further in Section 4.1.7.

Duration of treatment with niraparib is based on TTD data obtained from the NOVA trial. TTD from NOVA was based on investigator assessment (IA), and accepted as appropriate by the committee for TA528.[6] For the CDF submission, updated TTD data based on the latest 2020 data cut from NOVA was extrapolated using parametric survival distributions and is discussed in more detail in 4.1.4.3.

4.1.3 Modelling approach and model structure

The company has made no changes to the modelling approach and model structure for the CDF submission as this was accepted as adequate for decision-making in TA528.[3] As a reminder, the company developed a single *de novo* economic model in Microsoft Excel© to assess the cost-effectiveness of niraparib compared with routine surveillance for the non-gBRCAmut 2L+ and gBRCAmut 2L populations. A decision analytic model based on mean values for parameters (presented in Figure 5) was implemented (hereafter referred to as the "means-based" model). The model structure is comprised of three health states: progression free disease (PFD), progressive disease (PD), and dead. The model time horizon is 40 years and the cycle length is 28 days.

Figure 5. Model structure (taken from the economic model)



KEY: PFD; progression-free disease, PD; progressed disease, OS; overall survival

The means-based approach estimates survival curves for PFS and OS in order to calculate the area under the curve (AUC) using a trapezium rule, which essentially estimates two time periods from the survival curve to add together in order to calculate the mean time spent in the health state. Mean costs and utilities associated with the health state are then applied to the mean time spent in the health state.

The model structure presented in Figure 5 indicates that there are cycle transitions between each health state that occur over time, i.e. patients can remain or move between the health states after each cycle. However, in reality, all movements through the health states are determined by mean time spent in the health state such that all patients enter the model in the PFD state and have to pass through the PD health state in order to progress to the death state. One of the key issues the ERG had with the company's means-based model approach was that the time dependencies in the event rates of PFS and OS become hidden in the estimation of the means, resulting in oversimplified costs and QALY estimates. Please refer to the TA528 ERG report for further details on this issue.[6]

As mentioned previously, the means-based modelling approach was accepted as adequate for decision-making by the committee for TA528. However, this was based on a statement by the company during the committee meeting that the incremental cost-effectiveness ratio (ICER) difference between the means-based model and a partitioned survival model was around £1,000 per quality adjusted life year (QALY). However, the partitioned survival model was not presented to the ERG to verify the claim.

In response to an ERG request for the partitioned survival model quoted in the FAD, the company confirmed that this model was not provided as part of TA528 nor was the model supplied by the company during the clarification stage for the CDF review. Instead, the company assumed that the ERG's concerns were around how discounting was applied in the model and provided an Excel file with simplistic calculations based on dummy data (also provided in TA528) demonstrating the difference between instantaneous discounting versus per cycle discounting. In addition, the company stated that their model structure was based on technology appraisal 91 (TA91), which has been replaced by TA389.[7]

The ERG considers TA91 to reflect the available methods at that time (as it was published in 2005) but advances in methodology mean that more robust approaches are now available. Furthermore, the ERG considers that the means-based approach does not account for the time in the event rates of PFS and OS and as such the associated costs and QALYs. The ERG notes that more mature OS data are now available from NOVA (which was a limitation in TA528) allowing the company to change their approach to the model structure to estimate robust cost-effectiveness results. Furthermore, the ToE states that the company should fully investigate the most appropriate PFS and OS modelling using updated clinical trial data, which the ERG considers should have involved reviewing if the means-based model was fit for purpose in light of the updated data from NOVA.

As such, the ERG considers that the unverified partitioned survival model results quoted by the company in TA528 had an undue influence on the committee's decision to accept the means-based model structure. As the ERG has requested this model and it has not been supplied, the ERG considers it likely that the model doesn't exist. Therefore, the ERG recommends the committee should reconsider its decision to accept the means-based model structure, given the company has been unable to provide any evidence to validate their approach is equivalent to a more robust partitioned survival model. In addition, the ERG is concerned that this sets a dangerous precedent where companies can introduce unverified new evidence during a committee meeting, which influences committee decision making, but is never subsequently assessed.

4.1.4 Treatment effectiveness

In the Terms of Engagement, three key statements around modelling of treatment effectiveness were made by the committee and are as follows:

- The company should fully investigate the most appropriate PFS modelling using updated clinical trial data.
- The company should fully investigate the most appropriate OS modelling using updated clinical trial data.
- The time to treatment discontinuation, as measured in the NOVA trial, should be used to within the economic model.

In the company's CDF submission, updated data for OS and TTD have been provided based on the 2020 data cut from NOVA. The data used to inform PFS, based on independent review committee (IRC) assessment from the 2016 data cut from NOVA, remains unchanged. Each of the below subsections describes the company's updates to the modelling of PFS, OS and TTD in relation to the committee preferences outlined in the Terms of Engagement.

4.1.4.1 Progression-free survival

One of the key uncertainties raised by the ERG in TA528 was that the company's preferred extrapolation of PFS for niraparib for both the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups produced clinically implausible long tails. The long tails in the PFS extrapolations resulted in a small proportion of patients on niraparib assumed to have progression-free disease after 20 years, and required the company to apply an arbitrary cap on PFS of 20 years (i.e. no patients can be progression-free beyond 20 years). The ERG's clinical experts stated that they would expect patients

on niraparib would progress by 10 years and that patients on routine surveillance would progress by 5 years. Based on feedback from the ERG's clinical experts, alternative standard parametric distributions that had a natural decline to 10 years were selected for the ERG base case. However, clinical experts in attendance for the committee meeting for TA528 stated that it is biologically plausible that patients on niraparib could survive longer than 10 years, and therefore the ERG's assumption of 10-year survival was potentially pessimistic.

In their response the appraisal consultation document (ACD), the company explored flexible spline models for PFS for both the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups. However, the committee stated that, "*the scenario did not decrease the general uncertainty around the validity of any of the extrapolations*".[3] As such, in the ToE the committee requested the company to fully investigate the most appropriate PFS modelling using updated clinical trial data. For the CDF submission, the company resubmitted their preferred extrapolation for PFS for the gBRCAmut 2L subgroup from their original submission (lognormal) and the best fitting spline model for the non-gBRCAmut 2L+ subgroup from their ACD response (normal k=1 spline).

During the clarification stage, the ERG requested the company to provide further evidence to justify their preferred approach for PFS and in addition resubmit the flexible spline analysis provided in the company's response to the ACD for TA528.[8] In their response, the company stated that approximately 16% of olaparib patients were on treatment and therefore progression-free after 5 years, based on an abstract by Gourley *et al*.[9] The ERG notes that, based on Gourley *et al*.,[9] 10.8% of BRCAm patients and 12.3% of BRCAwt patients were on treatment for greater than 6 years. Furthermore, in Study 19 patients could be treated beyond progression if deemed appropriate by the investigator.[5] As such, on-treatment data from Study 19 may not be a reliable measure of long-term progression-free survival for niraparib.

The company also supplied the hazard function and log-cumulative hazard plot for PFS for the gBRCAmut 2L subgroup, which demonstrated that the hazards were non-monotonic and thus the log-normal distribution is appropriate. However, the ERG considers that the company's choice of log-normal distribution results in inflated PFS estimates, which require the company to apply an arbitrary cap at 20 years.

The ERG acknowledges the committee's consideration that its preferred PFS approach may be pessimistic and that the committee considered a flexible modelling approach maybe more

appropriate. As such, the ERG explored the company's flexible spline analysis and considers that the hazard k=1 spline provides a less pessimistic, but clinically plausible long-term extrapolation that more appropriately captures the hazard function and has included it in the ERG base case presented in Section 6.4. Figure 6 and Table 27 presents the proportion of niraparib patients that are progression-free at key timepoints for the lognormal, hazard k=1 spline and the Weibull distributions.

Figure 6. Alternative PFS distributions for niraparib – gBRCAmut 2L subgroup

Table 27. Proportion of patients progression-free at key time points for alternative PFS distributions – gBRCAmut 2L subgroup (adapted from company clarification response, Table 8)

Year	Lognormal (company base case)	Hazards k=1 spline (ERG preferred)	Weibull (TA528 ERG base case)
5	21.75%	21.36%	7.35%
10	8.97%	5.78%	0.18%
15	4.74%	1.69%	0.00%
20	2.85%	0.52%	0.00%

Abbreviations: ERG, Evidence Review Group; PFS, progression-free survival.

For the non-gBRCAmut 2L+ subgroup, the ERG explored the spline models supplied by the company and considered that the hazards k=1 spline was a plausible alternative to the company's selection of the normal k=1 spline, based on statistical and visual fit (Figure 7). However, long-term estimates of PFS based on the hazards k=1 spline for the non-gBRCAmut 2L+ subgroup (Table 28) were slightly more conservative compared with the company base case but aligned with the ERG's preferred long-term PFS estimates for gBRCAmut 2L subgroup (Table 27). The ERG explored the use of the hazards k=1 spline in a scenario presented in Section 6.3 and included it as part of the ERG preferred assumptions, presented in Section 6.4.

Figure 7. Alternative PFS distributions for niraparib – non-gBRCAmut 2L+ subgroup

Table 28. Proportion of patients progression-free at key time points for alternative PFS distributions – non-gBRCAmut 2L+ subgroup (taken from the economic model)

Year	Normal k=1 spline (company base case)	Lognormal (TA528 ERG base case)	Hazards k=1 spline
5	9.22%	2.91%	9.09%
10	3.89%	0.50%	3.10%
15	1.92%	0.15%	1.33%

20	0.75%	0.06%	0.65%

Abbreviations: ERG, Evidence Review Group; PFS, progression-free survival.

The ERG reiterates that because the PFS:OS relationship is still being used in the model, such that changes to mean PFS directly influence the calculation of mean OS (albeit now for routine surveillance, discussed in the next subsection), appropriate modelling of PFS is still a critical input in the model as it directly influences the benefit of niraparib. As such, the ERG's critique of the company's approach to PFS and the PFS:OS ratio presented in the TA528 ERG report and the ERG review of company's response to the ACD for still holds and should be referred to for more details.[6, 8]

An issue around PFS that has remained unresolved from TA528 is the discrepancy between IA PFS and IRC PFS. As mentioned in Section 3.1.1, the ERG remains concerned that the PFS benefit of niraparib is inflated based on the two different methods of assessment. In NOVA, treatment with niraparib was stopped if the investigator identified disease progression. As such, the ERG considers that "investigator determined" TTD and IA PFS from NOVA would be consistent. In TA528, the company declined to provide a scenario using IA PFS in the economic model. Thus, in the TA528 ERG report[6] and the ERG response to company ACD comments[8], the ERG explored scenarios that focussed on using equivalence of IRC PFS to estimate TTD and IA TTD (preferred by the committee) to estimate IA PFS to appropriately align the costs and benefits associated with niraparib.

During the clarification stage for the CDF submission, the ERG requested a scenario using IA PFS again, but the company maintained their position from TA528 and declined to provide the analysis, stating that the committee did not consider assessment of PFS as an uncertainty. Nonetheless, the ERG considers that exploring the discrepancy between IA and IRC PFS estimates is a resolvable issue but relies on the company providing analysis using IA PFS.

4.1.4.2 Overall survival

In the time that niraparib was in the CDF, OS data from NOVA matured and the company provided updated data from the 2020 data cut as part of their CDF submission. In NOVA, crossover to PARP inhibitors in the placebo arm post-progression or after withdrawal from the study was substantial, resulting in confounded OS estimates (see Section 3.1.2). As such, the company only implemented OS data from NOVA for the niraparib arm in the economic model. Mean OS for the routine surveillance arm in the company's base case analysis was estimated using a PFS:OS relationship of 1:1 in the economic model.

As mentioned in Section 3.1.2, the company confirmed in their clarification response that the definition of 2L for the gBRCAmut subgroup for OS was based on patients who have only had two lines of chemotherapy, both of which were platinum-based (n=100) and the same definition has been used for PFS and TTD.

Niraparib OS KM data from NOVA for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups were extrapolated in accordance with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidelines.[10] The company explored standard parametric distributions (Exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma) and selected the best fitting distribution based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics as well as visual inspection of the curves against the observed data. Please refer to Appendix 24 of the company CDF submission for AIC/ BIC statistics for the OS parametric distributions. In addition to statistical and visual fit, the company compared mean estimates of OS produced by selected curves against mean OS estimated from extrapolations of Study 19 data for the gBRCAmut and non-gBRCAmut subgroups.

For both the gBRCAmut 2L and non-gBRCAmut 2L+ subgroup, the company selected the lognormal curve for the extrapolation of OS for niraparib (presented in

Figure 8 and

Figure 9). As a scenario around the base case, the company explored the use of extrapolated BRCAmut and BRCAwt subgroup OS placebo data from Study 19 for the routine surveillance arm (also presented in

Figure 8 and

Figure 9). Table 29 presents the mean OS estimates for niraparib (NOVA) and routine surveillance (calculation and Study 19) for both subgroups.

Figure 8. OS Kaplan Meier and lognormal distribution for niraparib (NOVA) and routine surveillance OS from Study 19 (BRCAmut) - gBRCAmut 2L (taken from the economic model)

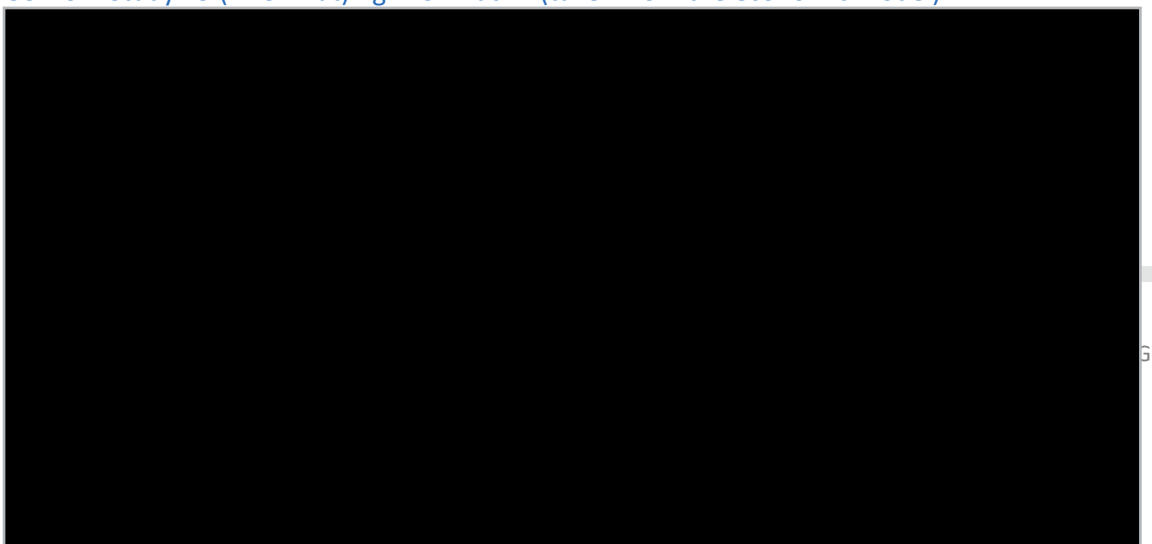
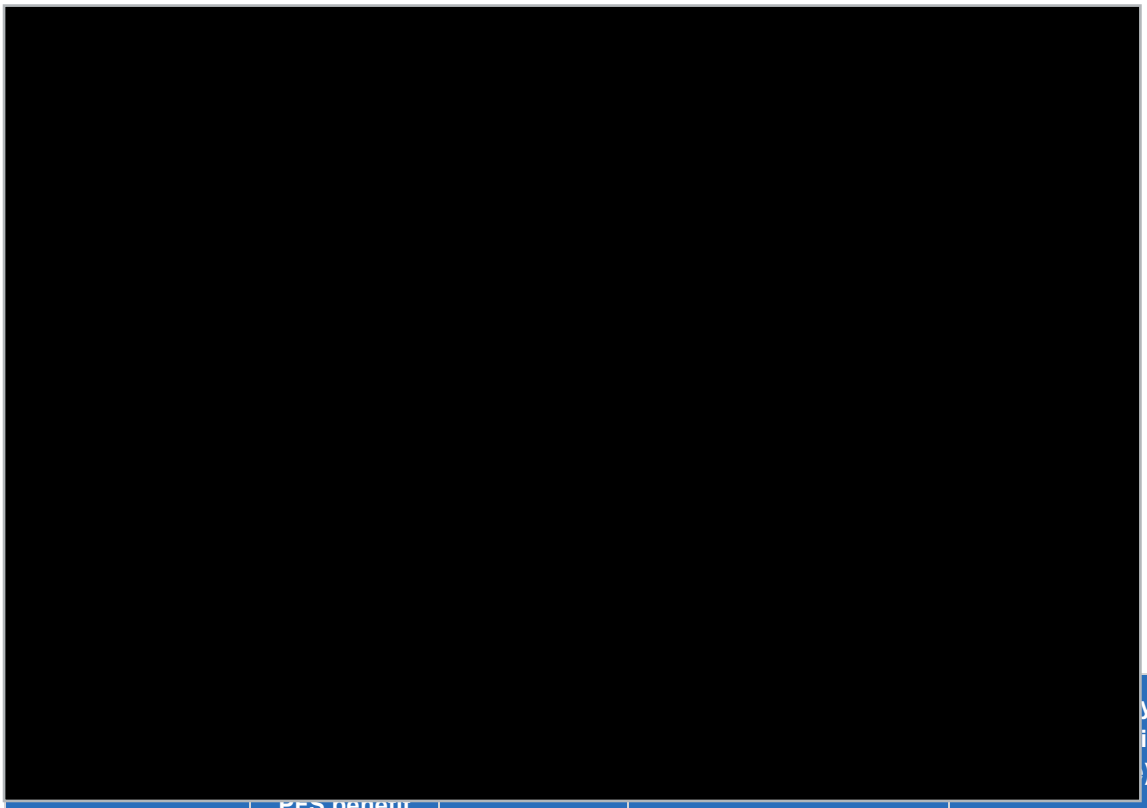


Figure 9. OS Kaplan Meier and lognormal distribution for niraparib (NOVA) and routine surveillance OS from Study 19 (BRCAwt) – non-gBRCAmut 2L+ (Figure 30, Appendix 22.2 of the company CDF submission



	PFS benefit			y 19 ine)
gBRCAmut 2L	2.96 years	[redacted]	[redacted] ([redacted] – 1*2.96)	3.70 years

non-gBRCAmut 2L+	1.09 years	[redacted]	[redacted] ([redacted]– 1*1.09)	2.97 years

Abbreviations: gBRCAmut, germline breast cancer susceptibility cancer mutation; OS, overall survival; PFS, progression-free survival.

*calculated using a PFS:OS ratio of 1:1.

The ERG considers that there are two key issues around the company's approach to modelling of OS, which include the appropriateness of the PFS:OS ratio and the estimation of OS for routine surveillance.

In the company's submission for TA528, lack of OS data was a key limitation in the analysis. Thus, to generate mean OS for niraparib for each of the subgroups, the company employed a PFS:OS ratio of 1:2 and the baseline OS curves used for routine surveillance were estimated from the placebo arm of Study 19 (BRCAmut and BRCAwt subgroups). However, as part of the CDF submission the company used a PFS:OS ratio of 1:1 to estimate OS for routine surveillance as a way to "bypass" the confounded OS data from the placebo arm in NOVA. The ERG fundamentally disagrees with the use of a PFS:OS ratio. As outlined in the TA528 ERG report[6], there is a lack of consistent evidence around the relationship between PFS to OS in advanced or metastatic cancer, making it an unreliable and uncertain measure. Furthermore, this approach intrinsically links changes to PFS to OS benefits.

Given that OS data from Study 19 were used for the routine surveillance arm in TA528, the ERG considers that it is still appropriate to use the same approach for the CDF submission, even though the data are based on naïve comparison. Please Section 3.3.1 for further details. The ERG notes that there are some differences in baseline characteristics between NOVA and Study 19 but considers the cohorts from the two trials are generally comparable. Furthermore, by using randomised control trial OS data from both studies, a like for like comparison is maintained in the model.

The ERG investigated the OS parametric distributions selected by the company for niraparib (based on NOVA) and routine surveillance (using Study 19 data). For both the gBRCAmut 2L and non-gBRCAmut 2L+ subgroup, the ERG considered that the company's selection of the lognormal distribution for both niraparib and routine surveillance was appropriate. Thus, for the ERG preferred analysis, the company's base case OS extrapolations for NOVA and Study 19 data has been implemented for the niraparib and routine surveillance arms for both subgroups, respectively.

4.1.4.3 *Time to maintenance treatment discontinuation*

For the CDF submission, the company updated the modelling of TTD to use data from the latest 2020 data cut from NOVA. Observed TTD from NOVA is based on investigator assessment and was accepted by the committee for TA528 as appropriate for use in the model. The company's approach to curve selection and final models chosen for the extrapolation of TTD for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups remained unchanged from their original submission.

Briefly, the company extrapolated Kaplan-Meier (KM) TTD data for niraparib over a lifetime horizon and independent parametric survival distributions were fit to the data. The company selected the best fitting distribution based on AIC and BIC statistics as well as visual inspection of the curves against the observed data. The following distributions were considered in accordance with NICE DSU TSD 14 guidelines; Exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma.[10] The company implemented 20-year cap on the extrapolation to ensure no patients were progression free or on maintenance treatment beyond this time point. Please refer to Appendix 25 of the company CDF submission for AIC/ BIC statistics for the TTD parametric distributions.

Based on the curve fitting exercise, the company selected the lognormal distribution for the extrapolation of TTD for the gBRCAmut 2L subgroup and the log-logistic distribution for the non-gBRCAmut 2L+ subgroup.

Figure 10 and

Figure 11 presents the TTD extrapolations for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups.

Figure 10. TTD Kaplan Meier and lognormal distribution for niraparib - gBRCA 2L (taken from the economic model)

Figure 11. TTD Kaplan Meier and log-logistic distribution for niraparib – non-gBRCA 2L+ (taken from the economic model)

As part of their clarification response, the company updated their base case to include a cap on TTD such that it could not exceed PFS. Based on the selected curves and the TTD cap, mean time on niraparib maintenance treatment was estimated to be ********** and ********** for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups, respectively. After interrogation of the application of TTD in the model, the ERG found that the TTD cap for the non-gBRCAmut 2L+ subgroup was

applied incorrectly, as it was capped to the company's selected standard parametric PFS curve rather than the flexible spline PFS curve used for their base case. Please refer Figure 12 and Figure 13 for an illustration of the issue. The ERG corrected this error (shown in Figure 13) and results are presented in Section 6.1. In a later round of clarification responses from the company, they accepted the TTD error and confirmed the results presented in Section 6.1.

Figure 12. Gompertz TTD extrapolation without TTD cap

Figure 13. Gompertz TTD extrapolation with company TTD cap and ERG correction

The ERG considers that the company's extrapolation of TTD for the gBRCAmut 2L subgroup is appropriate. However, for the non-gBRCAmut 2L subgroup, the ERG considers that the Gompertz curve better captures the tail of the KM curve (see

Figure 13) and has a similar statistical fit to the company's preferred log-logistic distribution. As such, the ERG explored the use of the Gompertz distribution for the non-gBRCAmut 2L subgroup TTD in a scenario, presented in Section 6.3 and included it as part of the ERG preferred assumptions, presented in Section 6.4.

4.1.5 Adverse events

The company has made no changes to the modelling of adverse events (AEs) for the CDF submission.

4.1.6 Health-related quality of life

In TA528, the company implemented treatment-specific health-state utility values (HSUVs) based on mapped EQ-5D-3L data from the NOVA trial (the EQ-5D-5L was used in the trial).[6] For the CDF submission, the company has updated the treatment-specific HSUVs using the later 2020 data cut from NOVA, presented in Table 30.

Table 30. Treatment specific mapped EQ-5D-3L utilities (adapted from Table 58 of the TA528 ERG report and Table 26, Appendix 26 of the company CDF submission)

Health state	Utility value (SE) – TA528[6]	Utility value (SE) – CDF update
Niraparib PFD	0.812 (0.004)	[redacted]
Niraparib PD	0.728 (0.015)	[redacted]
Placebo PFD	0.770 (0.008)	[redacted]
Placebo PD	0.705 (0.019)	[redacted]

Abbreviations: CDF, cancer drugs fund; PD, progressed disease; PFD, progression-free disease; SE, standard error.

In the ERG report for TA528, health-state utilities based on progression status were preferred for the ERG base case, as it was debatable that niraparib would be associated with higher health-related quality of life (HRQoL) when the adverse event rate was also higher compared with placebo.[6] Furthermore, in the clarification response for TA528 and the current CDF submission no statistical tests were performed, or results supplied to determine if the difference in utility values between niraparib and placebo were statistically significant.[6]

At the clarification stage, the ERG requested a scenario incorporating health state utility values based on progression status, which the company provided. Table 31 presents health state utilities based on the updated 2020 data cut from NOVA and from TA528. Results of the scenario are presented in Section 5.1.2.3, Table 41 and Table 42. The ERG notes that the company's scenario also removes disutility associated with AEs as per the ERG's preferred assumptions in TA528.

Table 31. Health state mapped EQ-5D-3L utilities (adapted from Table 60 of the TA528 ERG report and Table 26, Appendix 26 of the company CDF submission)

State	Utility value (SE) – TA528[6]	Utility value (SE) – CDF update
PFD	0.801 (0.004)	[redacted]
PD	0.719 (0.012)	[redacted]

Abbreviations: CDF, cancer drugs fund; PD, progressed disease; PFD, progression-free disease; SE, standard error.

The ERG maintains its position that utility values based on progression status alone are the most appropriate for the cost-effectiveness analysis and this position is supported by the ERG's clinical experts. As such, utility values based on progression status are included in the ERG's preferred assumptions, presented in Section 6.4.

4.1.7 Resource use and costs

In the company's updated base case for the CDF review, the mean technology cost for niraparib has been updated as a result of updated dose data from the latest 2020 data cut from the NOVA trial (described in Section 4.1.2). In addition to updated dose data, the company has also revised their PAS simple discount from [redacted] to [redacted]. Table 32 presents a comparison of the mean dose and cost per cycle for niraparib used in TA528 and the CDF submission.

Table 32. Costs per treatment cycle for niraparib (adapted from Table 63 of the TA528 ERG report and Table 27, Appendix 27 of the company CDF submission)

Cycle	TA528 (PAS = [redacted])[6]				CDF update (PAS = [redacted])			
	gBRCAmut 2L		Non-gBRCAmut 2L+		gBRCAmut 2L		Non-gBRCAmut 2L+	
	Mean dose per cycle	Mean cost per cycle	Mean dose per cycle	Mean cost per cycle	Mean dose per cycle	Mean cost per cycle	Mean dose per cycle	Mean cost per cycle
1	[redacted]							
2	[redacted]							
3	[redacted]							
4	[redacted]							
5+	[redacted]							

Abbreviations: gBRCAmut, germline BRCA mutation; mg, milligram.

Based on the updated data from NOVA, the mean dose of niraparib per cycle has reduced compared with the data used in TA528, resulting in a lower cost for niraparib irrespective of the updated PAS discount. In response to a clarification question about the change to the mean dose data from NOVA, the company explained that the dose data used in TA528 reflects the prescribed dose of niraparib, calculated as a weighted average based on the proportions of patients prescribed 300mg, 200mg or 100mg per day. However, niraparib dose data for the CDF submission is based on actual dose consumed, calculated as the dispensed dose minus the returned dose per cycle.

The ERG considers that in UK clinical practice, niraparib doses prescribed are unlikely to be returned to the NHS and reused. As such, the ERG considers that the company's original approach of using the prescribed dose data reflects that natural wastage that will occur in clinical practice. The company provided a scenario using the prescribed dose data from TA528 and results are presented in Section 5.1.2.3, Table 41 and Table 42. The ERG incorporated prescribed niraparib dose data in its preferred assumptions, presented in Section 6.4.

4.1.8 *Systemic anti-cancer therapy analysis*

As described in Section 3.2, between 1 June 2018 and 30 November 2019, 157 gBRCAmut 2L patients, and 859 non-gBRCAmut 2L+ patients were enrolled to receive treatment with niraparib through the SACT framework. In the time that niraparib was in the CDF, relatively mature data on OS and TTD were collected. The ERG considers that the type and maturity of the niraparib data collected in SACT is valuable and usually unavailable and a "real-world" cost-effectiveness analysis using SACT data warrants exploration. As such, the ERG requested the company to provide cost-effectiveness results using SACT data for niraparib and assumptions for routine surveillance. The company provided the SACT cost-effectiveness analysis and the methods employed are described below.

As with the company's approach to extrapolating OS from NOVA, niraparib OS KM data from SACT for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups were extrapolated in accordance with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidelines.[10] The company explored standard parametric distributions (Exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma) and selected the best fitting distribution based on AIC and BIC statistics (presented Table 1 of the company's response to clarification to B3 and B6) as well as visual inspection of the curves against the observed data.

For both the gBRCAmut 2L and non-gBRCAmut 2L+ subgroup, the company selected the log-logistic distribution for the extrapolation of OS for niraparib (presented in Figure 14 and Figure 15).

Figure 14. OS Kaplan Meier and log-logistic distribution for niraparib from SACT - gBRCAmut 2L subgroup (Figure 2 from the company's response to clarification to B3 and B6)

SACT data has been collected for 157 gBRCAmut 2L patients and 859 non-gBRCAmut 2L+ who have received niraparib treatment through the CDF. Median follow-up for OS was 20.3 months and 17.5 months for the gBRCAmut 2L and non-gBRCAmut 2L+ cohorts, respectively. Median OS was not reached for the gBRCAmut 2L cohort, but the survival rates show that 87% were alive at 12 months, which decreased to 64% at 24 months. For the non-gBRCAmut 2L+ cohort median OS was 22.6 months. The OS outcomes of patients in the non-gBRCAmut 2L+ SACT cohort are worse than for the equivalent cohort in NOVA (median OS 31.11 months). Although median OS is not yet reached for the gBRCAmut 2L cohort in SACT, it is likely to be shorter than the median OS observed for this population in NOVA. The SACT dataset provides important RWE of the efficacy of niraparib in UK clinical practice, but the company has not incorporated the SACT OS data in the updated economic model for this CDF review. However, in response to a clarification request the company provided a RWE scenario using SACT OS and TTD data for niraparib.

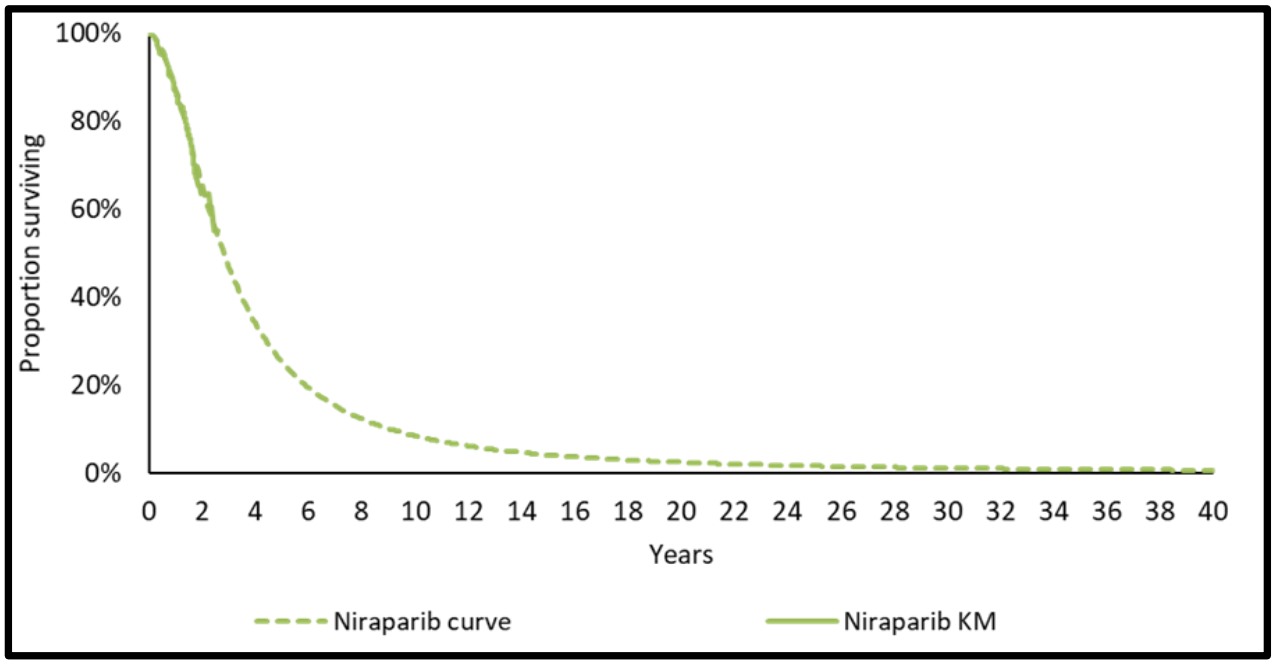
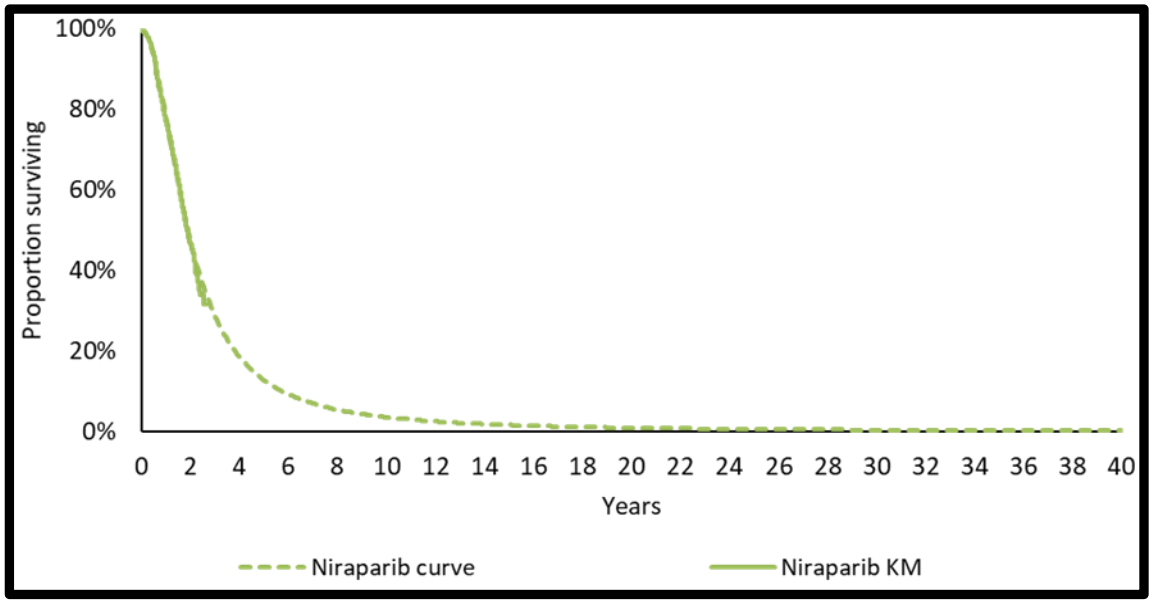


Figure 15. OS Kaplan Meier and log-logistic distribution for niraparib from SACT – non-gBRCAmut 2L+ subgroup (Figure 3 from the company's response to clarification to B3 and B6)



For SACT TTD, the company explored standard parametric distributions and selected the lognormal curve for both subgroups based on statistical and visual fit (Figure 16 and Figure 17). The ERG considers the company's extrapolations are appropriate.

Figure 16. SACT TTD scenario (lognormal extrapolation) – gBRCAmut 2L subgroup

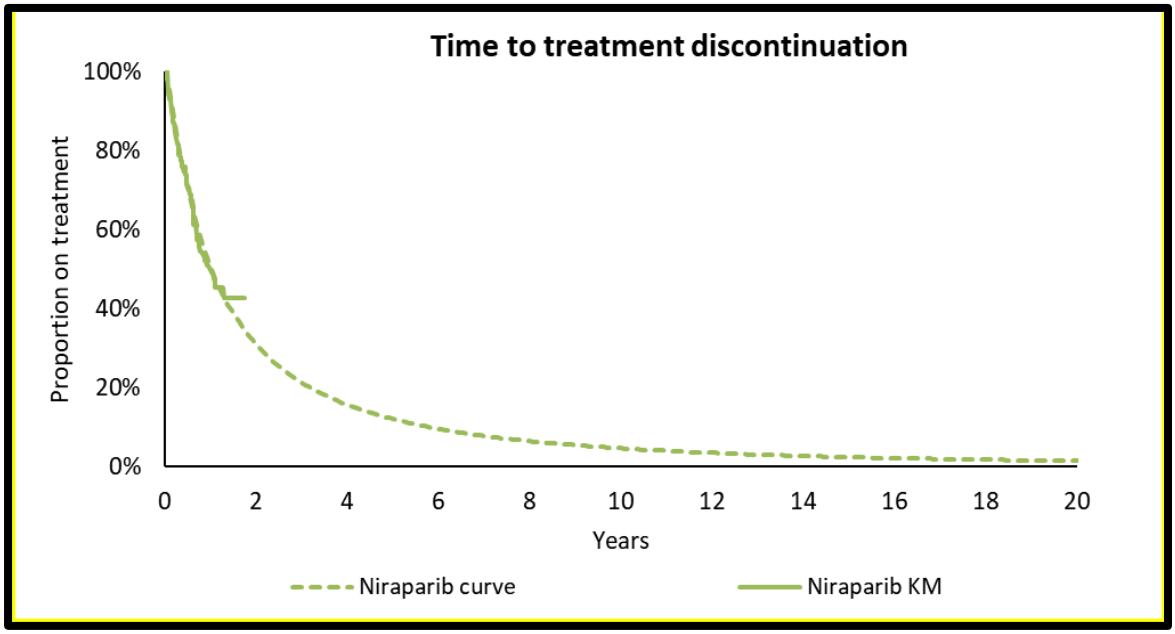
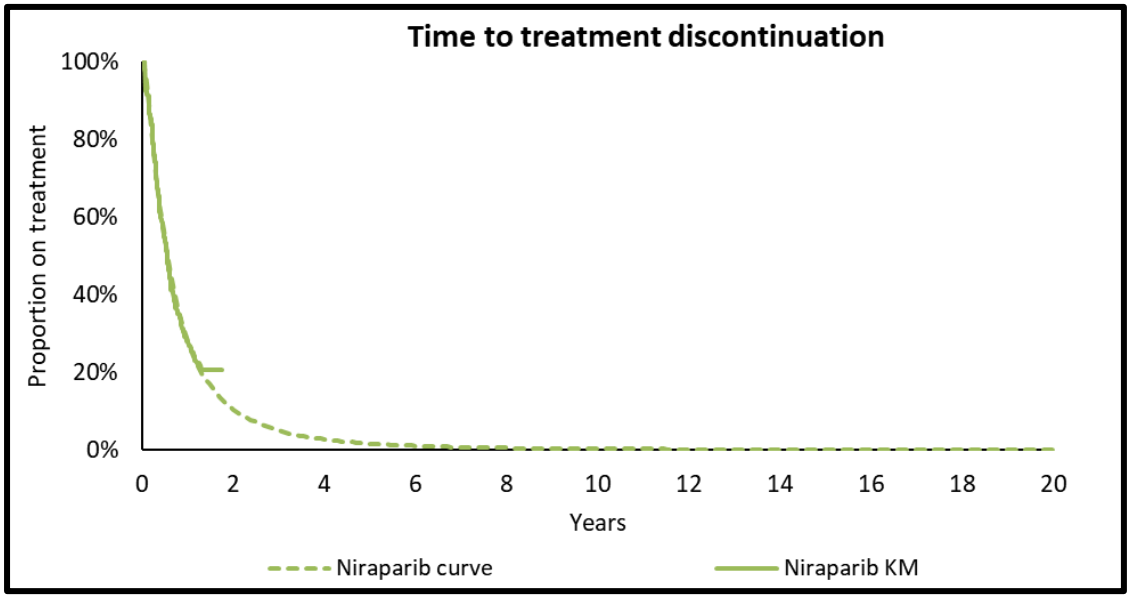


Figure 17. SACT TTD scenario (lognormal extrapolation) – non-gBRCAmut 2L+ subgroup



PFS outcomes were not collected in SACT database for niraparib and so the company simulated PFS using a PFS:TTD ratio applied to the SACT TTD extrapolations. The PFS:TTD ratio was calculated by dividing the company's base case mean TTD and mean PFS based on the NOVA extrapolations. Table 33 presents the data used to estimate the PFS:TTD ratio for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups. The company then used the Excel Goal seek function to estimate the HR based on the PFS:TTD ratio to be applied to the SACT TTD curve.

Table 33. Niraparib PFS:TTD ratio derived from NOVA (Table 3 from the company's response to clarification to B3 and B6)

Niraparib extrapolated outcomes – mean years	gBRCAmut 2L subgroup	Non-gBRCAmut 2L+ subgroup
PFS	3.63	1.92
TTD	2.48	1.50
PFS:TTD ratio	0.68	0.78

Abbreviations: PFS, progression-free survival; TTD, time to maintenance treatment discontinuation.

The remit of the SACT data collection was only focussed on patients receiving niraparib, therefore routine surveillance data for the SACT cost-effectiveness analysis needed to be estimated. As per the company base case, the company used a PFS:OS ratio of 1:1 to estimate mean OS. To estimate routine surveillance PFS, the NOVA PFS HR for each subgroup was applied to the estimated niraparib

PFS SACT curve. As a reminder, the NOVA PFS HR for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups was 0.22 (95% CI: 0.12 to 0.41) and 0.45 (95% CI: 0.34 to 0.61), respectively.

Table 34 presents the mean estimates used for the SACT cost-effectiveness analysis compared with the NOVA analysis. All other assumptions for costs and utilities remain as per the company's base case.

Table 34. NOVA vs SACT analysis mean survival estimates (adapted from Table 2, Table 4 and Table 7 from the company's response to clarification to B3 and B6)

Outcome (years)	gBRCAmut 2L subgroup		Non-gBRCAmut 2L subgroup	
	Niraparib	Routine surveillance	Niraparib	Routine surveillance
NOVA mean estimates				
PFS	3.63	0.66	1.92	0.83
OS	6.23	3.27	3.96	2.86
PD	2.60	2.61	2.04	2.03
TTD	2.48	n/a	1.50	n/a
SACT mean estimates				
PFS	3.42	0.44	1.19	0.47
OS	4.43	1.45	2.92	2.19
PD	1.01	1.01	1.73	1.72
TTD	2.34	n/a	0.93	n/a

Abbreviations: n/a, not applicable; OS, overall survival; PD, progressed disease; PFS, progression-free survival; TTD, time to maintenance treatment discontinuation.

Table 36 and Table 37 presents the company's SACT cost-effectiveness analysis results for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups.

Table 35. Company's deterministic SACT scenario results – gBRCAmut 2L subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	13,458	1.413	1.048	-	-	-	-
Niraparib	54,295	4.109	3.325	40,837	2.697	2.278	17,930

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; SACT, systemic anti-cancer therapy; QALY, quality-adjusted life-year.

Table 36. Company's deterministic SACT scenario results – non-gBRCAmut 2L+ subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	14,148	2.113	1.556	-	-	-	-
Niraparib	35,810	2.775	2.168	21,662	0.662	0.613	35,346

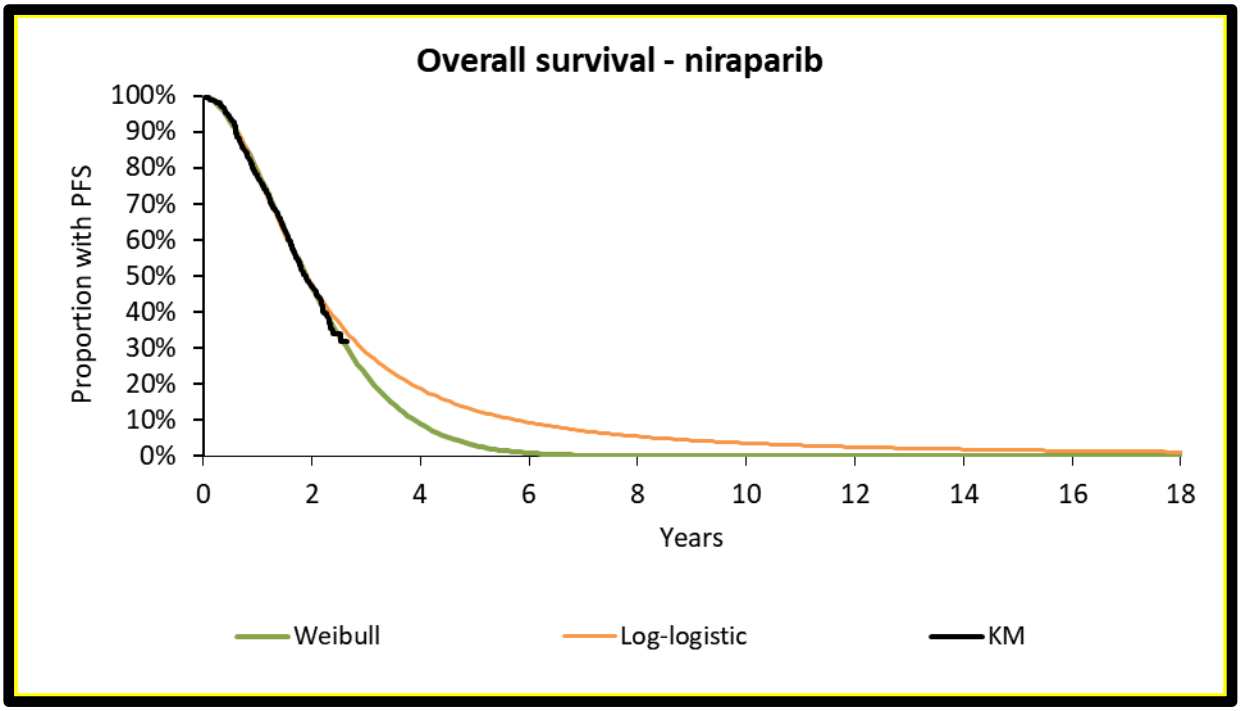
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; SACT, systemic anti-cancer therapy; QALY, quality-adjusted life-year.

The ERG considers that the company's SACT scenario analyses are valuable as they provide an estimate of the cost-effectiveness of niraparib when used in the NHS, where patients tend to have a poorer prognosis (typically due to being older and sicker) compared with patients eligible for trial inclusion (please see Section 3.2 for SACT and NOVA baseline characteristics). However, the ERG recognises that the SACT analyses rely heavily on assumptions that simulate a SACT-like routine surveillance arm as well as estimating niraparib PFS based on a NOVA PFS:TTD ratio. Nonetheless, the SACT survival estimates generated by the company do not exceed NOVA or Study 19 estimates. Furthermore, the SACT ICERs are lower than the company's base case ICERs.

The predominant difference between the NOVA and SACT company analyses was the shorter post-progression survival estimated in the SACT analysis (see Table 34). However, the ERG notes that the PFS:OS ratio of 1:1 was required to estimate the routine surveillance arm. In addition, TTD was shorter in the SACT cohort, resulting in lower niraparib acquisition costs.

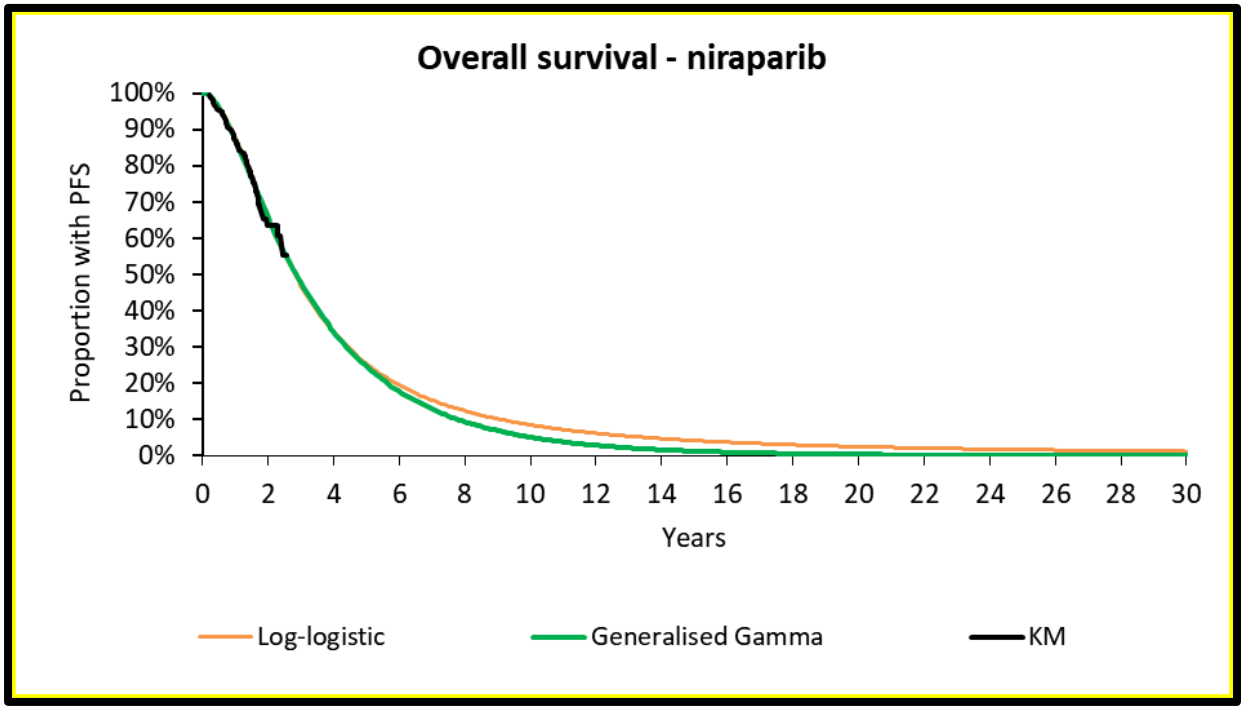
The primary issue the ERG has with the company's SACT analysis is the selection of extrapolation of niraparib OS for both subgroups. Based on the KM data in Figure 15 for the non-gBRCAmut 2L+ subgroup, the trajectory of the observed KM data appears to be on a constant steep decline. The rapid decline in overall survival may be clinically plausible when considering the baseline characteristics of the SACT non-gBRCAmut 2L+ patients and could be driven by short post-progression survival. The ERG's clinical expert advised that for the SACT non-gBRCAmut 2L+ cohort, survival beyond 6 or 7 years is unlikely. As such, the ERG considers that the Weibull distribution (presented in Figure 18) represents a more clinically plausible extrapolation for the SACT analysis, with a similar statistical and visual fit to the observed data compared with the company's selection of the log-logistic distribution.

Figure 18. Niraparib overall survival (SACT) – non-gBRCAmut 2L+ subgroup



For the SACT gBRCAmut 2L subgroup, the ERG's clinical expert advised that within the cohort, there may be a subset of patients who are "super beneficiaries" but considered that the company's extrapolation may be too optimistic. Based on the ERG's clinical expert opinion, the ERG considers the generalised gamma distribution (Figure 19) captures the "super beneficiaries" but also reflects the conservative prognosis of the SACT cohort.

Figure 19. Niraparib overall survival (SACT) – gBRCAmut 2L subgroup



The ERG preferred distributions for OS for the SACT analysis are presented in a scenario analysis in Section 6.3 and incorporated into an ERG SACT preferred base case in Section 6.4.

5 Cost effectiveness results

5.1.1 Company's cost effectiveness results

The company's updated base case results for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups are presented in Table 37 and Table 38. Results presented are inclusive of the company's updated patient access scheme (PAS) discount of [redacted].

Table 37. Company's deterministic base case results – gBRCAmut 2L subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,475

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Table 38. Company's deterministic base case results – non-gBRCAmut 2L+ subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,942*

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

*In a later clarification response, the company accepted an error with the TTD cap corrected by the ERG and as such, the results for this subgroup, presented in Section 6.1, reflect the correct ICER.

5.1.2 Company's sensitivity analyses

5.1.2.1 Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the base case results. The results are based on 1,000 PSA iterations. The results of the PSA for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups are given in Table 39 and Table 40, and scatterplots are presented in Figure 20 and

Figure 21, respectively.

Table 39. Company's probabilistic base case results - gBRCAmut 2L subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,545

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Table 40. Company's probabilistic base case results – non-gBRCAmut 2L+ subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,173*

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

*In a later clarification response, the company accepted an error with the TTD cap corrected by the ERG and as such, the results for this subgroup, presented in Section 6.1, reflect the correct ICER.

Figure 20. Scatterplot of probabilistic results for gBRCAmut 2L subgroup (Figure 2 of the company clarification response appendix)

Figure 21. Scatterplot of probabilistic results for non-gBRCAmut 2L+ subgroup (Figure 3 of the company clarification response appendix)

5.1.2.2 *One-way sensitivity analysis*

The company carried out one-way sensitivity analyses (OWSAs) to assess the impact of varying the values of parameters from their means by ±20%. The results of the OWSA carried out by the company for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups are presented in Figure 22 and Figure 23 for the 15 most influential parameters. Figure 22. Tornado diagram of niraparib versus routine surveillance for gBRCAmut 2L subgroup (Figure 5 of the company clarification response appendix)

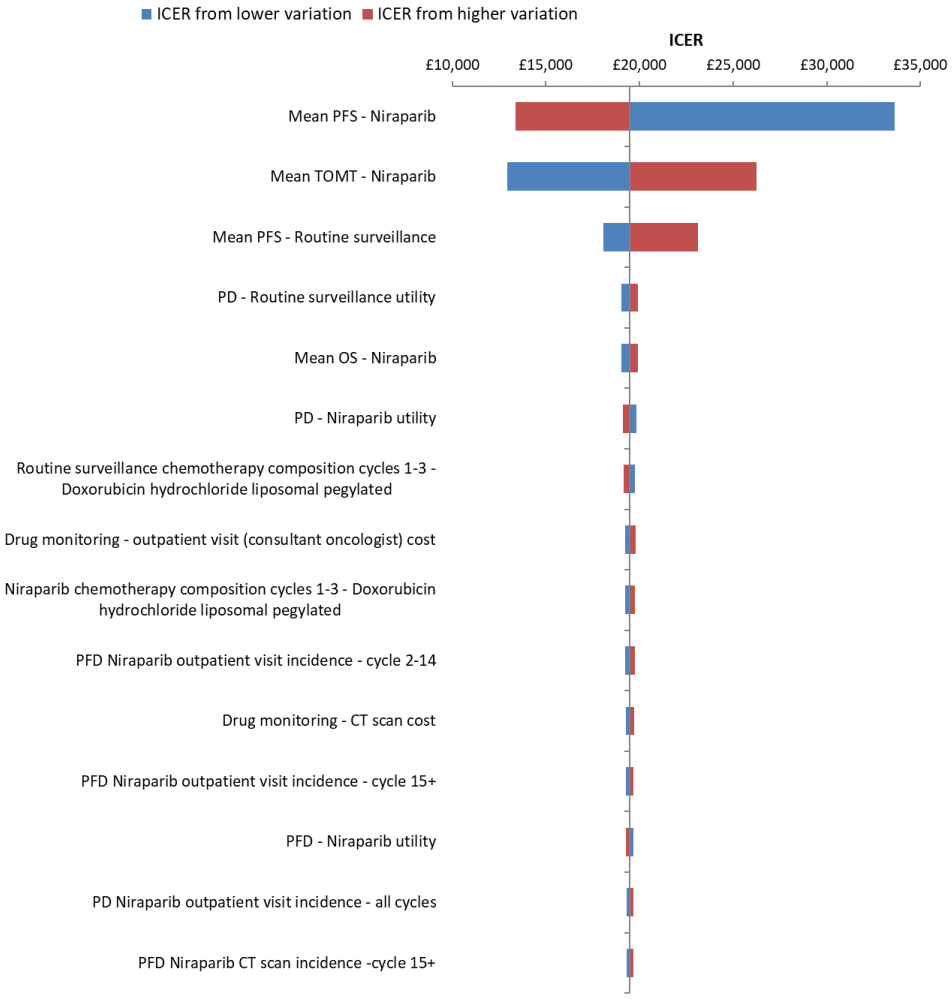
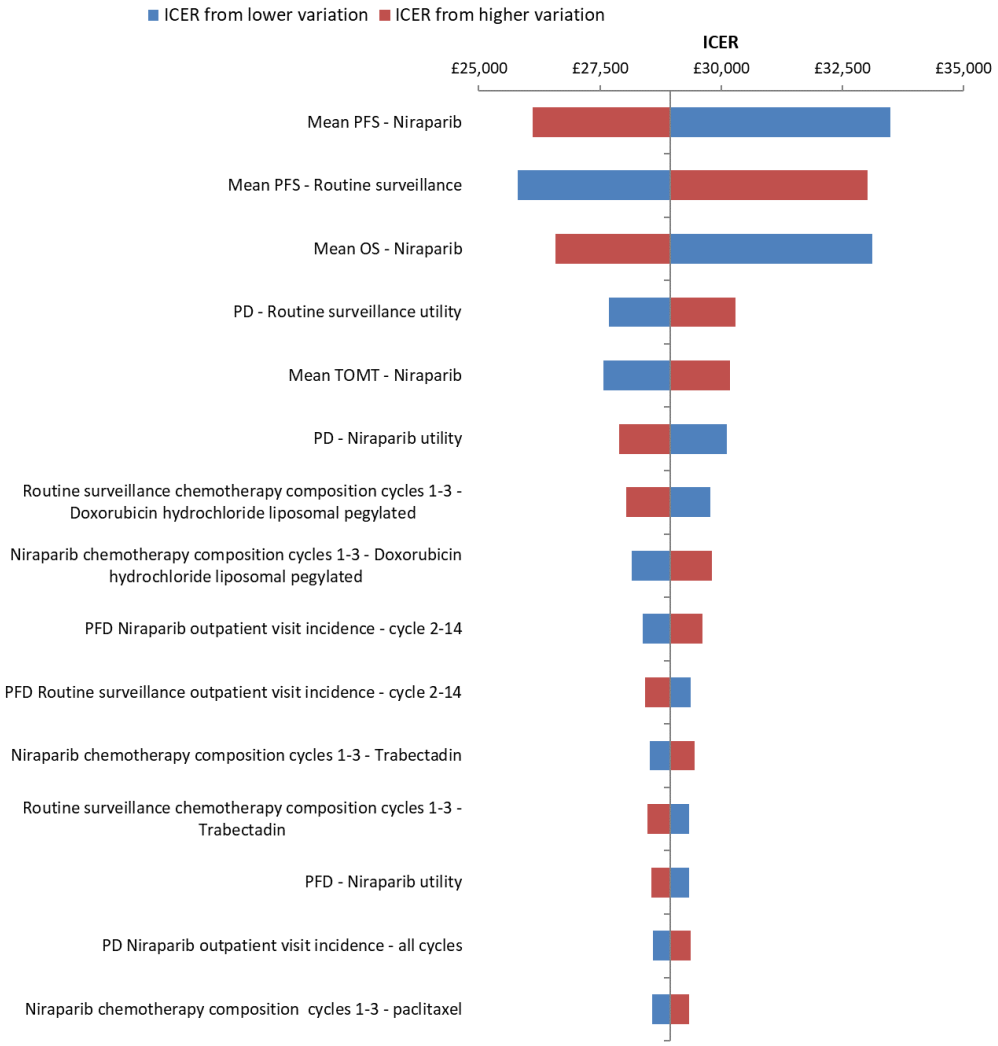

ICER from lower variation
ICER from higher variation
ICER
£10,000
£15,000
£20,000
£25,000
£30,000
£35,000
Mean PFS - Niraparib
Mean TOMT - Niraparib
Mean PFS - Routine surveillance
PD - Routine surveillance utility
Mean OS - Niraparib
PD - Niraparib utility
Routine surveillance chemotherapy composition cycles 1-3 - Doxorubicin hydrochloride liposomal pegylated
Drug monitoring - outpatient visit (consultant oncologist) cost
Niraparib chemotherapy composition cycles 1-3 - Doxorubicin hydrochloride liposomal pegylated
PFD Niraparib outpatient visit incidence - cycle 2-14
Drug monitoring - CT scan cost
PFD Niraparib outpatient visit incidence - cycle 15+
PFD - Niraparib utility
PD Niraparib outpatient visit incidence - all cycles
PFD Niraparib CT scan incidence -cycle 15+

Figure 23. Tornado diagram of niraparib versus routine surveillance for non-gBRCAmut 2L+ subgroup (Figure 6 of the company clarification response appendix)



5.1.2.3 Scenario analyses

Results of key scenario analyses conducted by the company for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups are presented in Table 41 and Table 42. In their clarification response, the company also provided a number of scenarios upon the request of the ERG, also presented in Table 41 and Table 42 for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups, respectively.

Table 41. Key scenario analyses – gBRCAmut 2L subgroup (Table 4 of the company clarification response

	Parameter	Base case	Scenario	ICER (£/QALY)
0	**Base case**			**19,475**
1	Overall survival for RS	PFS:OS ratio of 1:1	Extrapolated trial data from Study 19 for RS OS	22,205
2	Time to maintenance treatment discontinuation for niraparib	TTD data from NOVA	**B2 ERG clarification question** Niraparib TTD data sourced from SACT - gBRCAmut 2L	18,372
3	-	-	Scenario 1 and 2	20,943
4	Progression-free survival	PFS extrapolated using the lognormal curve	**B4 ERG clarification question** PFS extrapolated using the odds k=0 flexible curve	19,621
5			**B4 ERG clarification question** PFS extrapolated using the hazards k=1 flexible curve	22,058
6	Utilities	Treatment specific utilities	**B8 ERG clarification question** Non-treatment specific health state utilities	20,527
7	Niraparib dose	Actual niraparib dose NOVA 2020	**B9 ERG clarification question** Planned niraparib dose NOVA 2016	22,507

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention to treat; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; RS, routine surveillance; SACT, Systemic Anti-Cancer Therapy; TTD, time to maintenance treatment discontinuation.

Table 42. Key scenario analyses – non-gBRCAmut 2L+ subgroup

	Parameter	Base case	Scenario	ICER (£/QALY)
0	**Base case**			**28,942**
1	Overall survival for RS	PFS:OS ratio of 1:1	Extrapolated trial data from Study 19 for RS OS	31,449
2	Time to maintenance treatment discontinuation for niraparib	TTD data from NOVA	**B2 ERG clarification question** Niraparib TTD data sourced from SACT - non-gBRCAmut 2L+	24,197
3	-	-	Scenario 1 and 2	26,291

4	Utilities	Treatment specific utilities	**B8 ERG clarification question** Non-treatment specific health state utilities	32,287
5	Niraparib dose	Actual niraparib dose NOVA 2020	**B9 ERG clarification question** Planned niraparib dose NOVA 2016	31,270

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention to treat; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; RS, routine surveillance; SACT, Systemic Anti-Cancer Therapy; TTD, time to maintenance treatment discontinuation.

5.1.3 Model validation and face validity check

The company has not provided any details of their model validation. However, the Evidence Review Group (ERG) found and corrected one error related to the time on maintenance treatment (TTD) cap. Please refer to Section 6.1 for more details.

6 Additional economic analysis undertaken by the ERG

6.1 Model corrections

The Evidence Review Group (ERG) discovered an error in the application of the time on maintenance treatment (TTD) cap implemented by the company in their revised base case post clarification. For the non-gBRCAmut 2L+ subgroup, the progression-free survival curve is estimated using a flexible spline model. However, in the economic model the TTD cap was applied by referencing the best fit standard parametric model (i.e. TTD cannot be greater than the best fit standard parametric model). As such, the company's TTD cap resulted in a substantial reduction in the incremental cost-effectiveness ratio (ICER) from the original base case ICER of £36,449 to the revised ICER of £28,942.

The ERG corrected this error by creating a new mean estimate of TTD for the non-gBRCAmut 2L+ subgroup that referenced the selected PFS flexible spline curve for the TTD cap.

Table 43 presents the corrected company base case results for the non-gBRCAmut 2L+ subgroup. The ERG notes that it is the same as the company's original base case ICER, as their selected TTD curve (log-logistic) always remained below PFS. In a later round of clarification responses from the company, they accepted the TTD error and confirmed the results presented in Table 43.

Table 43. Corrected company's deterministic base case results – non-gBRCAmut 2L+ subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,449

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Table 44. Corrected company's probabilistic base case results – non-gBRCAmut 2L+ subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,934

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

6.2 Exploratory and sensitivity analyses undertaken by the ERG

The company provided key sensitivity and scenario analyses for both the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups as part of their Cancer Drugs Fund (CDF) submission. Furthermore, the ERG requested a number of scenarios during the clarification stage, which the company provided. Results of the key ERG requested scenarios can be found in Section 5.1.2.3, Table 41 and Table 42.

As mentioned in Section 4.1.4, the ERG preferred the use of the progression-free survival (PFS) hazard k=1 spline for both subgroups and the Gompertz distribution to extrapolate TTD for the non-gBRCAmut 2L+ subgroup. Results of the ERG scenarios are presented in Section 6.3, Table 45. The ERG notes that because a spline-based model is preferred for PFS over a standard parametric distribution for the gBRCAmut 2L subgroup, the ERG correction outlined in Section 6.1 is relevant for the scenario and has been applied.

In addition to scenarios around the company base case, the ERG explored an alternative overall survival (OS) scenario around the company's systemic anti-cancer therapy (SACT) analysis, also presented in Section 6.3.

6.3 ERG scenario analysis

Table 45 and Table 46 presents the deterministic results of the ERG exploratory analyses described in Section 6.2.

Table 45. Results of the ERG's scenario analyses – gBRCAmut 2L subgroup

	Results per patient	Niraparib	Routine surveillance	Incremental value
0	Company base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	19,475
1	Hazard k=1 spline for PFS + ERG TTD correction			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			21,838

Abbreviations: ERG, Evidence Review Group, ICER, incremental cost-effectiveness ratio; k, knot; PFS, progression-free survival; QALY, quality adjusted life year; TTD, time to maintenance treatment discontinuation.

Table 46. Results of the ERG's scenario analyses – non-gBRCAmut 2L+ subgroup

	Results per patient	Niraparib	Routine surveillance	Incremental value
0	Company base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	28,942
0a	Corrected company base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	36,449
1	Hazard k=1 spline for PFS			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	39,990
2	Gompertz distribution for TTD			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	40,518

Abbreviations: ERG, Evidence Review Group, ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TTD, time to maintenance treatment discontinuation.

Table 47. Results of the ERG's scenario analyses – SACT gBRCAmut 2L subgroup

	Results per patient	Niraparib	Routine surveillance	Incremental value
0	Company SACT scenario analysis			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]

	ICER (£/QALY)			17,930
1	Generalised gamma distribution for OS			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			18,312

Abbreviations: ERG, Evidence Review Group, ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality adjusted life year; SACT, systemic anti-cancer therapy.

Table 48. Results of the ERG's scenario analyses – SACT non-gBRCAmut 2L+ subgroup

	Results per patient	Niraparib	Routine surveillance	Incremental value
0	Company SACT scenario analysis			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			35,346
1	Weibull distribution for OS			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			37,986

Abbreviations: ERG, Evidence Review Group, ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality adjusted life year; SACT, systemic anti-cancer therapy.

6.4 ERG preferred assumptions

In this section, the ERG presents its base-case for niraparib compared with routine surveillance for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups. Deterministic results with the impact of individual assumption applied are presented in Table 50 and Table 51. Overall deterministic results are presented in Table 52 and Table 53. The ERG identified an error with the company's probabilistic sensitivity analysis (PSA) related to the use of Study 19 data, which was corrected by the company in a later clarification response. The company provided the PSA results for the ERG's base case and these are presented in Table 52 and Table 53.

The assumptions included in the ERG base case are as follows:

- Hazards k=1 spline for PFS (included ERG TTD correction for the gBRCAmut 2L subgroup).
- Overall (OS) data from Study 19 for routine surveillance.
- Gompertz distribution for TTD – non-gBRCAmut 2L+ subgroup.
- Utilities based on progression status and removal of disutility associated with adverse events (AEs).
- Prescribed dose data from TA528.

In addition to the ERG's preferred base case, the ERG presents a SACT scenario for both subgroups which incorporates the following assumptions:

- Generalised gamma distribution for OS for the gBRCAmut 2L subgroup.
- Weibull distribution for OS for the gBRCAmut 2L subgroup.
- Utilities based on progression status and removal of disutility associated with adverse events (AEs).
- Prescribed dose data from TA528.

The ERG's SACT scenarios are presented in Table 54 and Table 55. Overall deterministic and PSA results are presented in Table 56 and Table 57.

A summary of the ERG preferred NOVA and SACT cost-effectiveness results in presented in Table 49.

Table 49. Summary of company and ERG ICERs for NOVA and SACT analyses

	NOVA ICER	SACT ICER
gBRCAmut 2L		
Company deterministic base case	19,745	17,930
Company probabilistic base case	19,545	n/a*
ERG deterministic base case	27,399	21,683
ERG probabilistic base case	25,348	22,961
gBRCAmut 2L		
Company deterministic base case	36,449	35,346
Company probabilistic base case	37,934	n/a*

ERG deterministic base case	51,684	45,265
ERG probabilistic base case	50,328	45,454

Abbreviations: ERG, evidence review group; ICER, incremental cost-effectiveness ratio; SACT, systemic anti-cancer therapy.

*The ERG were unable to present PSA analyses for the company's SACT scenario due to paucity of time, as each run of PSA (1,000 simulations) took around 3 hours to run.

Table 50. ERG's preferred model assumptions – gBRCAmut 2L subgroup

Preferred assumption	Section in ERG report	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Cumulative ICER (£/QALY)
Company base case	5.1.1	[redacted]	[redacted]	19,475	-
Hazard k=1 spline for PFS + ERG TTD correction	4.1.4.1 & 6.1	[redacted]	[redacted]	21,838	21,838
OS based on Study 19 for routine surveillance	4.1.4.2	[redacted]	[redacted]	22,205	22,185
Utility values based on progression status + removal of disutility for AEs	4.1.6	[redacted]	[redacted]	20,527	23,685
Prescribed dose data from TA528	4.1.7	[redacted]	[redacted]	22,507	27,399
ERG preferred base case	**-**	[redacted]	[redacted]	**27,399**	**-**

Abbreviations: AE, adverse event; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; TTD, time to maintenance treatment discontinuation.

Table 51. ERG's preferred model assumptions - non-gBRCAmut 2L+ subgroup

Preferred assumption	Section in ERG report	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Cumulative ICER (£/QALY)
Company base case	5.1.1	[redacted]	[redacted]	28,942	-
Corrected company base case	6.1	[redacted]	[redacted]	36,449	-
Hazard k=1 spline for PFS	4.1.4.1	[redacted]	[redacted]	39,990	39,990
OS based on Study 19 for routine surveillance	4.1.4.2	[redacted]	[redacted]	39,608	39,634
Gompertz distribution for TTD	4.1.4.3	[redacted]	[redacted]	40,518	42,493

Utility values based on progression status + removal of disutility for AEs	4.1.6	[redacted]	[redacted]	40,662	48,096
Prescribed dose data from TA528	4.1.7	[redacted]	[redacted]	39,202	51,684
ERG preferred base case	**-**	[redacted]	[redacted]	**51,684**	**-**

Abbreviations: AE, adverse event; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; TTD, time to maintenance treatment discontinuation.

Table 52. ERG's base case results – gBRCAmut 2L subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,399
Probabilistic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,348

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Table 53. ERG's base case results – non-gBRCAmut 2L+ subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,684
Probabilistic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,328

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Table 54. ERG's preferred model assumptions – SACT gBRCAmut 2L subgroup

Preferred assumption	Section in ERG report	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Cumulative ICER (£/QALY)
Company base case	5.1.1	[redacted]	[redacted]	17,930	-
Generalised gamma distribution for OS	**Error! Reference source not found.**	[redacted]	[redacted]	18,312	18,312
Utility values based on progression status + removal of disutility for AEs	4.1.6	[redacted]	[redacted]	18,464	18,783
Prescribed dose data from TA528	4.1.7	[redacted]	[redacted]	20,695	21,683
ERG preferred SACT base case	-	[redacted]	[redacted]	**21,683**	-

Abbreviations: AE, adverse event; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; TTD, time to maintenance treatment discontinuation.

Table 55. ERG's preferred model assumptions - SACT non-gBRCAmut 2L+ subgroup

Preferred assumption	Section in ERG report	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Cumulative ICER (£/QALY)
Company base case	5.1.1	[redacted]	[redacted]	35,346	-
Weibull distribution for OS	**Error! Reference source not found.**	[redacted]	[redacted]	37,986	37,986
Utility values based on progression status + removal of disutility for AEs	4.1.6	[redacted]	[redacted]	39,798	41,695
Prescribed dose data from TA528	4.1.7	[redacted]	[redacted]	38,343	45,265
ERG preferred SACT base case	-	[redacted]	[redacted]	**45,265**	-

Abbreviations: AE, adverse event; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; TTD, time to maintenance treatment discontinuation.

Table 56. ERG's SACT results – gBRCAmut 2L subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,683
Probabilistic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,961

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

Table 57. ERG's SACT results – non-gBRCAmut 2L+ subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,265
Probabilistic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,454

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

6.5 Conclusions of the cost effectiveness sections

Between June 2018 and December 2020, niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer was made available through the CDF to enable further data collection from the NOVA study to be obtained by the company, as well as allow UK-based TTD and OS data to be collected through Systemic Anti-Cancer Therapy (SACT) database. The company's cost-effectiveness approach has remained largely unchanged from the

approach in TA528. However, the ERG considers that several of the uncertainties outlined by the committee in the Terms of Engagement (ToE) have not been fully resolved.

In the ToE the means-based model was listed to be used for the CDF review as the committee for TA528 considered that the company's means-based model approach was, "*adequate for decision-making and that the choice of model structure was not critical*". However, the committee's decision was based on a statement by the company during the committee meeting that the ICER difference between the means-based model and a partitioned survival model (the ERG's preferred model structure) was only around £1,000 per QALY. However, the company's partitioned survival model was not presented to the ERG to verify the claim and was not supplied upon request during the clarification stage of the CDF review. Furthermore, the ToE also stated that the company should fully investigate the most appropriate PFS and OS modelling using updated clinical trial data. The ERG notes that more mature OS data are now available from NOVA (which was a limitation in TA528) allowing the company to change their approach to the model structure to estimate robust cost-effectiveness results.

The ERG considers that the unverified partitioned survival model results quoted by the company in TA528 had an undue influence on the committee's decision to accept the means-based model structure and considers it likely that the model doesn't exist. Therefore, the ERG recommends the committee should reconsider its decision to accept the means-based model structure. In addition, the ERG is concerned that this sets a dangerous precedent where companies can introduce unverified new evidence during a committee meeting, which influences committee decision making, but is never subsequently assessed.

An issue around PFS that has remained unresolved from TA528 is the discrepancy between investigator assessed (IA) PFS and independent review committee (IRC) PFS. In NOVA, treatment with niraparib was stopped if the investigator identified disease progression. As such, the ERG considers that "investigator determined" TTD and IA PFS from NOVA would be consistent. In the economic model, PFS is based on IRC assessment. The ERG remains concerned that the PFS benefit of niraparib is inflated based on the two different methods of assessment. In TA528, the company declined to provide a scenario using IA PFS in the economic model, which is a position they have maintained for the CDF review. Thus, in the TA528 the ERG explored scenarios that focussed on using equivalence of IRC PFS to estimate TTD and IA TTD (preferred by the committee) to estimate IA PFS to appropriately align the costs and benefits associated with niraparib. Nonetheless, the ERG

considers that exploring the discrepancy between IA and IRC PFS estimates is a resolvable issue but relies on the company providing analysis using IA PFS.

With regards to the approach for extrapolating PFS (which was a key uncertainty in TA528), the committee considered that both the company's and ERG's preferred extrapolations did not resolve the uncertainty in the long-term estimates of PFS. For the CDF review, the company did not change their preferred PFS distributions for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups, which were the lognormal and normal k=1 spline, respectively. However, the ERG acknowledges the committee's consideration that the ERG preferred PFS approach may be pessimistic and a flexible modelling approach maybe more appropriate. As such, the ERG considers that the hazard k=1 spline for both subgroups provides a less pessimistic, but clinically plausible long-term extrapolation.

While niraparib was in the CDF, longer-term OS data from the NOVA study was collected, which was key limitation in TA528. More mature OS data for niraparib has been used in the economic model but OS data were confounded for the placebo arm. Thus, the company used a PFS:OS ratio of 1:1 to estimate OS for routine surveillance as a way to "bypass" the confounded OS data from the placebo arm in NOVA. The ERG fundamentally disagrees with the use of a PFS:OS ratio as there is a lack of consistent evidence around the relationship between PFS to OS in advanced or metastatic cancer, making it an unreliable and uncertain measure. Furthermore, this approach intrinsically links changes to PFS to OS benefits. The ERG considers that using randomised control trial OS data from both NOVA and Study 19, maintains a "like for like" comparison in the model. Thus, the ERG prefers the use OS data from Study 19 for the routine surveillance arm, as per the approach in TA528.

In TA528, the company implemented treatment-specific utilities based on data from NOVA. For the CDF review, the company has maintained their approach, but updated the utility analysis with the latest data cut from NOVA. In TA528, the ERG considered it was debatable that niraparib would be associated with higher health-related quality of life (HRQoL) when the adverse event rate was also higher compared with placebo. Furthermore, no statistical tests were performed by the company, or results supplied to determine if the difference in utility values between niraparib and placebo were statistically significant. As such, the ERG maintains its position that utility values based on progression status alone are the most appropriate for the cost-effectiveness analysis and this position is supported by the ERG's clinical experts.

In the company's updated base case for the CDF review, the company updated their patient access scheme simple discount to [redacted] but dosing data for niraparib has been changed to be based on actual dose received (defined as dispensed dose minus returned dose) as opposed to the prescribed dose data used in TA528. The ERG considers that in UK clinical practice, niraparib doses prescribed are unlikely to be returned to the NHS and reused. As such, the ERG prefers the company's original approach of using the prescribed dose data reflects that natural wastage that will occur in clinical practice.

In the time that niraparib was in the CDF, relatively mature data on OS and TTD were collected. The ERG considers that the type and maturity of the niraparib data collected in SACT is valuable and usually unavailable. As such, the ERG requested the company to provide a "real-world" cost-effectiveness analysis using SACT data for niraparib and assumptions for routine surveillance. The company provided the analysis, which demonstrated that ICERs were lower than the base case using NOVA data. The predominant difference between the NOVA and SACT company analyses was the shorter post-progression survival estimated in the SACT analysis. In addition, TTD was shorter in the SACT cohort, resulting in lower niraparib acquisition costs.

The ERG considers that the company's approach to extrapolating overall survival using SACT data resulted in optimistic estimates of survival, especially as the SACT cohort represent an older and sicker population compared with the NOVA cohort. As such, the ERG preferred a more conservative approach to overall survival and presented a SACT base case as part of the preferred assumptions.

The ERG concludes that while the company has adhered to the ToE in its approach to the CDF review, the additional data collected from NOVA warranted a reconsideration of the most robust methods to estimate the cost-effectiveness niraparib. Specifically, the company should have revisited the model structure and explored a partitioned survival approach, which would have subsequently removed the need for the PFS:OS ratio, addressing much of the committee's uncertainties. However, the ERG welcomes analyses based on SACT data, even though these analyses are heavily reliant on assumptions.

7 End of Life

NICE end-of-life status should be applied when the following criteria are satisfied:

(i) the treatment provides an extension to life of more than an average of three months compared to current NHS treatment, and;

(ii) the treatment is indicated for patients with a short life expectancy, normally a life expectancy of less than 24 months.

In TA528, the company put forward a case for applying end-of-life criteria for the subgroup of patients without a germline BRCA mutation (the non-gBRCAmut 2L+ subgroup). The committee considered that there are various estimates for life expectancy without niraparib for the non-gBRCAmut 2L+ subgroup and that the precise figure is uncertain. Based on the mean OS estimate for routine surveillance from the model that the committee accepted was suitable for decision making (2.87 years), the committee concluded that end of life criteria was not met.[3]

In the company's CDF submission, the base case mean OS estimate for routine surveillance for the non-gBRCAmut 2L+ subgroup is [redacted]. The company's mean estimate of OS for routine surveillance when using SACT data for niraparib is [redacted]. The company's estimates of OS for routine surveillance is based on a calculation using extrapolated OS data from NOVA (base case) and SACT (scenario) for niraparib and a 1:1 PFS:OS ratio. As such, the ERG considers that the committee decision still holds and the end of life criteria has not been met for the non-gBRCAmut 2L+ subgroup.

8 References

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (CDF review TA528) [ID1644]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 16 June 2021** 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.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Model structure for decision making

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 2, page 17: *"In TA528, the company's means-based model structure was accepted as adequate for decision-making and was listed in the CDF ToE to be used for the CDF review. However, the committee's decision was based on a statement made by the company during the committee meeting that the ICER difference between the means-based model and a partitioned survival model was only around £1,000 per QALY. However, the company's partitioned survival model was not presented to the ERG to verify the claim and was not be supplied during the clarification stage of the CDF review.* *The ERG considers that the unverified partitioned survival model results quoted by the company in TA528 had an undue influence on the committee's decision to accept the means-based model structure and considers it likely that the model doesn't exist. Therefore, the ERG recommends the committee should reconsider its decision to accept the means-based model structure as it*	The company asks for this issue to be reconsidered and removed given the justification provided in the 'Justification for amendment' column. Alternatively, if the ERG insists on retaining it, to represent the facts of the appraisal and ensure the paragraph is balanced, the company asks the ERG to add the following text from the FAD: *"In TA528, the company's means-based model structure was accepted* ***by the committee*** *as adequate for decision-making* ***and that the choice of model structure was not critical and therefore*** *was listed in the CDF ToE to be used for the CDF review. However, the committee's decision was based on a statement made by the company during the committee meeting that the ICER difference between the means-based model and a partitioned survival model was only around £1,000 per QALY. However, the company's partitioned survival model was not presented to the ERG to verify the claim and was not*	This issue was not one considered by the Committee as a source of uncertainty originally and is therefore irrelevant to the CDF review. The Committee's conclusion from TA528 was '*The committee accepted that the model was adequate for decision-making and that the choice of model structure was not critical'*.[1] This paragraph is unbalanced and does not reflect the facts of the appraisal; notably that the Final Appraisal Determination (FAD) stated that the model structure is not a source of uncertainty.[1] On this basis, the model to be used for the CDF review submission was outlined in the Terms of Engagement (ToE) document and was physically sent to the Company. This document highlighted that the economic model named "*ID1041 Niraparib CEM_Response to ACD v0.2 16.03.18 [ACIC]*" should be used. The model submitted for the CDF review submission *"[ID1644]_Cost_effectiveness_model_[ACIC*]" was an updated version of the decision analytic model specified in the ToE document.[2] The Company understands that there may be differences in the results between a partition survival model and the means-based model,	Not a factual inaccuracy – no change required.

potentially sets a dangerous precedent where companies can introduce unverified new evidence during a committee meeting, which influences committee decision making, but is never subsequently assessed." Paragraph 2, page 57: *"As mentioned previously, the means-based modelling approach was accepted as adequate for decision-making by the committee for TA528. However, this was based on a statement by the company during the committee meeting that the incremental cost-effectiveness ratio (ICER) difference between the means-based model and a partitioned survival model was around £1,000 per quality adjusted life year (QALY). However, the partitioned survival model was not presented to the ERG to verify the claim."* Paragraph 1, page 58: *"As such, the ERG considers that the unverified partitioned survival model results quoted by the company in TA528 had an undue influence on the committee's decision to accept the means-based model structure. As the ERG has requested this model and it has not been supplied, the ERG*	~~**be**~~ *supplied during the clarification stage of the CDF review.* ~~*The ERG considers that the unverified partitioned survival model results quoted by the company in TA528 had an undue influence on the committee's decision to accept the means-based model structure and considers it likely that the model doesn't exist.*~~ ***The committee accepted the model structure which was subsequently used to inform the ToE. NICE provided the means-based model on which the original decision was made to the company within the ToE.****."* *"As mentioned previously, the means-based modelling approach was accepted as adequate for decision-making* ***and that the choice of model structure was not critical*** *by the committee for TA528. However, this was based on a statement by the company during the committee meeting that the incremental cost-effectiveness ratio (ICER) difference between the means-based model and a partitioned survival model was around £1,000 per quality adjusted life year (QALY). However, the partitioned survival model was not presented to the ERG to verify the claim."*	which has been based on the concept from TA91.[3,4] It has been confirmed in the response to the ERG clarification question B1 that the Company did not provide a separate partitioned survival model in the original appraisal. Whilst structural uncertainty will always exist, across appraisals, it is not standard for companies to present multiple models to Committee as part of its submission. Even less so in a CDF re-submission in which there has been a previous decision made by the Committee that '*the choice of model structure is not critical to the decision making',* where the Company have re-submitted the specific model provided by NICE in the ToE. Persistently pursuing this stance could be deemed unfair. Rationale for using the means-based approach model, along with an explanation of the differences between the two modelling approaches, was provided; this was accepted by the Committee in the original submission. The model specified in the ToE document has been used to ensure the CDF review submission is aligned with expectations and that updated analyses and results could be provided in a step wise fashion whilst also being able to replicate the results of the original submission.	

considers it likely that the model doesn't exist. Therefore, the ERG recommends the committee should reconsider its decision to accept the means-based model structure, given the company has been unable to provide any evidence to validate their approach is equivalent to a more robust partitioned survival model. In addition, the ERG is concerned that this sets a dangerous precedent where companies can introduce unverified new evidence during a committee meeting, which influences committee decision making, but is never subsequently assessed."	*"As such, the ERG considers that the unverified partitioned survival model results quoted by the company in TA528 had an undue influence on the committee's decision to accept the means-based model structure. As the ERG has requested this model and it has not been supplied, the ERG considers it likely that the model doesn't exist.* ***Nonetheless the committee accepted the model structure which was subsequently used to inform the Terms of Engagement for the resubmission****."*		
Table 2, page 17: *"During the clarification stage, the ERG requested the company to supply the partitioned survival model quoted in TA528 but this was not supplied. The ERG considers that a partitioned survival model would be important to validate the results of the means-based model* ***as well as remove the need for the PFS:OS ratio, thus reducing the uncertainty around the cost-effectiveness results."*** Table 5, page 20:	The company asks the ERG to remove the following text: *"****as well as remove the need for the PFS:OS ratio, thus reducing the uncertainty around the cost-effectiveness results."*** The company asks the ERG to remove the following text: *"****In addition, using Study 19 OS data for routine surveillance, reinforces the suitability a***	As demonstrated in the Company's CDF review submission, a partitioned survival model is not required to remove the use of a progression-free survival: overall survival (PFS:OS) ratio to model OS, since scenarios have been provided where OS for both treatment arms has been extrapolated and the PFS:OS relationship is not used. In this instance the NOVA trial is used to model niraparib OS data and Study 19 or Lord et al. 2020 used to model routine surveillance OS. Therefore the submitted means-based model can be used regardless of the requirement for a PFS:OS ratio. As stated in the FAD, "*the committee accepted that the model was adequate for*	Not a factual inaccuracy – no change required.

"The ERG considers that using randomised control trial OS data from both NOVA and Study 19, maintains a "like for like" comparison in the model (i.e. RCT data compared with RCT data). Thus, the ERG prefers the use of OS data from Study 19 for the routine surveillance arm, as per the approach in TA528. ***In addition, using Study 19 OS data for routine surveillance, reinforces the suitability a partitioned survival model structure.****"* *"The company supplied the relevant Study 19 OS scenarios for routine surveillance in their CDF submission. However, the ERG considers that using Study 19 OS placebo data in a partitioned survival model structure is more appropriate and robust."*	***partitioned survival model structure.****"* Further to represent the facts of the appraisal and ensure the following paragraph is balanced, the company asks the ERG to add the following text from the FAD: *"The company supplied the relevant Study 19 OS scenarios for routine surveillance in their CDF submission. However, the ERG considers that using Study 19 OS placebo data in a partitioned survival model structure is more appropriate and robust.* ***Although the Committee accepted that the model was adequate for decision-making and that the choice of model structure was not critical."***	*decision-making and that the choice of model structure was not critical."* [1]	
Table 12, page 27: *"Furthermore, as survival analysis has been used to extrapolate PFS,* ***a partitioned survival model structure would be more robust than a means-based model to estimate costs and QALYs.*** *Furthermore, using randomised control trial OS data from both NOVA*	Further to represent the facts of the appraisal and ensure the following paragraph is balanced, the company asks the ERG to add the following text from the FAD: *"Furthermore, as survival analysis has been used to extrapolate PFS,* ***a partitioned survival model structure would be more robust than a means-based model to estimate costs and QALYs. Although the committee accepted***		

and Study 19 maintains a "like for like" comparison in the model ***and reinforces the suitability a partitioned survival model structure.****"*	***that the model was adequate for decision-making and that the choice of model structure was not critical."*** The company asks the ERG to remove the following text: *"****and reinforces the suitability a partitioned survival model structure.****"*		
Paragraph 2, Page 87: *"Specifically, the company should have revisited the model structure and explored a partitioned survival approach, which would have subsequently removed the need for the PFS:OS ratio, addressing much of the committee's uncertainties."*	The company asks the ERG to update the following text: *"Specifically, the company should have revisited the model structure and explored a partitioned survival approach,* ***~~which would have subsequently removed the need for the PFS:OS ratio, addressing much of the committee's uncertainties~~ nonetheless the committee accepted the model structure which was subsequently used to inform the ToE.****"*		
Page 57, paragraph 4*:* *"Furthermore, the ERG considers that the means-based approach does not account for the time in the event rates of PFS and OS and as such the*	To represent the facts of the appraisal and ensure the paragraph is balanced, the company asks the ERG to add the following text from the FAD: *"Furthermore, the ERG considers that the means-based approach*		

associated costs and QALYs. The ERG notes that more mature OS data are now available from NOVA (which was a limitation in TA528) allowing the company to change their approach to the model structure to estimate robust cost-effectiveness results. Furthermore, the ToE states that the company should fully investigate the most appropriate PFS and OS modelling using updated clinical trial data, which the ERG considers should have involved reviewing if the means-based model was fit for purpose in light of the updated data from NOVA."	*does not account for the time in the event rates of PFS and OS and as such the associated costs and QALYs. The ERG notes that more mature OS data are now available from NOVA (which was a limitation in TA528) allowing the company to change their approach to the model structure to estimate robust cost-effectiveness results.* ***However the current structure has still allowed the company to present extrapolated OS data per treatment arm in a scenario without the use of a PFS:OS relationship.*** *Furthermore, the ToE states that the company should fully investigate the most appropriate PFS and OS modelling using updated clinical trial data, which the ERG considers should have involved reviewing if the means-based model was fit for purpose in light of the updated data from NOVA.* ***However, the committee accepted the model structure which was subsequently used to inform the ToE and determine which model should be used by the company.****"*		
Paragraph 3, page 57: *"In addition, the company stated that their model structure was based on*	To represent the facts of the appraisal and ensure the following paragraph is balanced, the company	Even though TA91 has been replaced, it should be clarified that at the time of submission this was a relevant submission to compare with.	Not a factual inaccuracy – no change required.

technology appraisal 91 (TA91), which has been replaced by TA389.[7]"	asks the ERG to update this text as follows: *"In addition, the company stated that their model structure was based on technology appraisal 91 (TA91), which has been replaced by TA389,* ***however TA91 was the relevant submission at the time of the original appraisal****.[7]"*		

Issue 2 End of life

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 1, page 16 and Table 12, page 28: *"…the company has put forward evidence for end-of-life to be assessed* ***separately for the non-gBRCAmut 2L+ and the gBRCAmut 2L populations****."*	The Company asks for these statements to be reworded given the justification provided in the 'Justification for amendment' column *"…the company has put forward evidence for end-of-life to be assessed* ***for the non-gBRCAmut 2L+ population only****."*	The Company would like to correct this factual inaccuracy; evidence assessed for the non-g*BRCA*mut 2L+ population only was put forward.	The ERG report has been updated.
Paragraph 1, page 88: *"NICE end-of-life status should be applied when the following criteria are satisfied:* *(i) The treatment provides an extension to life of more than an average of three months*	The Company asks for these statements to be reworded given the justification provided in the 'Justification for amendment' column. Proposed rewording: "*In the case of a 'life-extending treatment at the end of life', the Appraisal*	The company asks the ERG to amend the text to accurately reflect the NICE Guide to the methods of technology appraisal 2013, Section 6.2.10.[5]	The ERG has removed the word "mean" from point (ii) in the ERG report.

compared to current NHS treatment, and; (ii) *the treatment is indicated for patients with a short life expectancy, normally a mean life expectancy of less than 24 months."*	*Committee will satisfy itself that all of the following criteria have been met:* • *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 has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.*		
Paragraph 3, page 88: *"In the company's CDF submission, the base case mean OS estimate for routine surveillance for the non-gBRCAmut 2L+ subgroup is [redacted].* *The company's estimate is based on a calculation using extrapolated OS data from NOVA for niraparib and a 1:1 PFS:OS ratio."*	The Company asks for additional text to be added as per justification provided in the 'Justification for amendment' column, to provide the committee additional information to help with its decision making. *"In the company's CDF submission, the base case mean OS estimate for routine surveillance for the non-gBRCAmut 2L+ subgroup is [redacted].* *The company's estimate is based on a calculation using extrapolated **mean** OS data from NOVA for niraparib and a 1:1 PFS:OS ratio.* ***The short life expectancy of patients without a BRCA mutation, normally less than 24 months, was supported***	The Company asks the ERG to please include the evidence provided by the Company on this point for balance and to acknowledge the real-world evidence (RWE) submitted. Use of RWE to inform the Committee's decision-making is aligned with the fourth pillar of NICE's newly launched five-year plan: Leadership in data, research, and science.[6] By providing published UK RWE from Lord et al. 2020, in addition to Systemic Anti-Cancer Therapy (SACT) data, the Company hope to support NICE in their ambition to "use real-world data to resolve issues of uncertainty and improve	Thank you for highlighting this error. However, the ERG considers this estimate relates to the discounted mean OS and as such has amended the ERG report to reflect the undiscounted mean OS of [redacted] years.

	by UK-based real-world data presented by the company. SACT non-gBRCAmut 2L+ niraparib arm median OS was 22.6 (95% CI 21.3 – 24.7) months.[17] In addition, Lord et al. 2020 ITT RS arm median OS was 19.3 (95% CI ± 2.4) months.[24]"	access to new innovations for patients".[6] NICE has committed to "reducing barriers to using data that is generated in routine clinical practice in health care decision-making, including addressing challenges with real world data discoverability, quality, and accessibility".[6] The Company therefore asks the ERG to include UK RWE in their assessment of the end-of-life status of niraparib in the non-g*BRCA*mut 2L population. The Company also notes that the NICE Guide to the methods of technology appraisal 2013, Section 6.2.1 does not specify whether mean or median OS estimates need to be considered,[5] and precedent from previous appraisals confirms this to be true. There is a debate to be had about which measure is most appropriate for quantifying life expectancy, and perhaps the most helpful approach is one of triangulating different estimates in order to determine the true estimate, as well as consultation with clinical experts. There is no doubt that this population represents patients	

		with a short life expectancy, albeit with some uncertainty on the precise estimate. Median data from two UK-based RWE sources have been provided; these have not been discussed in the ERG's assessment of the first criteria for end-of-life status. The Company asks the ERG to present the RWE submitted for balance.	
ERG report Version 2 additional comment: Paragraph 2, Page 101 *"The company's mean estimate of OS for routine surveillance when using SACT data for niraparib is [redacted] years."*	*"The company's mean estimate of OS for routine surveillance when using SACT data for niraparib is [redacted] years.* ***The ERG mean estimate of OS for routine surveillance when using SACT data for niraparib is [redacted] years"***	The Company asks the ERG to please include the estimated SACT mean OS using their preferred assumption of the Weibull curve for balance. The mean life expectancy of the non-gBRCAmut routine surveillance cohort is considerably below 24 months ([redacted] years) when the ERG's OS assumptions are applied, thereby satisfying the end of life criterion applied by NICE.	Not a factual inaccuracy – no change required.

Issue 3 ITT population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 12, page 26: ***"The ERG does not consider the ITT population of NOVA relevant to this***	The company asks for these statements to be reconsidered given the justification provided in the 'Justification for amendment' column.	The Company would like to clarify that the intention of presenting evidence for the pooled intention-to-treat (ITT) population is not to change the scope or decision	Not a factual inaccuracy – no change required.

appraisal *as the committee has concluded that niraparib could not be considered plausibly cost-effective compared with olaparib in people with BRCA mutation who have had 3 or more courses of chemotherapy.* ***The efficacy of niraparib versus routine surveillance is likely to be overestimated in the ITT population*** *which includes a proportion of patients with BRCA mutation who have had 3 or more courses of chemotherapy, who would be eligible for olaparib."* Paragraph 2, page 33: *"**The ERG does not consider the comparison of niraparib and routine surveillance in the ITT population of NOVA relevant to this CDF review. The efficacy of niraparib versus routine surveillance is likely to be overestimated in the ITT population,** which includes a proportion of patients with BRCA mutation who have had 3 or more courses of chemotherapy."*	Please amend the text as follows: *"**The ERG considers the ITT population of NOVA as one of the relevant populations to this appraisal, in the context of – rather than changing the populations under consideration by the committee – to utilise additional data that would enable comparisons to be made to long-term UK data from both SACT and Lord et al (which is only possible using an ITT population)**.* *The committee has concluded that niraparib could not be considered plausibly cost-effective compared with olaparib in people with BRCA mutation who have had 3 or more courses of chemotherapy **based on the initial patient access scheme discount used for decision making at the ACM.*** ***The efficacy of niraparib versus routine surveillance in the ITT population includes a proportion of patients with BRCA mutation*** *who have had 3 or more courses of*	problem of this re-appraisal. As previously discussed in a call with the ERG and NICE, the pooled ITT population analysis provides an additional helpful analysis to contextualise the NOVA 2020 data and this re-submission, as well as providing an insightful additional comparison compared with Lord et al. Analysis in the ITT population is informative as it allows OS outcomes of patients treated with niraparib to be compared to published, UK-based, RWE OS outcomes of patients on routine surveillance as seen in the Lord et al. 2020 publication.[7] The Lord et al. 2020 publication is not split into *BRCA* subgroups, and therefore can only be compared versus an overall recurrent OC population. Furthermore, the pooled ITT populations aligns with the marketing authorisation for niraparib and reflects the current use in UK clinical practice. ERG clarification question B3 shows an analysis which compares niraparib SACT outcomes to Lord et al outcomes; an analysis which utilises like for like UK RWE vs UK RWE data. Perhaps the addition of this new informative like for like analysis may help the ERG to	

	chemotherapy (gBRCAmut 3L+), who would be eligible for olaparib. ***The entire gBRCAmut (2L and 3L+) niraparib population, and gBRCAmut 2L niraparib population are similar, with similar survival outcomes. Therefore the pooled ITT population, though it contains a slightly broader population than the population within the scope of this appraisal, is informative."*** *"**The ERG considers the ITT population of NOVA as relevant to this appraisal**. **The efficacy of niraparib versus routine surveillance in the ITT population includes a proportion of patients with BRCA mutation,** which includes a proportion of patients with BRCA mutation who have had 3 or more courses of chemotherapy.* ***The entire gBRCAmut (2L and 3L+) niraparib population, and gBRCAmut 2L niraparib population are similar, with similar survival outcomes. Therefore the pooled ITT population, though it contains a slightly broader population than the***	reconsider the value of the ITT population. The second reason for this change is that, the only reason the NOVA gBRCAmut populations were split up was to facilitate the comparison versus olaparib in the gBCRAmut3L+ population (which was in routine commissioning, not in CDF and so a comparator to be considered). The pooled ITT population, (which contains gBRCAmut 2L+ and non-gBCRAmut 2L+ patients) is not inherently different to the combined NICE gBRCAmut 2L and non-gBCRAmut 2L+ populations. As outlined below, the NOVA gBCRAmut patient population is relatively homogenous regardless of prior lines of therapy. The patient baseline characteristics in the NOVA g*BRCA*mut cohort (n=203) included in the pooled ITT population and the NOVA broad g*BRCA*mut 2L cohort (n=116) relevant to the NICE population, outlined in TA528 Table 10 company submission and TA528 Table 5 company response to clarification questions respectively, are very similar across all characteristics.[4]	

	population within the scope of this appraisal, is informative."	Progression-free survival is aligned across the g*BRCA*mut NOVA patients. In the g*BRCA*mut cohort (n=203), the PFS hazard ratio (HR) was 0.27 (0.17-0.41). In the gBRCAmut 2L cohort (n=100), the PFS HR was [redacted]. Finally, to clarify the point regarding cost-effectiveness of niraparib compared with olaparib in the g*BRCA*mut 3L+ population; the patient access scheme (PAS) for niraparib was updated following the ACM. Therefore, the cost-effectiveness of niraparib compared with olaparib in the g*BRCA*mut 3L+ population using the current niraparib PAS was not appraised by the Committee.	
Paragraph 1, page 40: *"As the ITT population is of limited relevance to this CDF review and the data for the ITT population are based on an earlier data cut with shorter follow up and fewer patients, it is not discussed further in this report but can be found in the CS (Section A.6) and in the NHSE report."*	The Company asks for these statements to be reconsidered given the justification provided in the 'Justification for amendment' column. ***"The pooled ITT population is relevant to this appraisal**. The data for the ITT population are based on an earlier data cut with shorter follow up and fewer patients, **fully outlined in** CS (Section A.6) and in the NHSE report."*	As outlined above, the pooled ITT population analysis provides an additional helpful analysis to contextualise this re-submission.	Not a factual inaccuracy – no change required.
Paragraph 1, page 51:	The Company asks for these statements to be reconsidered given	As outlined above, the pooled ITT population analysis provides an	Not a factual inaccuracy – no change required.

"In addition, as the populations of interest to this CDF review are patients with and without BRCA mutation, which are not available for Lord et al. 2020, the ERG does not provide further description or critique of Lord et al. 2020 in this report."	the justification provided in the 'Justification for amendment' column. *"In addition, as the populations of interest to this CDF review are patients with and without BRCA mutation, which are not available for Lord et al. 2020.* ***The pooled ITT population is relevant to this appraisal and is available in Lord et al. 2020****. The ERG does ~~not~~ provide further description or critique of Lord et al. 2020 in this report."*	additional helpful analysis to contextualise this re-submission, specifically facilitating a comparison of the pooled ITT niraparib population to the Lord et al. 2020 routine surveillance ITT population. As mentioned above, the new data recently provided to the ERG in response to clarification question B3, whereby the Company compared the niraparib SACT data with the Lord et al data, may encourage the ERG to reconsider its stance on the Lord data. Lord et al. 2020 is an important piece of UK specific RWE on the survival outcomes experience in relapsed advanced ovarian cancer, which can contextualise the NOVA 2020 data. As outlined in company CDF re-submission Appendix A.22 a clinical expert and author of Lord et al who was consulted with considered the survival outcomes presented within the study to be reflective of outcomes of patients treated with routine surveillance and seen in current UK clinical practice.[7] Clinical opinion assessed the patients included within the Lord et al. 2020 study to be similar to patients recruited to clinical trials, given the strict inclusion criteria of the study and emphasis on recruiting patients with confirmed	

		complete or partial response after chemotherapy. As such, expert opinion considered the data from the Lord et al. 2020 study to be similar to what would be observed in the cohort of patients without crossover to PARPi or data missingness, and acts as a suitable proxy for the confounded placebo OS data from the NOVA trial, and is worthy of being presented and considered, particularly in the context of the more recent like for like RWE SACT to RWE Lord et al analysis that the company has provided to the ERG.	
Paragraph 3, page 53: *"As part of their CDF submission, the company presented new analyses for a post-hoc pooled intention-to-treat (ITT) population from the NOVA trial. The pooled ITT population is comprised of the randomised gBRCAmut 2L+ and non-gBRCAmut 2L+ population. The ERG notes that the pooled ITT analysis is not restricted to gBRCAmut patients who have only had two lines of platinum-based chemotherapy, as per the committee's preferred assumptions from the Terms of Engagement (ToE). As such, the ERG considers that the pooled*	The Company asks for these statements to be reconsidered given the justification provided in the 'Justification for amendment' column. *"As part of their CDF submission, the company presented new analyses for a post-hoc pooled intention-to-treat (ITT) population from the NOVA trial. The pooled ITT population is comprised of the randomised gBRCAmut 2L+ and non-gBRCAmut 2L+ population. The ERG notes that the pooled ITT analysis is not restricted to gBRCAmut patients who have only had two lines of platinum-based chemotherapy, as per the committee's preferred assumptions*	As outlined above, the pooled ITT population analysis provides an additional helpful analysis to contextualise this re-submission.	Not a factual inaccuracy – no change required.

analysis is outside the scope of the CDF review and will not be discussed any further for the remainder of this report."	*from the Terms of Engagement (ToE).* ***The pooled ITT population is relevant to this appraisal, which provides an additional analysis to contextualise the re-submission."***		

Issue 4 Investigator assessed versus independent review committee PFS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 4, page 19: *"The ERG, therefore, considers that using IA data for TTD and IRC data for PFS is fundamentally flawed as this leads to a disconnect between PFS and TTD."* Paragraph 3, page 29: *"As highlighted in the original appraisal, the ERG maintains that using IA data for TTD and IRC data for PFS is fundamentally flawed as this leads to a disconnect between PFS and TTD in the economic model (see Section* ***Error! Reference source not found.****)"*	The Company asks for this statement to be reconsidered and removed given the justification provided in the 'Justification for amendment' column.	This issue was not one considered by the Committee as a source of uncertainty in the original appraisal and is therefore irrelevant to the CDF review. As the company outlined in response to ERG clarification question B5, the Committee concurrently assessed time to treatment discontinuation (TTD) and the NOVA primary endpoint of PFS per independent review committee (IRC). As stated in the FAD for TA528, the Committee concluded 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"*. As part of the committee meeting, "*clinical experts explained that time to treatment discontinuation in the trial would*	Not a factual inaccuracy – no change required.

		more closely reflect treatment discontinuation in clinical practice than independent retrospective assessment of progression-free survival. The Committee concluded that the company's estimation of time to treatment discontinuation was more reflective of real-life clinical practice and therefore the most appropriate."[1] On this basis, the use of TTD and PFS per IRC was accepted and not included as an uncertainty which needed to be addressed in the FAD for TA528 or in the ToE for this CDF review. In line with the Committee's preferred assumptions, as outlined in the ToE document, TTD within the economic model follows TTD as measured in the NOVA trial, alongside IRC PFS as part of this review.	
Paragraph 2 and 3, page 62: *"An issue around PFS that has remained unresolved from TA528 is the discrepancy between IA PFS and IRC PFS.* *As mentioned in Section* ***Error! Reference source not found.****, the ERG remains concerned that the PFS benefit of niraparib is inflated based on the two different methods of assessment. In NOVA, treatment with niraparib was*	The Company asks for this issue to be reconsidered and removed given the justification provided in the 'Justification for amendment' column Alternatively, if the ERG insists on retaining it, the Company asks for these statements to be reconsidered given the justification provided in the 'Justification for amendment' column.	This issue was not one considered by the Committee in the original appraisal as a source of uncertainty and is therefore irrelevant to the CDF review. As the Company outlined in response to ERG clarification question B5, and above, the use of TTD and PFS per IRC was accepted and not included as an uncertainty which needed to be	Not a factual inaccuracy – no change required.

stopped if the investigator identified disease progression. As such, the ERG considers that "investigator determined" TTD and IA PFS from NOVA would be consistent. *In TA528, the company declined to provide a scenario using IA PFS in the economic model. Thus, in the TA528 ERG report and the ERG response to company ACD comments, the ERG explored scenarios that focussed on using equivalence of IRC PFS to estimate TTD and IA TTD (preferred by the committee) to estimate IA PFS to appropriately align the costs and benefits associated with niraparib.* *During the clarification stage for the CDF submission, the ERG requested a scenario using IA PFS again, but the company maintained their position from TA528 and declined to provide the analysis, stating that the committee did not consider assessment of PFS as an uncertainty. Nonetheless, the ERG considers that exploring the discrepancy between IA and IRC PFS estimates is a resolvable issue but relies on the company providing analysis using IA PFS."*	*"An issue **raised by the ERG** around PFS that has remained unresolved from TA528 is the discrepancy between IA PFS and IRC PFS. **This issue was not outlined as uncertainty in the FAD for TA528 or in the ToE for this CDF review**.* *As mentioned in Section **Error! Reference source not found.**, the ERG remains concerned that the PFS benefit of niraparib is inflated based on the two different methods of assessment. In NOVA, treatment with niraparib was stopped if the investigator identified disease progression. As such, the ERG considers that "investigator determined" TTD and IA PFS from NOVA would be consistent.* *In TA528, the company declined to provide a scenario using IA PFS in the economic model. Thus, in the TA528 ERG report and the ERG response to company ACD comments, the ERG explored scenarios that focussed on using equivalence of IRC PFS to estimate TTD and IA TTD (preferred **source of TTD data** by the committee) to estimate IA PFS to appropriately align the costs and benefits associated with niraparib.* *During the clarification stage for the CDF submission, the ERG requested a scenario using IA PFS again, but the*	addressed in the FAD for TA528 or in the ToE for this CDF review. There are additional methodological rationale for maintaining PFS per IRC in the model. The use of IA PFS is not considered appropriate, as it was not a primary or secondary endpoint of the NOVA trial. Therefore, IA PFS was not a defined endpoint and was only included as a sensitivity analysis to ensure robustness of the HR. As such, centres were not trained nor was there a standardised protocol for assessing progression by investigators. Ovarian cancer is an inherently difficult disease to measure via Response Evaluation Criteria in Solid Tumours (RECIST) and therefore in the absence of protocol driven assessment differences/errors in reporting were inevitable. Furthermore, the health state utilities derived for use in the submission are defined as pre-progression and post-progression based on the date of progression determined by IRC PFS. Therefore, disease progression outcomes are aligned with health-related quality of life (HRQoL). HRQoL should follow the true progression status, which is the IRC PFS.	

	company maintained their position from TA528 and declined to provide the analysis, stating that the committee did not consider assessment of PFS as an uncertainty, ***that health-related quality of life data should follow the true progression status in the economic model, which is the IRC PFS, and finally that IA PFS is not considered appropriate as it is not a primary or secondary endpoint of the NOVA trial****. Nonetheless, the ERG considers that exploring the discrepancy between IA and IRC PFS estimates is a resolvable issue but relies on the company providing analysis using IA PFS."*		

Issue 5 BRCAmut 2L population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 1, page 34: *"The company confirmed that the more specific definition was used for OS in the original submission and for the updated TTD and OS data presented in Table 16. It is unclear what definition was used for PFS in the original submission and this CDF review."*	Please amend the text as follows following additional clarification: *"The company confirmed that the more specific definition was used for OS in the original submission and for the updated TTD and OS data presented in Table 16.* ***The more specific definition was also used for PFS in the original submission and this CDF review."***	The Company can confirm that within the economic model, the data which feeds into the results for all endpoints (PFS, TTD and OS survival coefficient data) is correct for the g*BRCA*mut 2L (n=100) cohort, and aligns with Table 4 in the ERG clarification letter. Therefore the cost-effectiveness results, sensitivity and scenario	This has been addressed in the updated ERG report.

		analyses provided are correct for this subgroup.	
Paragraph 4, page 45: *"The ERG highlights that for the gBRCAmut 2L subgroup these characteristics, which were presented in the original appraisal of niraparib, are for the broader definition of 2L described in section 3.1.2.The baseline characteristics of the population for which data are presented in section 3.1.2 and which is informing the economic model are therefore likely to be somewhat different."*	Please amend the text as follows following additional clarification: *"The ERG highlights that for the gBRCAmut 2L subgroup these characteristics, which were presented in the original appraisal of niraparib, are for the broader definition of 2L described in section 3.1.2.The baseline characteristics of the population for which data are presented in section 3.1.2 and which is informing the economic model are therefore likely to be somewhat different.* ***The company has committed to providing the gBRCAmut 2L (n=100) baseline characteristics as soon as possible."***	The Company can confirm a request has been made internally for the g*BRCA*mut 2L subgroup (n=100) baseline characteristics. These will be provided as soon as possible and no later than June 30th.	The ERG awaits the company's response on the 30th June.
Paragraph 1, page 62: *"As mentioned in Section 3.1.2, the company confirmed in their clarification response that the definition of 2L for the gBRCAmut subgroup for OS was based on patients who have only had two lines of chemotherapy, both of which were platinum-based (n=100).* ***However, the ERG was unclear what definition of 2L has been used for PFS. At the time of writing this report, the ERG was awaiting clarification from the company.***"	Please amend the text as follows following additional clarification: *"As mentioned in Section 3.1.2, the company confirmed in their clarification response that the definition of 2L for the gBRCAmut subgroup for OS,* ***PFS and TTD*** *was based on patients who have only had two lines of chemotherapy, both of which were platinum-based (n=100)."*	The Company can confirm that within the economic model, the data which feeds into the results for all endpoints (PFS, TTD and OS survival coefficient data) is correct for the g*BRCA*mut 2L (n=100) cohort, and aligns with Table 4 in the ERG clarification letter. Therefore the cost-effectiveness results, sensitivity and scenario analyse provided are correct for this subgroup.	This has been addressed in the updated ERG report.

Issue 6 Comparison NOVA versus Study 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 2, page 46: *"A larger proportion of patients had a complete response to their most recent platinum-based therapy in the non-gBRCAmut group given niraparib (50%) in NOVA than in the BRCAwt group given placebo in Study 19 (41%). This is likely to benefit niraparib in this comparison. Response to the most recent therapy wasn't reported for the gBRCAmut 2L group in NOVA but for the full gBRCAmut cohort the proportion with a complete response was similar (51.4%) to the proportion in the BRCAmut subgroup in Study 19 (55%)."*	The Company asks the ERG to reconsider and amend the text as follows: *"A larger proportion of patients had a complete response to their most recent platinum-based therapy in the non-gBRCAmut group given niraparib (50%) in NOVA than in the BRCAwt group given placebo in Study 19 (41%). This is likely to benefit niraparib in this comparison. Response to the most recent therapy wasn't reported for the gBRCAmut 2L group in NOVA but for the full gBRCAmut cohort the proportion with a complete response was similar (51.4%) to the proportion in the BRCAmut subgroup in Study 19 (55%).* ***This is likely to benefit olaparib in this comparison."***	The Company accepts that an imbalance in prognostics factors may benefit or disadvantage an intervention in a naïve comparison. The imbalance in complete and partial response between trials is described as likely to benefit niraparib in the *BRCA*wt comparison. The imbalance in complete and partial response in the *BRCA*mut comparison, which is likely to benefit olaparib should also be included for balance.	Not a factual inaccuracy – no change required.
Paragraph 5, page 45: *"In both subgroups of Study 19, patients had a slightly better performance status, with a larger proportion of patients with ECOG 0, than the equivalent subgroup in NOVA."*	The Company asks the ERG to reconsider and amend the text as follows: *"In both subgroups of Study 19, patients had a slightly better performance status, with a larger proportion of patients with ECOG 0, than the equivalent subgroup in NOVA.* ***This is likely to benefit olaparib in this comparison."***	As above, the Company accepts that an imbalance in prognostics factors may benefit or disadvantage an intervention in a naïve comparison. The imbalance in ECOG performance status between trials, which is likely to benefit	Not a factual inaccuracy – no change required.

		olaparib, should also be included for balance.	
Paragraph 5, page 45: *"The comparison of niraparib and placebo in the gBRCAmut 2L and BRCAmut subgroups of NOVA and Study 19, respectively, is likely to provide a conservative estimate, whereas, the comparison in the non-gBRCAmut 2L+ and BRCAwt subgroups may potentially overestimate the difference between niraparib and placebo."*	The Company asks the ERG to reconsider and amend the text as follows: *"The comparison of niraparib and placebo in the gBRCAmut 2L and BRCAmut subgroups of NOVA and Study 19, respectively, is likely to provide a conservative estimate."*	As above, the Company accepts that an imbalance in prognostics factors may benefit or disadvantage an intervention in a naïve comparison. The Company do not believe the difference in complete and partial response between trials is in the non-g*BRCA*mut 2L+ and *BRCA*wt subgroups is sufficient evidence to state *"the difference between niraparib and placebo is potentially overestimated."* In addition to partial and complete response, there is an imbalance in ECOG performance status in the non-g*BRCA*mut 2L+ and *BRCA*wt subgroups between trials, which is likely to benefit olaparib.	Not a factual inaccuracy – no change required.

Issue 7 Progression-free survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 4, page 59: *"However, the ERG considers that the company's choice of log-normal distribution results in inflated PFS estimates, which require the company to apply an arbitrary cap at 20 years."*	The Company asks the ERG to reconsider and amend the text as follows: *"However, the ERG considers that the company's choice of log-normal distribution results in inflated PFS estimates, which require the company to apply a cap at 20 years.* ***Without a cap,***	The PFS cap applied was validated by clinical experts at the time of the original submission; it is not an arbitrary cap. Only a very small proportion of patients (2.85%)) are estimated to remain progression-free at 20 years when the log-	Not a factual inaccuracy – no change required.

	2.85% ***of patients would remain progression-free at 20-years using the log-normal distribution."***	normal curve is used therefore the application of the cap does not have a significant impact on the cost-effectiveness but ensures that the results are clinically valid.	
Paragraph 1, page 60: *"As such, the ERG explored the company's flexible spline analysis and considers that the hazard k=1 spline provides a less pessimistic,* ***but clinically plausible*** *long-term extrapolation that more appropriately captures the hazard function and has included it in the ERG base case presented in Section* ***Error! Reference source not found.****."*	The Company asks the ERG to reconsider and amend the text as follows: *"As such, the ERG explored the company's flexible spline analysis and considers that the hazard k=1 spline provides a less pessimistic, long-term extrapolation that more appropriately captures the hazard function and has included it in the ERG base case presented in Section* ***Error! Reference source not found.****."*	Study 19 reports that ~16% of olaparib patients were on treatment and therefore progression-free after 5 years.[8] At 5 years, the hazard k=1 curves estimates that 21.36% of patients remain progression-free at 5 years, making it a clinical plausible distribution when compared to Study 19 up to this point. However, between 10 and 20 years, the hazard k=1 curve estimates a significant decrease in the proportion of patients who remain progression-free; it is likely that patients who remain progression-free after 10 years will have a reduced risk of progression in the following years. The lognormal curve represents this situation more accurately with a less significant rate of decrease from year 10 compared with hazard k=1.	Not a factual inaccuracy – no change required.
Paragraph 5, page: 15: *"Progression-free survival (PFS) – No updated PFS data have been presented as independent review*	The Company asks the ERG to reconsider and amend the text as follows: *"As part of the ToE, the committee requested the company to fully*	Long-term PFS estimates for niraparib and routine surveillance were based on extrapolations of PFS patient-level data assessed by IRC from the NOVA data cut-off	Not a factual inaccuracy – no change required.

committee assessed PFS was the primary endpoint in the NOVA trial and this endpoint was met in data cut-off in May 2016. The company's modelling of PFS is, therefore, unchanged since the original appraisal." Table 3, page 18: *"As part of the ToE, the committee requested the company to fully investigate the most appropriate PFS modelling using updated clinical trial data. For the CDF submission, the company resubmitted their preferred extrapolation for PFS for the gBRCAmut 2L subgroup from their original submission (lognormal) and the best fitting spline model for the non-gBRCAmut 2L+ subgroup from their ACD response (normal k=1 spline)."*	*investigate the most appropriate PFS modelling using updated clinical trial data.* ***Updated IRC PFS was not available and as such, the PFS data was unchanged****. For the CDF submission, the company resubmitted their preferred extrapolation for PFS for the gBRCAmut 2L subgroup from their original submission (lognormal) and the best fitting spline model for the non-gBRCAmut 2L+ subgroup from their ACD response (normal k=1 spline)."*	(DCO) June 2016. At this cut-off, the primary PFS endpoint was met and no additional analysis was conducted beyond June 2016. Updated PFS data was therefore not available and the PFS IRC data accepted by the Committee in 2018 were used to inform the economic model. Alternative curves were considered in the context of updated OS and TTD and the lognormal and normal k=1 spline was assessed to be the most appropriate curves given the statistical fit and clinical plausibility for the g*BRCA*mut 2L and non-g*BRCA*mut 2L+ subgroups.	
Table 12, row 1, page 27: Column 3: *"Partially departing from assumption. The company's modelling of PFS is unchanged since the original appraisal"* Paragraph 4, page 51:	The Company asks the ERG to reconsider and amend the text as follows: Column 3: ***"Adhering to assumption. The company modelling of PFS has been updated since the original appraisal; exploring flexible modelling and more conservative long-term extrapolations for the pooled ITT, non-gBRCAmut 2L+ and gBRCAmut 2L populations."***	The Company believe that as per the ToE the most appropriate PFS modelling has been investigated - using the economic model highlighted in the ToE and the primary PFS endpoint data from NOVA. The use of flexible models to capture the long-term extrapolation of PFS has been fully investigated for the pooled ITT, non-gBRCAmut 2L+ and gBRCAmut 2L populations, because as per TA528	The text in the ERG report has been updated to highlight that the PFS data are unchanged since the original appraisal. With regards to the amendment suggested for paragraph 4, page 85, it is not a factual inaccuracy and so no change is required.

"The company's modelling of PFS is unchanged since the original appraisal , where the company used PFS assessed by an Independent Review Committee (IRC), which was the primary outcome of NOVA." Paragraph 4, page 85: *"For the CDF review, the company did not change their preferred PFS distributions for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups, which were the lognormal and normal k=1 spline, respectively."*	The Company asks the ERG to reconsider and amend the text as follows: ***"The company modelling of PFS has been updated since the original appraisal; exploring flexible modelling and more conservative long-term extrapolations for the pooled ITT, non-gBRCAmut 2L+ and gBRCAmut 2L populations.*** *The company used PFS assessed by an Independent Review Committee (IRC), which was the primary outcome of NOVA."* The Company asks the ERG to reconsider and amend the text as follows: "*For the CDF review, the company* ***updated and reviewed*** *their preferred PFS distributions for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups, which were the lognormal and normal k=1 spline, respectively."*	FAD Section 3.12 *"The committee welcomed this more conservative analysis."* [1] The clinical plausibility of the PFS curves modelling was re-assessed following the NOVA 2020 update to OS, comparing the validity versus external long-term PARPi PFS evidence.	

Issue 8 Overall survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 5, issue 4, page 20: *"The ERG fundamentally disagrees with the use of a PFS:OS ratio as there is a lack of consistent evidence around the relationship between PFS to OS in*	The Company asks the ERG to remove these sentences	The Company base case provided in the CDF review submission considers a 1:1 PFS:OS relationship which is aligned with the ERG's assumption as stated in the FAD, "[*the ERG] preferred to*	Not a factual inaccuracy – no change required.

advanced or metastatic cancer, making it an unreliable and uncertain measure" Paragraph 2, page 65: *"The ERG fundamentally disagrees with the use of a PFS:OS ratio."* Paragraph 1, page 86: *"The ERG fundamentally disagrees with the use of a PFS:OS ratio…"*		*assume that all patients, regardless of treatment, have the same post-progression risk of death (ratio of overall survival to progression-free survival of 1:1)."* [1] This was further stated in the ToE: *"The ERG preferred to assume a ratio of 1:1 (that all people have the same post-progression risk of death)."*[2] This was accepted by the Committee as stated in the FAD and also reported in the ToE, *"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 was uncertain whether the overall survival benefit would be equal to or exceed the progression-free survival benefit."*[2]	
Paragraph 2, page 66: *"The ERG notes that the OS extrapolation for the gBRCAmut 2L subgroup, which is also based on the lognormal distribution, appears to overpredict survival for the trial period (Figure 8)"*	The Company asks the ERG to remove this sentence	The Company would like to clarify that following response to ERG clarification question B6 and further clarification via email, the g*BRCA*mut 2L Kaplan Meir data, used for validation purposes only, was incorrect in the economic model. The correct g*BRCA*mut 2L Kaplan Meir data was implemented in the economic model and no longer *"appears to overpredict survival for the trial period".* The	This has been addressed in the updated ERG report.

		updated economic model has been shared with the ERG.	
Paragraph 2, page 66: *"As such, the ERG requested the company to investigate more flexible methods for extrapolating OS for the gBRCAmut 2L subgroup. Furthermore, the ERG requested the company to explore a scenario extrapolating OS data from SACT to provide a real-world cost-effectiveness analysis for niraparib. At the time of writing this report, the company were not able to provide this analysis but confirmed it would be available post submission of the ERG report."*	Please amend the text as follows following provision of additional information: *"As such, the ERG requested the company to investigate more flexible methods for extrapolating OS for the gBRCAmut 2L subgroup* ***which has been provided although, due to the correction of the gBRCAmut 2L Kaplan Meir data, was not required****. Furthermore, the ERG requested the company to explore a scenario extrapolating OS data from SACT to provide a real-world cost-effectiveness analysis for niraparib. At the time of writing this report, the company were not able to provide this analysis but confirmed it would be available post submission of the ERG report.* ***Subsequently it can be confirmed that this analysis has been provided by the company.****"*	The Company can confirm that both of these analyses were shared with the ERG on Monday June 14th.	This has been addressed in the updated ERG report.
Paragraph 2, Page 86: *"The ERG was concerned about the OS extrapolation for the gBRCAmut 2L subgroup, as it appeared to overpredict survival for the trial period and also lack of analyses using OS data from the SACT dataset and*	Please amend the text as follows following provision of additional information: *"The ERG was concerned about the OS extrapolation for the gBRCAmut 2L subgroup, as it appeared to overpredict survival for the trial period* ***however this has been corrected in the model by***	The Company can confirm that both of these analyses were shared with the ERG on Monday June 14th.	This has been addressed in the updated ERG report.

requested the company to run additional scenarios."	***the company. The** lack of analyses using OS data from the SACT dataset **were noted** and **the ERG** requested the company to run additional scenarios. **It can be confirmed that these analyses have been provided.**"*		

Issue 9 Time to treatment discontinuation non-gBRCAmut 2L subgroup

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 1, page 69: *"However, for the non-gBRCAmut 2L**+** subgroup, the ERG considers that the Gompertz curve better captures the tail of the KM curve (see **Error! Reference source not found.**) and has a similar statistical fit to the company's preferred log-logistic distribution."*	To represent the facts of the appraisal and ensure the paragraph is balanced, the company asks the ERG to add the following text: *"However, for the non-gBRCAmut 2L**+** subgroup, the ERG considers that the Gompertz curve better captures the tail of the KM curve (see **Error! Reference source not found.**) and has a similar statistical fit to the company's preferred log-logistic distribution. **However, the log-logistic curve was a more clinically plausible choice when compared to SACT KM data and the lognormal curve for SACT TTD within the non-gBCRAmut 2L+ cohort."***	It is important to ensure the wording is balanced to reflect the justification for the company's preferred log-logistic distribution. The log-logistic distribution used to model TTD for the non-g*BRCA*mut 2L+ subgroup estimated [redacted]% of niraparib patients on treatment at 10 years. This aligns with the modelling of SACT non-g*BRCA*mut 2L+ via the best fitting lognormal distribution whereby [redacted]% of patients are on treatment at 10 years. The Gompertz however overestimates with [redacted]% of patients on treatment at 10 years.	Not a factual inaccuracy – no change required.

Issue 10 Treatment specific utilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 6, page 21: *"In TA528, the company implemented treatment-specific utilities based on data from NOVA. For the CDF review, the company has maintained their approach, but updated the utility analysis with the latest data cut from NOVA. In TA528, the ERG considered it was debatable that niraparib would be associated with higher HRQoL when the adverse event rate was also higher compared with placebo. Furthermore, no statistical tests were performed by the company, or results supplied to determine if the difference in utility values between niraparib and placebo were statistically significant."* Paragraph 1, page 71:	To represent the evidence provided in the appraisal and ensure the paragraph is balanced, the company asks the ERG to add the following text: *"In TA528, the company implemented treatment-specific utilities based on data from NOVA. For the CDF review, the company has maintained their approach, but updated the utility analysis with the latest data cut from NOVA. In TA528, the ERG considered it was debatable that niraparib would be associated with higher HRQoL when the adverse event rate was also higher compared with placebo**, although the company provided published clinical evidence to support the use of treatment-specific utilities.** Furthermore, no statistical tests were performed by the company, or results supplied to determine if the difference in utility values between niraparib and placebo were statistically significant. **Upon flagging this paucity of statistical tests, the company provided results of a patient-level data regression analysis using quality of life data from NOVA 2020. Results indicate that niraparib patients reported statistically significantly***	It is important to ensure that the wording is balanced and clarifying that clinical evidence was provided in the CDF submission in support of using treatment-specific utilities. Niraparib patients have a higher quality of life whilst progression-free compared to routine surveillance patients due to lowering symptoms associated with disease and prior chemotherapy such as pain levels.[9] Adopting treatment-specific utilities captures the quality of life benefit observed with niraparib. On the other hand, were the ERG's assumption of non-treatment specific utilities adopted, niraparib patients would have the same quality of life compared to routine surveillance, which contradicts the available evidence for niraparib. In addition, evidence is available from a time without symptoms and toxicity (TWiST) analysis demonstrating that treatment with niraparib resulted in mean TWiST benefit compared to placebo, therefore patients receiving niraparib within the NOVA trial	Not a factual inaccuracy – no change required. The company's proposed amendment suggests that the referenced analysis has been provided to the ERG. However, the ERG can confirm that this analysis has not been provided to the ERG as part of the CDF review for verification.

"Furthermore, in the clarification response for TA528 and the current CDF submission no statistical tests were performed, or results supplied to determine if the difference in utility values between niraparib and placebo were statistically significant.[6]" Paragraph 2, page 70: *"In the ERG report for TA528, health-state utilities based on progression status were preferred for the ERG base case, as it was debatable that niraparib would be associated with higher health-related quality of life (HRQoL) when the adverse event rate was also higher compared with placebo.[6] "* Paragraph 3, page 71 *"The ERG maintains its position that utility values based on progression status alone are the most appropriate for the cost-effectiveness analysis and this position is supported by the ERG's clinical experts.* Paragraph 3, page 86:	***higher quality of life than patients receiving routine surveillance."*** *"Furthermore, in the clarification response for TA528 and the current CDF submission no statistical tests were performed, or results supplied to determine if the difference in utility values between niraparib and placebo were statistically significant.[6]* ***Upon flagging this paucity of statistical tests, the company provided results of a patient-level data regression analysis using quality of life data from NOVA. Results indicate that niraparib patients reported statistically significantly higher quality of life than patients receiving routine surveillance."*** *"In the ERG report for TA528, health-state utilities based on progression status were preferred for the ERG base case, as it was debatable that niraparib would be associated with higher health-related quality of life (HRQoL) when the adverse event rate was also higher compared with placebo.[6]* ***However, the company provided clinical evidence from NOVA to support the use of treatment-specific utilities."*** *"The ERG maintains its position that utility values based on progression status alone are the most appropriate for the cost-effectiveness analysis and this*	spent more time without symptoms or symptomatic toxicities compared to patients receiving placebo.[10] To further support the use of treatment-specific utilities, a mixed effect linear regression model was performed to investigate differences in quality of life data between treatment arms in the NOVA trial. Results indicate that niraparib is associated with statistically significantly better quality of life than routine surveillance (p-value < 0.05).	

"In TA528, the ERG considered it was debatable that niraparib would be associated with higher health-related quality of life (HRQoL) when the adverse event rate was also higher compared with placebo. Furthermore, no statistical tests were performed by the company, or results supplied to determine if the difference in utility values between niraparib and placebo were statistically significant."	*position is supported by the ERG's clinical experts.* ***However, in the event of statistically significant differences in utility values between niraparib and placebo, an approach using treatment-specific utility values is acceptable.****"* *"In TA528, the ERG considered it was debatable that niraparib would be associated with higher health-related quality of life (HRQoL) when the adverse event rate was also higher compared with placebo.* ***However, the company provided clinical evidence from NOVA to support the use of treatment-specific utilities.*** *Furthermore, no statistical tests were performed by the company, or results supplied to determine if the difference in utility values between niraparib and placebo were statistically significant.* ***Upon flagging this paucity of statistical tests, the company provided results of a patient-level data regression analysis using quality of life data from NOVA. Results indicate that niraparib reported statistically significantly higher quality of life than patients receiving routine surveillance.****"*		

Issue 11 Updated niraparib dose data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 1 and 2, page 72 *"However, niraparib dose data for the CDF submission is based on actual dose consumed, calculated as the dispensed dose minus the returned dose per cycle.* *The ERG considers that in UK clinical practice, niraparib doses prescribed are unlikely to be returned to the NHS and reused. As such, the ERG considers that the company's original approach of using the prescribed dose data reflects that natural wastage that will occur in clinical practice."*	The company asks the ERG to reconsider and amend the text as follows: *"However, niraparib dose data for the CDF submission is based on actual dose consumed, calculated as the dispensed dose minus the* ***unused*** *dose per cycle.* *The ERG considers that in UK clinical practice, niraparib doses prescribed are unlikely to be returned to the NHS and reused.* ***Unused dose can be carried over by the patient and utilised during subsequent cycles.*** *As such, the ERG considers that the company's original approach of using the prescribed dose data reflects that natural wastage that will occur in clinical practice."*	The Company would like to clarify the concept of 'returned dose'. The updated NOVA 2020 dosing data captured the dose returned by patients to the investigator during the trial. The Company agree that *"niraparib doses prescribed are unlikely to be returned to the NHS and reused",* however the Company understand that the unused dose can be retained by the patients and utilised during subsequent treatment cycles. As outlined in the company response to ERG clarification question B9, it is important to capture the actual consumed dose, due to the nature of how niraparib is used. Dose titration may be used to manage adverse events and as such, it is not uncommon for a patient's dose to be down-titrated in the first few weeks of treatment. The mean actual dose consumed per cycle in Cycle 1 is below the starting dose of 300 mg per day x 28 days; for example, Cycle 1 mean actual dose: [redacted] mg for g*BRCA*mut 2L per cycle versus	Not a factual inaccuracy – no change required.

		Cycle 1 mean planned dose: 8400.00 mg. Using the Cycle 1 mean planned dose assumes that patients will use all 8,400.00 mg or eight-four 100 mg capsules. In reality, the dose is often down-titrated and the mean actual dose of [redacted] mg indicates that [redacted] 100mg capsules will be used. The [redacted] unused capsuled should be factored in. The utilisation of this unused dose is typical of NHS clinical practice, where pharmacists and prescribers will discuss medicines supply with patients before issuing an entirely new supply of medicine. The Company have made niraparib available only in 100mg capsules to allow for simple dose adjustments and so that spare capsules can be used in subsequent cycles with minimal wastage. This is contrary to other available PARPis which require a further prescription of an alternative dose to allow down-dosing which can incur increased wastage.	

Issue 12 Probabilistic sensitivity analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 1, page 22: *"The ERG identified an error with the company's probabilistic sensitivity analysis (PSA) related to the use of Study 19 data but was unable to correct this due to paucity of time. As such, the ERG are unable to present PSA ERG base case ICERs."* Paragraph 1, page 82: *"The ERG identified an error with the company's probabilistic sensitivity analysis (PSA) related to the use of Study 19 data but was unable to correct this due to paucity of time. As such, the ERG are unable to present PSA ERG base case ICERs."*	The Company asks the ERG to reword the statement as follows: Paragraph 1, page 22: *"The ERG identified an error with the company's probabilistic sensitivity analysis (PSA) related to the use of Study 19 data but was unable to correct this due to paucity of time. As such, the ERG* ***were*** *unable to present PSA ERG base case ICERs;* ***however, following the ERG's request, the company provided the ERG with PSA results and confirmed that there was no error in the model; only that the PSA takes considerable time to run****.* ***The gBRCAmut 2L ERG probabilistic ICER was £25,348 per QALY gained aligned with the deterministic ICER of £27,399 per QALY gained. The non-gBRCAmut 2L+ ERG probabilistic ICER was £50,328 per QALY gained aligned with the deterministic ICER of £51,684 per QALY gained."*** Paragraph 1, page 82: *"The ERG identified an error with the company's probabilistic sensitivity analysis (PSA) related to the use of Study 19 data but was unable to correct*	The Company provided the ERG with PSA ERG base case results on Tuesday 15th June.	This has been addressed in the updated ERG report.

	this due to paucity of time. As such, the ERG ***were*** *unable to present PSA ERG base case ICERs;* ***however, following the ERG's request, the company provided the ERG with PSA results and confirmed that there was no error in the model; only that the PSA takes considerable time to run****. The gBRCAmut 2L ERG probabilistic ICER was £25,348 per QALY gained aligned with the deterministic ICER of £27,399 per QALY gained. The non-gBRCAmut 2L+ ERG probabilistic ICER was £50,328 per QALY gained aligned with the deterministic ICER of £51,684 per QALY gained."*		

Issue 13 Protocol amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 2, page 31: *"The company reports that a protocol amendment allowed data entry of last known survival update or death based on public records. Due to this protocol amendment, there was a smaller but still considerable amount of missing survival data in both trial arms of the gBRCAmut 2L+ and non-gBRCAmut 2L+ cohorts at the final data cut-off (Table 14).* ***The ERG has not been able to find a reference to this amendment in the***	The Company asks the ERG to reconsider and remove this statement or amend the text as follows: *"The company reports that a protocol amendment allowed data entry of last known survival update or death based on public records. Due to this protocol amendment, there was a smaller but still considerable amount of missing survival data in both trial arms of the gBRCAmut 2L+ and non-gBRCAmut*	The Company will provide the amended protocol for clarification. The relevant sections of the amended protocol are: Synopsis and Section 5.5, Blinding and Breaking the Blind, and Section 4.4.2, Discontinuation from the Study. Section 6.2.9 Overall Survival Time referenced by the ERG regarding telephone contact would only apply to patients who had not withdrawn	The ERG thanks the company for providing the updated protocol. The text has been amended in the updated ERG report.

provided protocol, and notes that it is stated in the protocol that survival status was to be collected for all patients, using any acceptable means of collection, including telephone contact*."*	*2L+ cohorts at the final data cut-off (Table 14)."*	from the study. The protocol amendment allowed for *"the inclusion of information on survival status obtained from Investigator review of public records for those patients withdrawn or lost to follow-up is also permitted, dependent upon local regulations*."	

Issue 14 SACT data

Description of problem	Description of proposed amendment	Justification for amendment	
Paragraph 1, page 41: *"Although there are clear differences in the absolute results between the SACT cohorts and the equivalent subgroups in NOVA, it is unclear if the differences between the patient cohorts and settings will have an effect on the relative efficacy between niraparib and routine surveillance"*	The Company asks the ERG to add the additional text as follows: *"Although there are clear differences in the absolute results between the SACT cohorts and the equivalent subgroups in NOVA, it is unclear if the differences between the patient cohorts and settings will have an effect on the relative efficacy between niraparib and routine surveillance.* ***The company did attempt to access additional SACT baseline characteristics data, specifically, to further understand the differences with the NOVA population and reduce this uncertainty, however the study proposal was rejected on the grounds that niraparib is still in the CDF."***	The Company agrees that there is uncertainty between the two studies and wonders whether it would be interesting to highlight that the proposed study to resolve this was rejected by NHSE and SACT. The Company believes that it would have provided additional useful information and would have been helpful to decision makers for this appraisal and also for appraisals with similar questions in the future.	Not a factual inaccuracy – no change required.

Issue 15 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 1, page 49: *"In comparison, median OS was 31.11 months for patients in the **gBRCAmut 2L** subgroup treated with niraparib on NOVA."*	Please amend the text as follows: *"In comparison, median OS was 31.11 months for patients in the **non-gBRCAmut 2L+** subgroup treated with niraparib on NOVA."*	Typographical error	Thank you for highlighting this error. It has now been amended in the updated ERG report.
Paragraph 2, page 49 *"In comparison median OS was [redacted] months for patients treated with niraparib in the gBRCAmut 2L subgroup of NOVA."*	Please amend the text as follows: *"In comparison median OS was [redacted] months for patients treated with niraparib in the gBRCAmut 2L subgroup of NOVA."*	Typographical error. This value represents the median OS in the broad g*BRCA*mut 2L population and needs updating to the median in the specific g*BRCA*mut 2L population.	Thank you for highlighting this error. It has now been amended in the updated ERG report.
Paragraph 3, page 55: *"However, the company noted that data from NOVA indicated that on average in clinical practice, the full dose of niraparib may not be consumed by patients and instead used data on prescribed dose received to **calculated** a mean daily dose per treatment cycle (28 days) to inform the model for TA528."*	Please amend the text as follows: *"However, the company noted that data from NOVA indicated that on average in clinical practice, the full dose of niraparib may not be consumed by patients and instead used data on prescribed dose received to **calculate** a mean daily dose per treatment cycle (28 days) to inform the model for TA528."*	Typographical error	Thank you for highlighting this error. It has now been amended in the updated ERG report.
Paragraph 1, page 61:	Please amend the text as follows:	Typographical error	Thank you for highlighting this error. It has now been

<table>
<tr>
<td>“The ERG explored the use of the hazards k=1 spline in a scenario presented in Section 0 and included it as part of the ERG preferred assumptions , presented in Section 6.4”</td>
<td>“The ERG explored the use of the hazards k=1 spline in a scenario presented in Section 6.3 and included it as part of the ERG preferred assumptions , presented in Section 6.4”</td>
<td></td>
<td>amended in the updated ERG report.</td>
</tr>
<tr>
<td>Table 24, page 65, Mean PFS (niraparib)
<table>
<tr><th>Subgroup</th><th>Mean PFS (niraparib)</th><th>Mean OS (niraparib)</th></tr>
<tr><td>gBRCAmut 2L</td><td>2.96 years</td><td>[redacted]</td></tr>
<tr><td>non-gBRCAmut 2L+</td><td>1.09 years</td><td>[redacted]</td></tr>
<tr><td colspan="3">Abbreviations: gBRCAmut, germline breast cancer susceptibilit survival.
*calculated using a PFS:OS ratio of 1:1.</td></tr>
</table></td>
<td>Please amend the heading of column two to “Mean incremental niraparib PFS benefit”:
<table>
<tr><th>Subgroup</th><th>Mean incremental niraparib PFS benefit</th><th>Mean OS (niraparib)</th><th>Mean OS* (routine surveillance)</th><th>M (s su</th></tr>
<tr><td>gBRCAmut 2L</td><td>2.96 years</td><td>[redacted]</td><td>[redacted] ([redacted] – 1*2.96)</td><td>3</td></tr>
<tr><td>non-gBRCAmut 2L+</td><td>1.09 years</td><td>[redacted]</td><td>[redacted] ([redacted] – 1*1.09)</td><td>2</td></tr>
<tr><td colspan="5">Abbreviations: gBRCAmut, germline breast cancer susceptibility canc OS, overall survival; PFS, progression-free survival.
*calculated using a PFS:OS ratio of 1:1.</td></tr>
</table></td>
<td>Typographical error. The values stated in column two are the incremental PFS benefit of niraparib compared to routine surveillance, not the mean PFS.</td>
<td>Thank you for highlighting this error. It has now been amended in the updated ERG report.</td>
</tr>
</table>

Issue 16 SACT data incorrectly marked – has been amended

Issue 17 SACT scenario analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Row 2, Table 8, Page 24: Also Paragraph 2, Page 85: *"The ERG's clinical expert advised that for the SACT non-gBRCAmut 2L+ cohort, survival beyond 6 or 7 years is unlikely. As such, the ERG considers the company's log-logistic extrapolation to be optimistic."*	The Company asks the ERG to add the additional text as follows: *"The ERG's clinical expert advised that for the SACT non-gBRCAmut 2L+ cohort, survival beyond 6 or 7 years is unlikely. As such, the ERG considers the company's log-logistic extrapolation to be optimistic.* ***The log-logistic and Weibull curves estimate approximately 7.01% and 0.20% of patients are alive at 7 years, respectively."***	The Company ask for completeness that the percentage of patients surviving at the time point suggested by the clinical expert for each of the curve choices be included. The Company agrees that the log-logistic and Weibull curves represent similar statistical and visual fit to the non-g*BRCA*mut 2L+ SACT OS data.	Not a factual inaccuracy – no change required.
Row 2, Table 8, Page 24 Also Paragraph 3, Page 85: *"For the SACT gBRCAmut 2L subgroup, the ERG's clinical expert advised that within the cohort, there may be a subset of patients who are "super beneficiaries" but considered that the company's extrapolation may also be too optimistic."* Row 3, Table 8, Page 24	The Company asks the ERG to add the additional text as follows: *"Based on the ERG's clinical expert opinion, the ERG considers the generalised gamma distribution for the SACT gBRCAmut 2L subgroup captures the "super beneficiaries" but also reflects the conservative prognosis of the SACT cohort.* ***However, the generalised***	The Company ask that the percentage of patients surviving at the time point suggested by the clinical expert for each of the curve choices be included. The log-logistic curve is more clinically plausible for long term extrapolations based on the available published data in this setting. Using the log-logistic, [redacted]% of patients are alive at 10 years which is more conservative than that extrapolated from NOVA (DCO October 2020)	Not a factual inaccuracy – no change required.

Also Paragraph 1, Page 86: *"Based on the ERG's clinical expert opinion, the ERG considers the generalised gamma distribution for the SACT gBRCAmut 2L subgroup captures the "super beneficiaries" but also reflects the conservative prognosis of the SACT cohort."*	***gamma distribution is more pessimistic than the company's selection of the log-logistic distribution."***	([redacted]%) and the OS extrapolated from the olaparib arm of Study 19 ([redacted]%).[2] Using the generalized gamma curve [redacted]% of patients are alive at 10 years, which is pessimistic for the gBCRAmut 2L population based on the clinical evidence referenced above.	
Paragraph 3, page 83 *"The remit of the SACT data collection was only focused on patients receiving niraparib, therefore routine surveillance data for the SACT cost-effectiveness analysis needed to be estimated. As per the company base case, the company used a PFS:OS ratio of 1:1 to estimate mean OS. To estimate routine surveillance PFS, the NOVA PFS HR for each subgroup was applied to the estimated niraparib PFS SACT curve."* Paragraph 2, page 84 *"However, the ERG recognises that the SACT analyses rely heavily on assumptions that simulate a SACT-like routine surveillance arm as well as estimating niraparib PFS based on a NOVA PFS:TTD ratio."*	The Company asks the ERG to add the additional text as follows: *"The remit of the SACT data collection was only focused on patients receiving niraparib, therefore routine surveillance data for the SACT cost-effectiveness analysis needed to be estimated. As per the company base case, the company used a PFS:OS ratio of 1:1 to estimate mean OS. To estimate routine surveillance PFS, the NOVA PFS HR for each subgroup was applied to the estimated niraparib PFS SACT curve.* ***As per the ERG's suggestion in clarification question B3 an alternative approach using "real world" data for the routine surveillance arm was provided for the combined ITT cohort. Routine surveillance was modelled using RWE from Lord et al. 2020 for OS and PFS.***	The Company would like to highlight that in clarification question B3 the ERG note that *"it is useful for the committee to see a "real world" base case using SACT data for niraparib. An alternative to the above approach which yields similar results would also be considered appropriate."* The company have endeavoured to fully respond to question B3 by providing a comparison using UK RW data for both the niraparib and routine surveillance arms. Niraparib RW outcomes are available via the SACT data, however as noted by the ERG no equivalent routine surveillance RW outcomes are included in the SACT report. Lord et al. 2020 is an important piece of UK specific RWE on the survival outcomes experience in relapsed advanced ovarian cancer. As outlined in company CDF re-submission Appendix A.22 a clinical expert and author of Lord et al. 2020 who was consulted with considered the survival outcomes presented within the study to be reflective of outcomes of patients treated with routine surveillance and seen in current UK	Not a factual inaccuracy – no change required.

	Thus both arms are based on RWE." The Company asks the ERG to add the additional text as follows: *"However, the ERG recognises that the SACT analyses rely heavily on assumptions that simulate a SACT-like routine surveillance arm as well as estimating niraparib PFS based on a NOVA PFS:TTD ratio.* ***The company provided an alternative approach to simulation of a SACT-like routine surveillance arm, where routine surveillance was modelled using RWE from Lord et al. 2020 for OS and PFS."***	clinical practice and the study therefore provides an excellent RW routine surveillance comparator. Furthermore, the ERG highlighted the uncertainty that current SACT analysis '*relies heavily on assumptions that simulate a SACT-like routine surveillance arm".* It should be noted within the report that the company included an approach, using the Lord et al. 2020 study as a RWE routine surveillance comparator, which removes the first uncertainty and provides highly relevant and important evidence, that the Committee should be given the opportunity to consider.	
Paragraph 1, Page 55 *In addition, as the populations of interest to this CDF review are patients with and without BRCA mutation, which are not available for Lord et al. 2020, the ERG does not provide further description or critique of Lord et al. 2020 in this report.*	The Company asks the ERG to amend the text as follows: *~~"In addition, as~~ The populations of interest to this CDF review are patients with and without BRCA mutation,* ***and also the ITT population of NOVA which enables comparisons to be made between long-term UK data from both SACT and Lord et al. 2020 (which is only possible using an ITT population)."***	The Company would like to clarify that the intention of presenting evidence for the pooled ITT population is not to change the scope or decision problem of this re-appraisal. As highlighted above, using the Lord et al. 2020 study as a RW routine surveillance comparator versus RW niraparib SACT data is a valuable comparison which should be presented to the committee. It is the understanding of GSK that even if these data are presented, a Committee decision can still be taken based on the original populations. It might be worth pointing out that the 2L population currently covered by the NICE guidance is in fact a broad ITT population, who can be treated with niraparib irrespective of	Not a factual inaccuracy – no change required.

		biomarker. The Lord et al. 2020 study and therefore the pooled ITT population is relevant and central to this re-appraisal.	

References

1. NICE. TA528 Final Appraisal Determination (FAD). 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>
2. NICE. TA528 Niraparib CDF review. Terms of Engagement v1.0. 2021.
3. NICE. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer | Guidance | TA389 (review of TA91). at <https://www.nice.org.uk/guidance/ta389/history>
4. NICE. TA528 Committee papers. at <https://www.nice.org.uk/guidance/ta528/documents/committee-papers-2>
5. National Institute for Clinical and Care Excellence. Guide to the methods of technology appraisal 2013. 2013. at <https://www.nice.org.uk/process/pmg9/chapter/foreword>
6. NICE. NICE strategy 2021 to 2026: Dynamic, Collaborative, Excellent. 2021.

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8. Gourley C., Friedlander M., Matulonis U.A., *et al.* Clinically significant long-term maintenance treatment with olaparib in patients (pts) with platinum-sensitive relapsed serous ovarian cancer (PSR SOC). *J Clin Oncol* 2017. 35:
9. Oza AM, Matulonis UA, Malander S, *et al.* Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA): results from a double-blind, phase 3, randomised controlled trial. *Lancet Oncol* 2018. 19: 1117–1125.
10. Matulonis UA, Walder L, Nøttrup TJ, *et al.* Niraparib Maintenance Treatment Improves Time Without Symptoms or Toxicity (TWiST) Versus Routine Surveillance in Recurrent Ovarian Cancer: A TWiST Analysis of the ENGOT-OV16/NOVA Trial. *J Clin Oncol* 2019. 37: 3183–3191.

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Technical engagement response form

Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (CDF review TA528) [ID1644]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG 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 key issues below. You do not have to provide a response to every issue. 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 included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Wednesday 14 July 2021**

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 ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- 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.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- 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.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- 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 3.1.23 to 3.1.29) 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	**GlaxoSmithKline UK**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Model structure accepted for decision making in TA528.	Yes	The model structure was not considered by the Committee as a source of uncertainty during the original appraisal. The Committee's conclusion from TA528 was *'The committee accepted that the model was adequate for decision-making and that the choice of model structure was not critical'*.[1] On this basis, the model to be used for the CDF review submission was outlined in the Terms of Engagement (ToE) document. This document highlighted that the economic model named *"ID1041 Niraparib CEM_Response to ACD v0.2 16.03.18 [ACIC]*" should be used.[2] This model was supplied to the Company and was resubmitted in line with NICE's CDF process; that the model presents updated analyses and results were provided in a step wise fashion whilst also enabling the results of the original submission to be replicated. The means-based decision analytic model was based on the concept that was accepted in TA91 and the rationale for using the means-based approach model, was accepted by the Committee in the original submission.[3,4] The decision analytic model does not require two extrapolated curves to be drawn, unlike the PSM, and allows the full spectrum of parametric curves to be assessed for clinical, visual and statistical fit. As such, the means-based decision analytic model was considered to be the most appropriate model structure given the data available at the time. Whilst structural uncertainty will always exist, across appraisals, it is not standard for companies to present multiple models to Committee as part

of its submission. Even less so in a CDF re-submission in which there has been a previous decision made by the Committee that *'the choice of model structure is not critical to the decision making'.*[1]

It has been confirmed in the response to the ERG clarification question B1 that the Company did not provide a separate PSM in the original appraisal. As discussed in the technical engagement call, further clarification has been provided by the Company below regarding the difference in the results between the submitted decision analytic model structure and a PSM.

The model structure was assessed early in the Company's decision-making process prior to the original submission and a PSM was explored. Due to the immaturity of the NOVA overall survival (OS) data, a progression-free survival (PFS):OS relationship was used to model niraparib OS based upon a routine surveillance (RS) OS anchor using mature Study 19 data. An early PSM and decision analytic model were developed to assess the suitability of the model structures and compare any difference in results. Since a niraparib OS curve was not extrapolated, a comparison between the decision analytic model and a PSM was performed using an exponential curve for OS. A hypothetical exponential curve was drawn in the PSM to estimate the mean niraparib OS from the decision analytic model (based on the PFS:OS relationship). Using an exponential curve allowed use of the goal seek function to identify the coefficient required for the exponential curve to achieve the estimated mean niraparib OS from the decision analytic model. The results derived from the early models for the g*BRCA*mut and non-g*BRCA*mut cohorts are presented in the table below. As shown in this table, the ICERs derived from the early PSM and decision analytic models differ by less than £1,000 per QALY gained.

Technologies	Total costs (£)	Total LYG (years)	Total QALYs	Incremental. costs (£)	Incremental LYG (years)	Incremental QALYs	Incremental ICER (£/QALY)
g*BRCA*mut 2L – DA model: Exponential PFS:OS curves							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,917

<table>
<tr><td></td><td></td><td>
<table>
<tr><td colspan="8">gBRCAmut 2L – PSM: Exponential PFS:OS curves</td></tr>
<tr><td>Routine surveillance</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Niraparib</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>27,643</td></tr>
<tr><td colspan="8">Assumptions: PFS – Exponential; TTD – Lognormal; OS anchor (Study 19 BRCAmut 2L+ CSI) – Exponential; Mean niraparib OS estimated from hypothetical exponential curve: 7.72 years; 20 year PFS/ TTD cap; Treatment specific utilities; Simple discount Patient Access Scheme (PAS) of [redacted]%</td></tr>
<tr><td colspan="8">non-gBRCAmut 2L – DA model: Exponential PFS:OS curves</td></tr>
<tr><td>Routine surveillance</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Niraparib</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>51,708</td></tr>
<tr><td colspan="8">non-gBRCAmut 2L – PSM: Exponential PFS:OS curves</td></tr>
<tr><td>Routine surveillance</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Niraparib</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>50,779</td></tr>
<tr><td colspan="8">Assumptions: PFS – Exponential; TTD – Log-logistic; OS anchor (Study 19 ITT) – Exponential; Mean niraparib OS estimated from hypothetical exponential curve: 4.14 years; 20 year PFS/ TTD cap; Treatment specific utilities; Simple discount Patient Access Scheme (PAS) of [redacted]%</td></tr>
</table>
</td></tr>
<tr><td>Issue 2:
Extrapolation of PFS</td><td>No</td><td><u>PFS for the gBRCAmut 2L subgroup</u>

The company believe the lognormal curve is a clinically plausible representation for long term PFS within the gBRCAmut 2L subgroup. The lognormal curve, between 10 and 20 years, estimates a reduced rate of disease progression compared to the hazard k=1 curve; it is likely that patients who remain progression-free after 10 years will have a reduced risk of progression in the following years. However, due to the lack of data available to validate the long-term PFS at the 10- and 20- year points, the company has included the ERGs hazard k=1 curve for the gBRCAmut 2L PFS analysis, as a conservative estimate.

<u>PFS for the non-gBRCAmut 2L+ subgroup</u></td></tr>
</table>

The company believe the normal k=1 spline is a clinically plausible representation for long term PFS extrapolation within the non-g*BRCA*mut 2L+ subgroup. The ERG's preferred curve, hazards k=1 spline, estimates almost identical proportion of patient's progression free at various time points, as demonstrated in ERG report Table 28 copied below. The normal k=1 spline provides a sufficiently conservative estimate, compared with Study 19 which reports that ~14% of olaparib patients were on treatment and therefore progression-free after 5 years.[5] Any PFS estimates lower than the normal k=1 spline estimates do not fully capture the long term impact of niraparib on progression.

Table 28. adapted from the ERG report - Proportion of patient's progression-free at key time points for alternative PFS distributions

Year	Company's selection: normal k=1 spline	ERG's selection: hazards k=1 spline
5	9.22%	9.09%
10	3.89%	3.10%
15	1.92%	1.33%
20	0.75%	0.65%

The statistical fit for the normal k=1 spline is better than hazards k=1 spline (AIC [redacted] versus [redacted]). The visual fit of the normal k=1 spline and the hazards k=1 spline, as shown in ERG report figure 7, are also almost identical.

		Figure 7. from the ERG report - Alternative PFS distributions for niraparib – non-gBRCAmut 2L+ subgroup  In summary, the company cannot see any rationale to change from the company proposed normal k=1 spline and believe it should be the base case long term PFS extrapolation for the non-gBRCAmut 2L+ subgroup.
Issue 3: Investigator assessed versus independent review committee PFS	**No**	This issue was not one considered by the Committee as a source of uncertainty in the original appraisal and is therefore not relevant to the CDF review. As the company outlined in response to ERG clarification question B5, during TA528 the Committee concurrently assessed time to treatment discontinuation (TTD) and the NOVA primary endpoint of PFS per independent review committee (IRC). As stated in the FAD, the Committee concluded 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"*. As part of the committee meeting, *"clinical experts explained that time to treatment discontinuation in the trial would more closely reflect treatment discontinuation in clinical practice than independent retrospective assessment of progression-free*

		survival. The Committee concluded that the company's estimation of time to treatment discontinuation was more reflective of real-life clinical practice and therefore the most appropriate."[1] In line with the Committee's preferred assumptions, as outlined in the ToE document, TTD within the economic model follows TTD as measured in the NOVA trial, alongside IRC PFS. There are additional methodological reasons for maintaining PFS per IRC in the model. The use of IA PFS is not considered appropriate, as it was not a primary or secondary endpoint of the NOVA trial. Therefore, IA PFS was not a defined endpoint and was only included as a sensitivity analysis to ensure robustness of the hazard ratio. As such, centres were not trained nor was there a standardised protocol for assessing progression by investigators. Ovarian cancer is an inherently difficult disease to measure via Response Evaluation Criteria in Solid Tumours (RECIST) and therefore in the absence of protocol driven assessment, differences/errors in reporting were inevitable. In summary, the Company maintain that IRC PFS is correct and is appropriate to use within the economic modelling.
Issue 4: OS for routine surveillance	**No**	The Company considers the use of a 1:1 PFS:OS relationship to estimate the routine surveillance overall survival within the model is appropriate. This methodology is aligned with the ERG's assumption as stated in the FAD, *"[the ERG] preferred to assume that all patients, regardless of treatment, have the same post-progression risk of death (ratio of overall survival to progression-free survival of 1:1)."* [1] This was accepted by the Committee as stated in the FAD and also reported in the ToE, *"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 was uncertain whether the overall survival benefit would be equal to or exceed the progression-free survival benefit."* [1,2] The Company also consider that is it appropriate to use extrapolated *BRCA*mut and *BRCA*wt subgroup OS placebo data from Study 19 for the routine surveillance arm in the economic model. In summary, the Company accepts use of extrapolated *BRCA*mut and *BRCA*wt subgroup OS placebo data from Study 19 for the routine surveillance arm within the base-case. However, the use of a 1:1

		PFS:OS relationship to estimate the routine surveillance OS should be included as a scenario for consideration by the Committee.
Issue 5: Treatment specific utilities	No	As per the TA528 submission and as maintained throughout the TA528 process, the Company believe using treatment-specific utilities captures the quality of life benefit observed with niraparib more fully than an approach using treatment agnostic utilities. The numerical difference between niraparib and placebo reported utilities was captured during the NOVA trial, outlined in Table 26 from company submission appendix below. Patients treated with niraparib have a higher quality of life whilst progression-free compared to patients who receive routine surveillance due to lowering symptoms associated with disease and prior chemotherapy such as pain levels.[6] The impact of niraparib on quality of life was specifically noted by patients with ovarian cancer consulted for this CDF appraisal's patient organisation submission; *"It has given me sufficient quality of life to continue to enjoy my "new normal" as a cancer patient.", "It has given me a certain quality of life back, and would really champion that other women have the chance to try it too.", "My quality of life is excellent, and, every day, I feel grateful for Niraparib, the NHS & Oncology Department."*.[7] Further, as discussed in the technical engagement call, the additional benefit of niraparib - that of providing an active treatment in what otherwise would be a watch and wait situation, was not captured due to the double-blind nature of NOVA. The niraparib treatment specific utility values captured in NOVA, even without capturing this additional benefit, show a numerical difference between niraparib and placebo reported utilities. Patients value maintence therapy options as they feel they can take control of their disease and do something proactively to slow progression, which comes through within the patient group submissions multiple times; *"(it was) a relief to have an alternative other than having to waiting for the another round of chemo…The real advantage is the mental health effects. I can relax a little and not be constantly worrying that my cancer is growing or not stable."* [8]This has not been captured in this appraisal and is an unaccounted-for additional benefit of treatment. The use of treatment specific, as opposed to treatment agnostic utilities goes some way to capture the differential advantage, though unfortunately cannot fully capture it.

The Company maintain that utility values as reported by niraparib and placebo patients within the NOVA trial should be implemented in the model. It does not make sense to use pooled utility data across treatment arms, when granular treatment specific utility data are available and can provide a more accurate representation of the quality of life impact.

Table 26. Company submission appendix - Health state utility data – NOVA ITT population, NOVA DCO October 2020

State	Utility value (SE, N)
Mapped EQ-5D-3L data from the NOVA trial	
PFD	[redacted]
PD	[redacted]
Treatment specific mapped EQ-5D-3L utilities from the NOVA trial	
Niraparib PFD	[redacted]
Niraparib PD	[redacted]
Placebo PFD	[redacted]
Placebo PD	[redacted]

To further support the use of treatment-specific utilities, a mixed effect linear regression model was performed to investigate differences in quality of life data between treatment arms in the NOVA trial. Results demonstrate that niraparib is associated with statistically significantly improved quality of life compared with routine surveillance (p-value < 0.05). The Company will endeavour to provide more detail on the statistical difference between treatment specific and treatment agnostic utilities in advance of the appraisal committee meeting.

Issue 6: Dose data for niraparib	**No**	The Company would like to clarify the concept of 'returned dose'. The updated NOVA 2020 dosing data captured the dose returned by patients to the investigator during the trial. The Company agree that *"niraparib doses prescribed are unlikely to be returned to the NHS and reused"*, however the Company

		understand that the unused dose can be retained by the patients and utilised during subsequent treatment cycles. Dose titration may be used to manage adverse events and as such, it is not uncommon for a patient's dose to be down-titrated in the first few weeks of treatment. The Company have made niraparib available only in 100mg capsules to allow for simple dose adjustments and so that unused capsules can be used in subsequent cycles with minimal wastage. The utilisation of this unused dose is typical of NHS clinical practice, where pharmacists and prescribers will discuss medicines supply with patients before issuing an entirely new supply of medicine. As advised by the ERG during the technical engagement TC, the Company have sought clinical input to validate this statement. The Company have spoken with a number of oncology pharmacists regarding the current dispensing and usage practices for NHS patients. It was flagged that a specific Commissioning for Quality and Innovation (CQUIN) standard has been implemented to support Medicines Optimisation.[9] This standard, implemented across NHSE, is evidence that pharmacists are aiming to reach a standardised approach to monitoring medicines waste and promoting schemes to minimise waste. Furthermore, an oncology pharmacist advised that prescriptions are managed through e-prescribing systems to ensure that patients are screened and any repeat prescriptions delayed until needed based on their previously dispensed, additional, niraparib capsules.
Issue 7: OS extrapolation for SACT	**No**	**<u>OS for the gBRCAmut 2L subgroup</u>** The Company agrees that the log-logistic and generalised gamma curves represent similar statistical and visual fit to the gBRCAmut 2L SACT OS data. Using the ERG's preferred curve, generalised gamma, [redacted] of patients are alive at 10 years, which is pessimistic for the g*BRCA*mut 2L compared with OS extrapolated from NOVA (DCO October 2020) ([redacted]%) and the OS extrapolated from the olaparib arm of Study 19 ([redacted]%).[10]

		In summary, the company accepts use of the ERG's preferred curve, generalized gamma, however it should be noted that this is a conservative curve choice for this population. **<u>OS for the non-gBRCAmut 2L subgroup</u>** The Company agrees that the log-logistic and Weibull curves represent similar statistical and visual fit to the non-gBRCAmut 2L+ SACT OS data. In summary, the company accepts use of the ERG's preferred Weibull curve, however it should be noted that this is a conservative curve choice for this population.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: End of Life (EOL) criteria for the non-g*BRCA*mut 2L+ population	Section 7, Page 102	Yes	During the CDF review kick-off meeting, the Company discussed with NICE the possibility of reintroducing consideration for the EOL criteria to be applied in this review, which was then outlined in the company submission • The non-g*BRCA*mut 2L+ population meets the EOL criteria; new SACT data and published real world evidence (RWE) from Lord et al. 2020 support the assertion that patients treated with routine surveillance has a life expectancy of less than 24 months. • Conversely the g*BRCA*mut 2L population does not meet the EOL criteria. Approximately 80% of patients with advanced OC do not have a g*BRCA* mutation, and as such the non-g*BRCA*mut 2L+ population forms the majority of patients with relapsed OC treated in clinical practice; this highlights the significant unmet need in this group of patients. Regarding the first criterion - *The treatment is indicated for patients with a short life expectancy, normally less than 24 months,* the company believe that all appropriate available data on life expectancy should be presented to the committee for consideration. The ERG report presents only some of the mean routine surveillance values. Further, published OS outcomes for non-gBRCAmut 2L+ population routine surveillance and placebo patients are also relevant to decision making. Most importantly, UK specific real-world survival outcomes data for the non-gBRCAmut 2L+ population have become available since TA528 and should be outlined to the Committee to aid decision making.

The following relevant life expectancy estimates, from both the published literature, and from the economic model using both the NOVA and the real-world evidence, are currently not outlined in Section 7, End of Life, of the ERG report.

Life expectancy	Data source	Notes
Medians		
22.6 months[11] (95% CI 21.3 – 24.7) months	SACT non-g*BRCA*mut 2L+ niraparib arm median OS	Population is treated with niraparib; highly likely routine surveillance patients will have lower OS.
19.3 months (95% CI ± 2.4)[12]	Lord et al. 2020 ITT routine surveillance arm median OS	Population is all-comers and therefore contains gBRCAmut patients and non-gBRCAmut patients; likely a non-gBRCAmut only population will have lower OS.
Means*		
[redacted]	CEM SACT non-gBRCAmut 2L+ routine surveillance mean OS, using 1:1 PFS:OS ratio to estimate OS	Using 1:1 PFS:OS ratio to estimate OS. Estimated real world routine surveillance calculated using the NOVA PFS HR applied to the estimated niraparib PFS SACT curve, and used as the PFS:OS ratio anchor.

*all means undiscounted

Regarding the second criterion - *There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment* - Yes, mean OS estimated in the updated company base-case for the non-gBRCAmut 2L+ population, based on the NOVA 2020 niraparib OS data and Study 19 placebo OS data, is [redacted] and [redacted] years respectively; the difference in terms of life extension in this scenario is [redacted] years.

In scenario analysis, using the PFS:OS 1:1 to relationship to estimate routine surveillance OS, the mean OS is [redacted] and [redacted] years for

			niraparib and RS, respectively. Therefore, the difference in terms of life extension is [redacted] years. Both indicate that there is an additional 3-month OS gain for patients treated with niraparib. Furthermore, the RWE scenarios included in the submission also demonstrate the additional 3-month OS gain for patients treated with niraparib. The non-gBRCAmut 2L+ population, based on the SACT niraparib OS data and using the PFS:OS 1:1 to relationship to estimate real world routine surveillance OS, is [redacted] and [redacted] years for niraparib and RS respectively; the difference in terms of life extension in this scenario is [redacted] years. Mean OS estimated in the company SACT scenario analysis for the combined ITT population, based on the SACT ITT niraparib OS data and the Lord et al routine surveillance OS, is [redacted] and [redacted] years respectively; the difference in terms of life extension in this scenario is [redacted] years.

Additional issue 2: ITT population and comparison versus Lord et al. 2020	Section 2.3 Critique of company's adherence to committees preferred assumptions from the Terms of Engagement; page 31 Section 3.12; page 38 Section 3.32; *Lord et al. 2020,* page 54	No	The Company would like to reassert the value of presenting the ITT comparison versus Lord et al to the Committee, particularly the latterly submitted analysis, in which SACT niraparib data were compared with Lord et al routine surveillance in a like for like analysis. The company would like to additionally clarify that the intention of presenting evidence for the pooled intention-to-treat (ITT) population is not to change the scope or decision problem of this re-appraisal. As outlined during the clarification process, the pooled ITT population analysis provides an additional helpful analysis to contextualise the NOVA 2020 data and this re-submission, as well as providing an insightful additional comparison compared with Lord et al. 2020. It is the understanding of GSK that even if these data are presented, a Committee decision can still be taken based on the original populations. Analysis in the ITT population is informative as it allows OS outcomes of patients treated with niraparib to be compared to published, UK-based, RWE OS outcomes of patients on routine surveillance as seen in the Lord et al. 2020 publication. The Lord et al. 2020 publication is not split into BRCA subgroups, and therefore can only be compared versus an overall, all comers, recurrent OC population. Real-world scenarios have been included in the company clarification response [Company clarification response B3 and B6, and Section 4.1.8 of the ERG report], as requested by the ERG, *"it is useful for the committee to see a "real world" base case using SACT data for niraparib. An alternative to the above approach which yields similar results would also be considered appropriate."* The Company have endeavoured to fully respond to question B3 by providing a comparison using niraparib SACT

			ITT outcomes to Lord et al. 2020 outcomes; an analysis which utilises and compares UK RWE vs UK RWE data. Lord et al. 2020 is an important piece of UK specific RWE on the survival outcomes experienced in relapsed advanced OC. As outlined in company CDF re-submission Appendix A.22 a clinical expert and author of Lord et al. 2020 who was consulted with considered the survival outcomes presented within the study to be reflective of outcomes of patients treated with routine surveillance and seen in current UK clinical practice and the study therefore provides an excellent real world routine surveillance comparator. The ERG highlighted the uncertainty that the current SACT analysis '*relies heavily on assumptions that simulate a SACT-like routine surveillance arm*". Using the Lord et al. 2020 study as an RWE routine surveillance comparator, removes this uncertainty and provides highly relevant and important evidence, that the Committee should be given the opportunity to consider. Furthermore, the 2L population currently covered by the NICE guidance is in fact a broad ITT population, who can be treated with niraparib irrespective of biomarker. The Lord et al. 2020 study and therefore the pooled ITT population is relevant and central to this re-appraisal.

<table>
<tr>
<td>Additional issue 3:
Scenario analysis</td>
<td>Section 5.1.2.3, page 87</td>
<td>Yes</td>
<td>
The company request that the various scenario analyses conducted in the company submission, to assess alternate model settings and structural uncertainty of the base case analysis, be presented to the committee. The scenario analysis tables from the company submission and ERG report, are presented below, using the updated company basecase:

Adapted from Table 10 of company submission. Key scenario analyses – Pooled ITT
<table>
<tr><th></th><th>Basecase</th><th>Scenario</th><th>ICER</th></tr>
<tr><td>Basecase</td><td></td><td></td><td>35,579</td></tr>
<tr><td>1</td><td>Extrapolated trial data from Study 19 for RS OS</td><td>Extrapolated trial data from Lord et al. 2020 for RS OS</td><td>23,147</td></tr>
<tr><td>2</td><td>Extrapolated trial data from Study 19 for RS OS</td><td>1:1 PFS:OS ratio for RS OS</td><td>25,875</td></tr>
<tr><td>3</td><td>Niraparib TTD data sourced from NOVA 2020</td><td>Niraparib TTD data sourced from SACT</td><td>21,782</td></tr>
<tr><td>4</td><td>Extrapolated trial data from Study 19 for RS OS and niraparib TTD data sourced from NOVA 2020</td><td>Extrapolated trial data from Lord et al. 2020 for RS OS and niraparib TTD data from SACT</td><td>14,238</td></tr>
<tr><td>5</td><td>Extrapolated trial data from Study 19 for RS OS and niraparib TTD data from NOVA 2020</td><td>1:1 PFS:OS ratio for RS OS and niraparib TTD data from SACT</td><td>15,893</td></tr>
</table>
The revised base-case for the pooled ITT population uses extrapolated RS OS data from Study 19.

Adapted from Table 11 of company submission and Table 1 ERG report. Key scenario analyses – gBRCAmut 2L subgroup
<table>
<tr><th></th><th>Parameter</th><th>Base case</th><th>Scenario</th><th>ICER (£/QALY)</th></tr>
<tr><td>0</td><td colspan="3">Base case</td><td>22,185</td></tr>
</table>
</td>
</tr>
</table>

			1	Overall survival for RS	21,838	PFS:OS ratio of 1:1	21,838
			2	Time to maintenance treatment discontinuation for niraparib	20,769	**B2 ERG clarification question** Niraparib TTD data sourced from SACT - gBRCAmut 2L	20,769
			3	-	20,445	Scenario 1 and 2	20,769
			4	Progression-free survival	22,205 21,900	PFS extrapolated using the lognormal curve	20,445
			5			PFS extrapolated using the normal k=1 flexible curve	22,205
			6	Utilities	23,686	**B8 ERG clarification question** Non-treatment specific health state utilities	21,900
			7	Niraparib dose	25,663	**B9 ERG clarification question** Planned niraparib dose NOVA 2016	23,686
			Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention to treat; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; RS, routine surveillance; SACT, Systemic Anti-Cancer Therapy; TTD, time to maintenance treatment discontinuation.			

Adapted from Table 12 of company submission and Table 22 ERG report. Key scenario analyses – non-gBRCAmut 2L+ subgroup

	Parameter	Base case	Scenario	ICER (£/QALY)
0	**Base case**			39,608
1	Overall survival for RS	36,449	PFS:OS ratio of 1:1	36,449
2	Time to maintenance treatment discontinuation for niraparib	26,299	**B2 ERG clarification question** Niraparib TTD data sourced from SACT - non-gBRCAmut 2L+	26,299
3	-	24,204	Scenario 1 and 2	24,204
4	Utilities	44,716	**B8 ERG clarification question** Non-treatment specific health state utilities	44,716
5	Niraparib dose	Actual niraparib dose NOVA 2020	**B9 ERG clarification question** Planned niraparib dose NOVA 2016	42,601

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention to treat; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; RS, routine surveillance; SACT, Systemic Anti-Cancer Therapy; TTD, time to maintenance treatment discontinuation.

Additional issue 4: **Non-gBCRAmut 2L+ TTD**	Section 4.1.4.3	No	The company maintain that the log-logistic curve is the most appropriate long-term extrapolation for the non-g*BCRA*mut 2L+ population, and do not accept the ERG's use of the Gompertz curve for this extrapolation. The log-logistic curve has the best statistical fit, with a lower AIC and BIC that the Gompertz curve (AIC [redacted] versus [redacted], and BIC [redacted] versus [redacted] for the log-logistic and Gompertz curves respectively). The log-logistic is also the more clinically plausible curve; the log-logistic curve estimated [redacted]% of niraparib patients on treatment at 10 years. This aligns with the modelling of SACT non-gBRCAmut 2L+ via the best fitting lognormal distribution whereby [redacted]% of patients are on treatment at 10 years. The Gompertz however overestimates with [redacted]% of patients on treatment at 10 years. In summary, the log-logistic curve is the most appropriate long-term extrapolation for non-gBRCAmut 2L+ based on statistical fit and is a conservative curve choice compared with extrapolation of UK real world time on treatment data for this population.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

gBCRAmut 2L

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Issue 2: Extrapolation of PFS - gBRCAmut 2L	Company curve choice for gBRCAmut 2L PFS curve was lognormal.	Updated curve choice for gBRCAmut 2L PFS is hazard k=1 spline.	Base-case: £21,838 (+£2,363 impact)
Issue 4: OS for routine surveillance	Mean OS for the routine surveillance arm in the company's base case analysis was estimated using a PFS:OS relationship of 1:1	OS based on Study 19 for routine surveillance (lognormal)	Base-case: £22,205 (+£2,730 impact)
Company's preferred base case following technical engagement	Base-case incremental QALYs: [redacted] (-[redacted] impact)	Base-case incremental costs: £41,895 (-£743 impact)	Base-case: £22,185 (+£2,710 impact)

Non-gBCRAmut 2L+

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER

Issue 4: OS for routine surveillance	Mean OS for the routine surveillance arm in the company's base case analysis was estimated using a PFS:OS relationship of 1:1	OS based on Study 19 for routine surveillance (lognormal)	Base-case: £39,608 (+£3,159 impact)
Company's preferred base case following technical engagement	Base-case incremental QALYs: [redacted] ([redacted] impact)	Base-case incremental costs: [redacted] ([redacted] impact)	Base-case: £39,608 (+£3,159 impact)

g*BRCA*mut 2L: SACT analysis

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Issue 7: OS extrapolation for SACT	Company curve choice for g*BRCA*mut 2L OS curve was log-logistic.	Updated curve choice for g*BRCA*mut 2L OS is generalised gamma.	Scenario analysis: £18,312 (+£382 impact)
Company's preferred base case following technical engagement	Scenario analysis incremental QALYs: [redacted] ([redacted] impact)	Scenario analysis incremental costs: [redacted] ([redacted] impact)	Scenario analysis: £18,312 (+£382 impact)

Non-gBCRAmut 2L+: SACT analysis

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER

Issue 7: OS extrapolation for SACT	Company curve choice for non-g*BRCA*mut 2L+ OS curve was loglogistic.	Updated curve choice non-g*BRCA*mut 2L+ OS is Weibull.	Scenario analysis: £37,986 (+£2,640 impact)
Company's preferred base case following technical engagement	Scenario analysis incremental QALYs: [redacted] ([redacted] impact)	Scenario analysis incremental costs: [redacted] ([redacted] impact)	Scenario analysis: £37,986 (+£2,640 impact)

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(3) NICE. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer | Guidance | TA389 (review of TA91) https://www.nice.org.uk/guidance/ta389/history (accessed 2021 -06 -17).
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(11) Public Health England. Niraparib for Treating Ovarian Cancer (TA528). Niraparib Overall Survival (OS) Refresh (Patient Trace 3rd February 2021). February 2021.
(12) Lord, R.; Rauniyar, J.; Morris, T.; Condon, O.; Jones, R.; Miller, R.; Hall, M.; Lofts, F.; Glasspool, R. M.; Hudson, E. Real World Outcomes in Platinum Sensitive Relapsed Ovarian, Fallopian Tube, or Peritoneal Cancer Treated in Routine Clinical Practice in the United Kingdom Prior to Poly-ADP Ribose Polymerase Inhibitors. *Int J Gynecol Cancer* **2020**, *30* (7), 1026–1033. https://doi.org/10.1136/ijgc-2019-000973.

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Technical engagement proposed new evidence form (company only)

Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (CDF review TA528) [ID1644]

As the company for this appraisal, you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses will be 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. As part of your response, you may intend to provide new evidence to address some or all of the key issues identified in the executive summary of the ERG report (that is, evidence that has not already been provided during the appraisal).

We would like to understand the extent of new evidence that you propose to provide in your response to technical engagement. This will help the ERG to plan its critique of your response. You do not have to provide new evidence in response to every issue. However, in general, any new evidence provided should have the purpose of addressing a key issue identified in the executive summary of the ERG report. Decisions about whether NICE will accept new evidence will be made on a case by case basis. Please note that NICE may need to extend timelines and reschedule the appraisal committee meeting to allow new evidence to be considered. Therefore, it is important that you notify NICE about new evidence in advance by completing this form as comprehensively as possible. Please be aware that NICE will not routinely accept new evidence provided after the deadline for technical engagement responses.

Deadline for returning this form: **Wednesday 7 July 2021**

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 ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses.
- Please ensure your response clearly identifies which key issue from the executive summary of the ERG report your proposed new evidence is intended to address. Please use the same issue numbers that have been used in the executive summary of the ERG report.
- If you intend to provide new evidence to address issues in the ERG report that have not been identified as key issues, please make this clear.
- 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.

NICE National Institute for Health and Care Excellence

Summary of proposed new evidence

Please use the table below to provide details of any proposed new evidence that you intend to submit in response to technical engagement.

Please be as comprehensive as possible.

<table>
<tr><th>Key issue(s) that the new evidence will address</th><th>Summary of the proposed new evidence (short title)</th><th>How will the new evidence address the key issue(s)?</th><th>Is the new evidence expected to alter the company's base-case ICER?</th><th>Additional details about the proposed new evidence (if available)</th></tr>
<tr><td>Section 3.3 of the ERG report - Alternative data sources for overall survival on routine surveillance. Table 24.</td><td>Baseline characteristics from NOVA in the gBRCAmut 2L (n=100) subgroup</td><td>The Company would like to provide the baseline characteristics for the gBRCAmut 2L (n=100) subgroup. At the clarification stage the Company explained that the gBRCAmut 2L subgroup data outlined in the clinical section and used in the economic modelling is a specific definition of 2L which includes patients who have only had two lines of chemotherapy, both of which were platinum-based.</td><td>No</td><td>Table 5. adapted from Company submission TA528, clarification response A10 - Patient baseline characteristics for the gBCRA 2L
<table>
<tr><th>Characteristic</th><th colspan="2">gBRCAmut 2L (n=116)</th><th colspan="2">gBRCAmut 2L (n=100)</th></tr>
<tr><th></th><th>Niraparib (n=79)</th><th>Placebo (n=37)</th><th>Niraparib (n=70)</th><th>Placebo (n=30)</th></tr>
<tr><td>Median age, years (range)</td><td>56.6 (37, 83)</td><td>57.3 (38, 71)</td><td>56.5 (37, 83)</td><td>58.0 (38, 71)</td></tr>
<tr><td colspan="5">Age (years), n (%)</td></tr>
<tr><td>18–64</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>65–74</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td></tr>
</table>

				≥65	[redacted]	[redacted]	[redacted]	[redacted]
				≥75	[redacted]	[redacted]	[redacted]	[redacted]
				Race, n (%)				
				White	[redacted]	[redacted]	[redacted]	[redacted]
				Black	[redacted]	[redacted]	[redacted]	[redacted]
				Asian	[redacted]	[redacted]	[redacted]	[redacted]
				American Indian/Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]
				Native Hawaiian/Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]
				Unknown	[redacted]	[redacted]	[redacted]	[redacted]
				BMI (kg/m2), n	[redacted]	[redacted]	[redacted]	[redacted]
				Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
				Median	[redacted]	[redacted]	[redacted]	[redacted]
				Min, Max	[redacted]	[redacted]	[redacted]	[redacted]

				Eastern Cooperative Oncology Group performance status, n (%)				
				0	[redacted]	[redacted]	[redacted]	[redacted]
				1	[redacted]	[redacted]	[redacted]	[redacted]
				Primary tumour site, n (%)				
				Ovary	[redacted]	[redacted]	[redacted]	[redacted]
				Primary peritoneum	[redacted]	[redacted]	[redacted]	[redacted]
				Fallopian tube	[redacted]	[redacted]	[redacted]	[redacted]
				Histologic subtype				
				Serous	[redacted]	[redacted]	[redacted]	[redacted]
				Endometrioid	[redacted]	[redacted]	[redacted]	[redacted]
				Mucinous	[redacted]	[redacted]	[redacted]	[redacted]
				Others	[redacted]	[redacted]	[redacted]	[redacted]
				Geographic region, n (%)				
				US and Canada	[redacted]	[redacted]	[redacted]	[redacted]

				Western Europe, Australasia and Israel	[redacted]	[redacted]	[redacted]	[redacted]
				Eastern Europe, Latin America and Asia	[redacted]	[redacted]	[redacted]	[redacted]
				Cancer stage at time of diagnosis, n (%)				
				I or II	[redacted]	[redacted]	[redacted]	[redacted]
				III	[redacted]	[redacted]	[redacted]	[redacted]
				IV	[redacted]	[redacted]	[redacted]	[redacted]
				Months of penultimate platinum-based therapy, n (%)				
				6 to <12 months	[redacted]	[redacted]	[redacted]	[redacted]
				≥12 months	[redacted]	[redacted]	[redacted]	[redacted]
				Total duration of last platinum-based therapy, months				
				Mean (range)	[redacted]	[redacted]	[redacted]	[redacted]
				Germline BRCA mutation, n (%)				
				BRCA1	[redacted]	[redacted]	[redacted]	[redacted]

				BRCA2	[redacted]	[redacted]	[redacted]	[redacted]
				BRCA1, BRCA2 rearrangement, or both	[redacted]	[redacted]	[redacted]	[redacted]
				Duration since diagnosis (years), n				
				Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
				Median	[redacted]	[redacted]	[redacted]	[redacted]
				Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
				Previous lines of therapy, n (%)				
				1	[redacted]	[redacted]	[redacted]	[redacted]
				2	[redacted]	[redacted]	[redacted]	[redacted]
				≥3	[redacted]	[redacted]	[redacted]	[redacted]
				Number of lines of platinum therapy, n (%)				
				1	[redacted]	[redacted]	[redacted]	[redacted]
				2	[redacted]	[redacted]	[redacted]	[redacted]
				>2	[redacted]	[redacted]	[redacted]	[redacted]

				Missing [redacted] [redacted] [redacted] [redacted]
				Number of metastatic sites, n (%)
				<3 [redacted] [redacted] [redacted] [redacted]
				≥3 [redacted] [redacted] [redacted] [redacted]

Please use this box to provide any other comments that may be useful at this time.

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Niraparib for maintenance treatment of platinum-sensitive ovarian cancer after second response to chemotherapy (CDF review of TA528) [ID1644]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing 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. The ERG report and stakeholder 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.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

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Please return this form by **5pm** on **[insert deadline for comments]**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

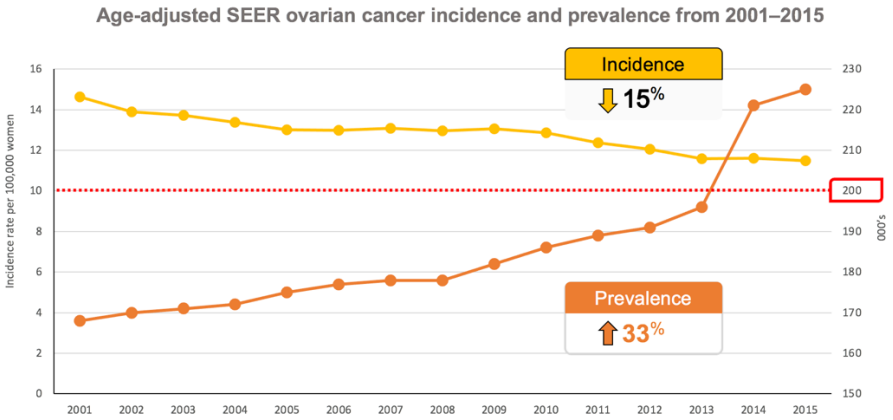
Important information on completing this expert statement

- 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 want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- 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.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 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with platinum-sensitive ovarian cancer after second response to chemotherapy and current treatment options	
About you	
1. Your name	**Jonathan A Ledermann**
2. Name of organisation	**UCL Cancer Institute and UCL Hospitals, London UK**
3. Job title or position	**Professor of medical oncology**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with platinum-sensitive ovarian cancer after second response to chemotherapy? ☒ a specialist in the clinical evidence base for platinum-sensitive ovarian cancer after second response to chemotherapy? ☐ 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	☒ 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.)

nominating organisation's submission)	
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 after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No past or current links to funding from the tobacco industry**
The aim of treatment for platinum-sensitive ovarian cancer after second response to chemotherapy	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Recurrent ovarian cancer has been historically considered to be an incurable disease in nearly all patients. The aim of treating recurrent ovarian cancer is to prolong survival with as little toxicity as possible. In the past this has been achieved using multiple lines of cytotoxic chemotherapy, given and intervals of decreasing frequency due to the emergence of drug resistance until the tumour becomes totally drug resistant. The introduction of PARP inhibitor maintenance therapy delays the need to restart chemotherapy, and in general is associated with low toxicity. In a small proportion of patients, maintenance therapy sustains the state of response (ie freedom from disease progression/need to restart chemotherapy) for a very long time (years). For most, it has the effect of significantly delaying the above progression events; in generally, the delay of these events is longest in patients with either a germ-line or somatic BRCA mutations.

9. 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.)	The key aim of maintenance therapy is to delay progression of tumour and the need to restart chemotherapy. Patients start taking PARP inhibitor maintenance therapy after a response to platinum-based chemotherapy. Thus, response is not a key indicator of the success of maintenance therapy. However, all trials with PARP inhibitors have shown that if a patient has measurable residual disease after chemotherapy, a proportion of these women will have a further reduction in tumour size during maintenance therapy. This demonstrates that the anti-tumour effect of PARP inhibitors is to 'deepen' the response as part of the process of prolonging disease control (ie delaying tumour progression).
10. In your view, is there an unmet need for patients and healthcare professionals in platinum-sensitive ovarian cancer after second response to chemotherapy?	The progression-free survival among patients receiving the placebo control arm maintenance in the four randomised trials with PARP inhibitor maintenance therapies (olaparib/niraparib/rucaparib) have shown remarkably consistent results, even though there were differences in the percentage of patients with BRCA mutations and differences in the number of prior lines of therapy. The median time to progression following enrolment into the trials after the completion of chemotherapy was 5.5 months. Thus, patients can be expected to be on chemotherapy again around 6 months after the previous course of treatment, which is a fairly grim statistic. Drugs that extend this period allow women to enjoy a fuller life, without symptoms of disease and the need to restart chemotherapy. Overall survival depends on how many prior lines of treatment the patient has received. Data from the GOG218 trial with bevacizumab showed that the median survival time following first recurrence was ~25 months. Few of these patients would have had access to PARP inhibitors, as the results of this trial were published in 2011. Thus, survival of patients with ovarian cancer pre-PARP inhibitors has been poor and population data showing an increase in survival beyond 2 years is something patients and doctors are seeking. Similarly, it is encouraging to see from USA registry data (SEER) that the prevalence of ovarian cancer suddenly changed

	around the introduction of PARP inhibitors in the USA, such that is now much higher than the incidence. Patients are living longer.  SEER=Surveillance, Epidemiology and End Results. 1. National Cancer Institute Surveillance, Epidemiology and End Results Program (SEER). SEER Cancer Statistics Review (CSR) 1975-2015 - Ovary. 2015; https://seer.cancer.gov/csr/1975_2015/sections.html. Accessed Aug 14, 2018.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Trials with PARP inhibitors have consistently shown the median time to disease progression on placebo after chemotherapy is 5.5 months. Through the CDF patients responding to platinum-based therapy can be offered PARP inhibitors (eg niraparib) and there is a high uptake of this opportunity to extend PFS. The greatest benefit is seen in patients with either a germline or somatic BRCA mutation. Management of PARP inhibitor treatment is straightforward in the majority of cases and during the last 18 months (Covid pandemic) many consultations have

	shifted to telephone/remote, aided by GSK's Homecare programme, testing patients' blood and BP at home. This has helped resource use in hospitals. The number of patients accessing PARP inhibitors for recurrent disease is declining a little as most patients with BRCA mutations will be offered first line olaparib maintenance (NICE CDF). Recent additions to the CDF have expanded the opportunity for treating non-BRCA mutated ovarian cancer with maintenance PARP inhibitors in the first-line setting. Whilst this continues, it will reduce the number of patients accessing PARP inhibitors in the second and subsequent lines of treatment.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	**ESMO** guidelines have been updated with e-update that includes PARP inhibitor for recurrence and the main guidelines are currently being revised to include this (https://www.esmo.org/guidelines/gynaecological-cancers/newly-diagnosed-and-relapsed-epithelial-ovarian-carcinoma) **ASCO (**DOI: 10.1200/JCO.20.01924 Journal of Clinical Oncology 38, no. 30 (October 20, 2020) 3468-3493) **and NCCN** have guidelines recommending the use of maintenance PARP inhibitors in the recurrent disease setting following platinum-based chemotherapy. UK national guidelines (**BGCS**) have not been updated since 2017
• 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 from outside England.)	The pathway is well defined and shown in an algorithm published following the **ESMO-ESGO Ovarian cancer consensus** meeting in 2018. In England/Wales and Scotland there is no access to bevacizumab which is licensed for use in patients undergoing platinum-based therapy for recurrent ovarian cancer. This drug is given with chemotherapy and as maintenance until disease progression. Thus, in the UK there is no alternative choice for maintenance therapy.
• What impact would the technology have on the current pathway of care?	For patients who have not received a PARP inhibitor in the front line, it would significantly extend the time to progression and delay in the need for further chemotherapy. From the NOVA trial, the median PFS extended from median of 5.5 to 21 months in the gBRCA cohort and from a median of 3.9 to 9.3 months in the non-gBRCA cohort

	These results show a clinically meaningful increase in time to progression and thus the need for further chemotherapy
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, for patients who have not had a PARP inhibitor and have responded to platinum-based therapy
• How does healthcare resource use differ between the technology and current care?	Patients have been accessing niraparib via the CDF. If this technology is approved, its use is unlikely to increase much over current levels as a proportion of patients are receiving PARP inhibitors in the front-line setting. For those who have not received front-line PARP inhibitors, use of niraparib in recurrent disease will increasingly become the norm, as bevacizumab is not available. The alternative of 'no maintenance treatment' means that further lines of chemotherapy will be given earlier.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Niraparib should be used in secondary care within specialist clinics. The current recommendations are that ovarian cancer should be treated through specialist centres, and niraparib therapy falls into this category
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Facilities currently exist to manage PARP inhibitor therapy. Whether in first or second/subsequent line use, the facilities needed are similar and hospitals are adapting clinics to manage such patients (medical/ specialist nursing/ pharmacist/ remote etc). The Homecare programme provided by GSK has facilitated the care pathway and is much more convenient for patients who need to travel less.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. As stated above. The expected median progression free survival from the placebo arm of PARP inhibitor studies has been remarkably consistent around a median of 5.5 months PFS. This is very short, and with non-PARP treatments the median survival from first relapse is around 24 months. Whilst it is difficult to show overall survival differences in the PARP inhibitor studies due to cross-over and long post progression survival, the median survival has been 42-44 months in the gBRCA cohorts [50% had received 2 prior lines; the remainder were ≥ 2 lines) and 31-37 months in the non-g BRCA cohorts [66% 2 prior lines; the remainder ≥2]

• Do you expect the technology to increase length of life more than current care?	Yes, see above. Without PARP inhibitors, the expectation from modern chemotherapy is that the median OS is around 24 months (*see Rose et al Nomogram for Predicting Individual Survival After Recurrence of Advanced-Stage, High-Grade Ovarian Carcinoma Obstet & Gynecol 2019 10.1097/aog.0000000000003086*).
• Do you expect the technology to increase health-related quality of life more than current care?	HR QoL is a complex evaluation, and most instruments were designed to evaluate QoL during treatment, such as cyclical chemotherapy. It has not been specifically set up to measure QoL in maintenance therapies. Here, patients enter maintenance after a response to treatment, so their QoL is good. It is unlikely to get better on treatment, other than by delaying the symptoms of progression- Studies were not specifically set up to evaluate this. As chemotherapy and disease recurrence both negatively impact on QoL, the delay in either or both of these will positively impact on a patient's QoL. The data from the niraparib trial shows that in spite of toxicity, QoL is maintained. Secondary analyses, such as TWiST (Time without symptoms of Toxicity) have shown a positive effect of PARP inhibitors (*Matulonis et al J Clin Oncol. 2019 Dec 1;37(34):3183-3191. doi: 10.1200/JCO.19.00917*)
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with either a gBRCA or sBRCA (tumour) mutation are likely to derive greater benefit, but there is a subgroup of around 10% patients without mutations who are long-term responders. Ie much longer than the median with freedom from recurrence for years
The use of the technology	
15. 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	There is already good experience using PARP inhibitors in the NHS. There has been use of these drugs through the CDF and NICE approvals. No new processes will be required

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Guidelines exist about the use of niraparib in this condition, as defined within the CDF
17. 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?	It depends on how QALY are calculated in relation to current or historical control data. There is good evidence that the introduction of PARP inhibitors through licensing of the drugs, and in the UK through the CDF is turning ovarian cancer into a more chronic disease with survival being extended. For a small subset (~10%) disease control is exceptional with patients surviving progression free for many years
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes. See above. Survival times are improving. The prevalence of the disease is now greater than the incidence

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes. It is the biggest change in therapeutic management of ovarian cancer for more than 2 decades
• Does the use of the technology address any particular unmet need of the patient population?	Yes. The survival of advanced ovarian cancer is very poor; patients taking PARP inhibitors are living longer
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	For the majority the side effects are manageable, and patients can remain on these drugs long-term. Around 12% patients are not able to tolerate PARP inhibitors despite dose-adjustments. For most patients, there is an extended time without chemotherapy, reduced dependence on hospital attendance and treatment. Many patients can now be successfully cared for through remote consultations with fewer hospital visits
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. Patients in the UK were included in the trials and UK practice is aligned to the international guidelines for treatment of the disease, using the technologies and drugs where available through the NHS
• If not, how could the results be extrapolated to the UK setting?	N/A

• What, in your view, are the most important outcomes, and were they measured in the trials?	The key outcome is the extension in progression free survival, the magnitude of benefit has not been seen in any other trials in this disease. Secondary outcomes such as Time to First subsequent treatment supports this as does PFS2/Time to second subsequent treatment, recognising that with increasing time and treatments post progression, the magnitude of difference decreases due to placebo patients crossing over to a PARP inhibitor after a subsequent line of treatment. Toxicity and acceptability are good
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogates such as TFST and PFS2/TSST are helpful
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The main long-term risk, recognised but clarified further through longer-term follow up is the risk of myelodysplasia/ Acute Myeloid Leukaemia. This is low (around 1%) and appears greater in patients with a germ line BRCA mutation. However, the risk of early death from ovarian cancer is a far greater risk to patients
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Since the trial, there has been a greater use of the lower dose of niraparib. Most clinicians use the lower dose of 200mg daily rather than 300 mg as the default starting dose, even among patients who are > 77Kg and with platelets > 150,000. This lower dose is cheaper and associated with less toxicity

22. How do data on real-world experience compare with the trial data?	Real world data provides valuable information for clinicians when the quality of the collected data is good. Published data using 200mg niraparib (above) shows it to be less toxic that the trial data (300 mg starting dose). There is also a learning curve to manage toxicity from using drugs in the real world. With increasing use, toxicity becomes more manageable.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
24. a) Would you expect a different prognosis for people who have a germline BRCA mutation and have had 2 prior lines of platinum-based chemotherapy (gBRCAmut 2L) or people who do	a) 1. The expectation is that patients with BRCA mutations (germline or somatic) do better than patients without these mutations. That is, their PFS is numerically longer and the difference in PFS between PARP inhibitor and placebo is greater than non-BRCA patients. (NB in the non-gBRCA cohort are patients with somatic BRCA mutations)

not have a germline BRCA mutation and have had 2 or more prior lines of platinum-based chemotherapy (non-gBRCAmut 2L+)? b) What is the expected survival for these two groups? What proportion would expect to be alive at 2, 5 and 10 years?	2. There are some patients without BRCA mutations who are 'super-responders' and may remain progression-free for many years 3. The effect size (HR) of PARP inhibitors is similar in 2L and 2L+ but numerically the PFS is greater in 2L compared with 2L+. There are other factors that interplay with this too, such as whether the patient is in a CR or PR when starting chemotherapy b) Survival of patients with BRCA mutations is longer, and among BRCA2 patients the survival is better than BRCA1 1. In the NOVA data OS curves$$
25. Would you expect a proportion of patients to receive a "super benefit" from treatment? Please provide an estimate of this proportion if possible.	From Study 19 it was 11% receiving olaparib for ≥6 yrs, and this was evenly divided between BRCA-mutated and BRCA-wild type tumours For SOLO2 (BRCA-mutated population) it was 22% receiving drug for ≥5 yrs. Although in both olaparib studies, patients were allowed to continue post progression, the number doing so (for more than 3 months) was small- around 30 in both trials. For niraparib and rucaparib treatment stopped at progression. The long-term, ≥2 yr data were recently presented at ASCO 2021 Kwan et al 21.1% rucaparib patients treated ≥2 yrs versus 2.1% placebo. Many but not all of these patients had either BRCA or RAD51 mutations. Ie some benefitted without HRR gene mutations as in study 19

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Issue 1: Model structure accepted for decision making in TA528.	
Issue 2: Extrapolation of PFS	
Issue 3: Investigator assessed versus independent review committee PFS	
Issue 4: OS for routine surveillance	The difficulty in using trial placebo for routine surveillance is that there has been an increasing percentage of PARP cross over in the control arm over the last 5-6 years. Study 19 will have the lowest percentage cross over, but other historical data without PARP inhibitors gives an indication the survival of patients

	after recurrence. As a result of long post-progression survival and cross over it is very difficult to demonstrate clear OS differences from a trial conducted several years before death
Issue 5: Treatment specific utilities	
Issue 6: Dose data for niraparib	See earlier comments re: dose
Issue 7: OS extrapolation for SACT	
Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Significant prolongation of PFS among all groups of patients responding to platinum-based therapy
- Without maintenance therapy the outlook for women with recurrent ovarian cancer is poor

- Survival of ovarian cancer patients is increasing with prevalence now greater than incidence - women are living with ovarian cancer, and living longer
- Niraparib is a well-tolerated drug and the option to start patients at a lower starting dose reduces major toxicity

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Niraparib for maintenance treatment of platinum-sensitive ovarian cancer after second response to chemotherapy (CDF review of TA528) [ID1644]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Wednesday 14 July 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important 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 want 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 15 pages.

PART 1 – Living with or caring for a patient with platinum-sensitive ovarian cancer and current treatment options	
About you	
1.Your name	**Rachel Downing**
2. Are you (please tick all that apply):	☐ a patient with platinum-sensitive ovarian cancer? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with platinum-sensitive ovarian cancer? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Target Ovarian Cancer
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☒ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with platinum-sensitive ovarian cancer? If you are a carer (for someone with platinum-sensitive ovarian cancer) please share your experience of caring for them.	
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for platinum-sensitive ovarian cancer on the NHS?	

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of **current NHS treatments** for platinum-sensitive ovarian cancer (for example how the treatment is given or taken, side effects of treatment etc) please describe these	
Advantages of this treatment	
9a. If there are advantages of niraparib over current treatments on the NHS please describe these. For example, the impact on your Quality of Life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	

9c. Does niraparib help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	
Disadvantages of this treatment	
10. If there are disadvantages of Niraparib over current treatments on the NHS please describe these? For example, are there any risks with Niraparib? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	
Patient population	
11. Are there any groups of patients who might benefit more from niraparib or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with	

mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
Equality	
12. Are there any potential equality issues that should be taken into account when considering platinum-sensitive ovarian cancer and niraparib? Please explain if you think any groups of people with platinum-sensitive ovarian cancer are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found	

at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14a. What are the main benefits of niraparib for	**Choice** – niraparib gives clinicians and women another option for extending progression free survival (PFS). There are also no maintenance treatments available in routine commissioning from the second line of treatment for women who do not have a BRCA mutation.

patients? If there are several benefits please list them in order of importance. Are there any benefits of niraparib that have not been captured? 14b. What are the benefits of niraparib for carers?	**Best possible care** – often women are aware of the poor outcomes associated with ovarian cancer. By accessing niraparib as part of their treatment plan, they may feel they are giving themselves the best possible chance of prolonging the disease-free interval. **Physical wellbeing** - once a woman has recurrent ovarian cancer she will inevitably go through further treatment cycles for subsequent recurrences. Niraparib offers women the opportunity to extend their PFS and therefore the interval between chemotherapy, this benefit is likely for many to outweigh the possible side effects associated with niraparib. A longer PFS may be beneficial in terms of supporting a better physical recovery from chemotherapy, enabling the individual to successfully undergo subsequent treatment. It is thought that prolonging the interval between treatments is likely to make subsequent treatment more effective. **Emotional/mental health** – once a woman has been diagnosed with recurrent ovarian cancer, further recurrence will be expected as the cancer runs its course. For many, receiving the news that their cancer has returned can be more devastating than the initial ovarian cancer diagnosis. Improvement in PFS offered by niraparib will allow give women valuable time to recover from the mental impact of recurrence and treatment, allowing them to resume normality, and live their lives as fully as possible. **Mode of delivery** – niraparib is administered orally which is well tolerated and means that patients do not need to attend a hospital setting to receive the treatment.
15. Are there any important issues that have been missed in ERG report?	The ERG report does not consider the value that PFS has to women with ovarian cancer and their families. Recurrent disease has a huge impact on women and their families and the ability to take a treatment that may give them months of PFS where they can recover physically and emotionally from chemotherapy treatment and do not have to attend a hospital setting is hugely important.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- 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.
- Women diagnosed with ovarian cancer are likely to experience multiple recurrences. Extending PFS is beneficial in supporting a woman's physical and emotional recovery between chemotherapy treatment.
- Multiple rounds of platinum-based chemotherapy are associated with cumulative toxicities eg peripheral neuropathy, and an increased likelihood of developing drug resistance. Maintenance therapies like niraparib which extend the time between platinum-based chemotherapy may reduce toxic effects and prolong tumour response to chemotherapy.
- Niraparib is available to women regardless of BRCA mutation which means more women will be able to access the treatment. There are currently no maintenance treatments available in routine commissioning for women who do not have a BRCA mutation.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Technical engagement response form

Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (CDF review TA528) [ID1644]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG 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 key issues below. You do not have to provide a response to every issue. 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 included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Wednesday 14 July 2021**

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 ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- 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.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- 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.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- 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 3.1.23 to 3.1.29) 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	**GlaxoSmithKline UK**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
Issue 1: Model structure accepted for decision making in TA528.	Yes	The model structure was not considered by the Committee as a source of uncertainty during the original appraisal. The Committee's conclusion from TA528 was *'The committee accepted that the model was adequate for decision-making and that the choice of model structure was not critical'*.[1] On this basis, the model to be used for the CDF review submission was outlined in the Terms of Engagement (ToE) document. This document highlighted that the economic model named *"ID1041 Niraparib CEM_Response to ACD v0.2 16.03.18 [ACIC]*" should be used.[2] This model was supplied to the Company and was resubmitted in line with NICE's CDF process; that the model presents updated analyses and results were provided in a step wise fashion whilst also enabling the results of the original submission to be replicated. The means-based decision analytic model was based on the concept that was accepted in TA91 and the rationale for using the means-based approach model, was accepted by the Committee in the original submission.[3,4] The decision analytic model does not require two extrapolated curves to be drawn, unlike the PSM, and allows the full spectrum of parametric curves to be assessed for clinical, visual and statistical fit. As such, the means-based decision analytic	The ERG welcomes the presentation of the results from the company's preliminary model structure assessment exercise, but notes that the model that the results are based on has not been supplied. As such, the results cannot be verified. Nonetheless, based on the description provided by the company, it is unsurprising the hypothetical PSM model yielded similar results to the means-based model as it has been calibrated to produce the same mean OS estimate. During the

		model was considered to be the most appropriate model structure given the data available at the time. Whilst structural uncertainty will always exist, across appraisals, it is not standard for companies to present multiple models to Committee as part of its submission. Even less so in a CDF re-submission in which there has been a previous decision made by the Committee that *'the choice of model structure is not critical to the decision making'*.[1] It has been confirmed in the response to the ERG clarification question B1 that the Company did not provide a separate PSM in the original appraisal. As discussed in the technical engagement call, further clarification has been provided by the Company below regarding the difference in the results between the submitted decision analytic model structure and a PSM. The model structure was assessed early in the Company's decision-making process prior to the original submission and a PSM was explored. Due to the immaturity of the NOVA overall survival (OS) data, a progression-free survival (PFS):OS relationship was used to model niraparib OS based upon a routine surveillance (RS) OS anchor using mature Study 19 data. An early PSM and decision analytic model were developed to assess the suitability of the model structures and compare any difference in results. Since a niraparib OS curve was not extrapolated, a comparison between the decision analytic model and a PSM was performed using an exponential curve for OS. A hypothetical exponential curve was drawn in the PSM to estimate the mean niraparib OS from the decision analytic model (based on the PFS:OS relationship). Using an exponential curve allowed use of the goal seek function to identify the coefficient required for the exponential curve to achieve the estimated mean niraparib OS from the decision analytic model. The results derived from the early models for the g*BRCA*mut and non-g*BRCA*mut cohorts are presented in the table below. As shown in this table, the ICERs derived from the early PSM and decision analytic models differ by less than £1,000 per QALY gained.	clarification stage, the ERG suggested an alternative approach to estimate OS for niraparib which rely on implementing hazard ratios (HRs) based on mature OS data derived from the study by Ledermann *et al.* 2016 which compared olaparib versus routine surveillance. However, estimating OS for niraparib is moot as mature OS data is available from NOVA. As such, the ERG maintains that for the CDF review, the company should have explored a PSM, at the very least to validate that their means-based approach produces reliable results.

Technologies	Total costs (£)	Total LYG (years)	Total QALYs	Incremental. costs (£)	Incremental LYG (years)	Incremental QALYs	Incremental ICER (£/QALY)
g*BRCA*mut 2L – DA model: Exponential PFS:OS curves							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,917
g*BRCA*mut 2L – PSM: Exponential PFS:OS curves							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,643
Assumptions: PFS – Exponential; TTD – Lognormal; OS anchor (Study 19 BRCAmut 2L+ CSI) – Exponential; Mean niraparib OS estimated from hypothetical exponential curve: 7.72 years; 20 year PFS/ TTD cap; Treatment specific utilities; Simple discount Patient Access Scheme (PAS) of [redacted]%							
non-g*BRCA*mut 2L – DA model: Exponential PFS:OS curves							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,708
non-g*BRCA*mut 2L – PSM: Exponential PFS:OS curves							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,779

		Assumptions: PFS – Exponential; TTD – Log-logistic; OS anchor (Study 19 ITT) – Exponential; Mean niraparib OS estimated from hypothetical exponential curve: 4.14 years; 20 year PFS/ TTD cap; Treatment specific utilities; Simple discount Patient Access Scheme (PAS) of [redacted]%	
Issue 2: Extrapolation of PFS	**No**	**PFS for the gBRCAmut 2L subgroup** The company believe the lognormal curve is a clinically plausible representation for long term PFS within the g*BRCA*mut 2L subgroup. The lognormal curve, between 10 and 20 years, estimates a reduced rate of disease progression compared to the hazard k=1 curve; it is likely that patients who remain progression-free after 10 years will have a reduced risk of progression in the following years. However, due to the lack of data available to validate the long-term PFS at the 10- and 20- year points, the company has included the ERGs hazard k=1 curve for the g*BRCA*mut 2L PFS analysis, as a conservative estimate. **PFS for the non-g*BRCA*mut 2L+ subgroup** The company believe the normal k=1 spline is a clinically plausible representation for long term PFS extrapolation within the non-g*BRCA*mut 2L+ subgroup. The ERG's preferred curve, hazards k=1 spline, estimates almost identical proportion of patient's progression free at various time points, as demonstrated in ERG report Table 28 copied below. The normal k=1 spline provides a sufficiently conservative estimate, compared with Study 19 which reports that ~14% of olaparib patients were on treatment and therefore progression-free after 5 years.[5] Any PFS estimates lower than the normal k=1 spline estimates do not fully capture the long term impact of niraparib on progression.	The ERG welcomes the company's alignment with its preferred PFS extrapolation for the gBRCAmut 2L subgroup. While the ERG agrees that PFS estimates for the company and ERG preferred extrapolations are similar, the rationale for selecting the hazards k=1 spline (as outlined in the ERG report) was to ensure that long-term (15 years onwards) PFS estimates were aligned with PFS estimates for the gBRCAmut 2L subgroup based on the hazards k=1 spline. For example, the 15-year PFS estimate for the gBRCAmut 2L subgroup using the hazards k=1 spline is 1.69%, which is

Table 28. adapted from the ERG report - Proportion of patient's progression-free at key time points for alternative PFS distributions

Year	Company's selection: normal k=1 spline	ERG's selection: hazards k=1 spline
5	9.22%	9.09%
10	3.89%	3.10%
15	1.92%	1.33%
20	0.75%	0.65%

The statistical fit for the normal k=1 spline is better than hazards k=1 spline (AIC 888.52 versus 893.00). The visual fit of the normal k=1 spline and the hazards k=1 spline, as shown in ERG report figure 7, are also almost identical.

Figure 7. from the ERG report - Alternative PFS distributions for niraparib – non-gBRCAmut 2L+ subgroup

slightly lower than the company's preferred PFS estimate for the non-gBRCAmut 2L+ subgroup (1.92%) and may not be clinically plausible. As such, the ERG maintains that hazards k=1 spline may be more clinically valid for the PFS extrapolation for the non-gBRCAmut 2L+ subgroup.

		In summary, the company cannot see any rationale to change from the company proposed normal k=1 spline and believe it should be the base case long term PFS extrapolation for the non-gBRCAmut 2L+ subgroup.	
Issue 3: Investigator assessed versus independent review committee PFS	**No**	This issue was not one considered by the Committee as a source of uncertainty in the original appraisal and is therefore not relevant to the CDF review. As the company outlined in response to ERG clarification question B5, during TA528 the Committee concurrently assessed time to treatment discontinuation (TTD) and the NOVA primary endpoint of PFS per independent review committee (IRC). As stated in the FAD, the Committee concluded 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"*. As part of the committee meeting, *"clinical experts explained that time to treatment discontinuation in the trial would more closely reflect treatment discontinuation in clinical practice than independent retrospective assessment of progression-free survival. The Committee concluded that the company's estimation of time to treatment discontinuation was more reflective of real-life clinical practice and therefore the most appropriate."*[1] In line with the Committee's preferred assumptions, as outlined in the ToE document, TTD within the economic model follows TTD as measured in the NOVA trial, alongside IRC PFS. There are additional methodological reasons for maintaining PFS per IRC in the model. The use of IA PFS is not considered appropriate, as it was not a primary or secondary endpoint of the NOVA trial. Therefore, IA PFS was not a defined endpoint and was only included as a sensitivity analysis to ensure robustness of the hazard ratio. As such, centres were not trained nor was there a standardised protocol for assessing progression by investigators. Ovarian cancer is an inherently difficult disease to measure via Response Evaluation Criteria in Solid	As mentioned in the ERG report, this is a resolvable issue and relies on the company providing the requested scenario using IA PFS to align with the TTD (given that NOVA TTD was accepted by the committee for TA528). As per the SmPC for niraparib, treatment should be continued until disease progression or toxicity. However, this is not what is currently modelled as IRC PFS is longer than TTD. Therefore, the PFS and TTD estimates are not aligned, as they would be in clinical practice. The impact of this in terms of cost-effectiveness is that niraparib costs do not reflect the expected benefit of treatment.

		Tumours (RECIST) and therefore in the absence of protocol driven assessment, differences/errors in reporting were inevitable. In summary, the Company maintain that IRC PFS is correct and is appropriate to use within the economic modelling.	
Issue 4: OS for routine surveillance	**No**	The Company considers the use of a 1:1 PFS:OS relationship to estimate the routine surveillance overall survival within the model is appropriate. This methodology is aligned with the ERG's assumption as stated in the FAD, *"[the ERG] preferred to assume that all patients, regardless of treatment, have the same post-progression risk of death (ratio of overall survival to progression-free survival of 1:1)."* [1] This was accepted by the Committee as stated in the FAD and also reported in the ToE, *"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 was uncertain whether the overall survival benefit would be equal to or exceed the progression-free survival benefit."* [1,2] The Company also consider that is it appropriate to use extrapolated *BRCA*mut and *BRCA*wt subgroup OS placebo data from Study 19 for the routine surveillance arm in the economic model. In summary, the Company accepts use of extrapolated *BRCA*mut and *BRCA*wt subgroup OS placebo data from Study 19 for the routine surveillance arm within the base-case. However, the use of a 1:1 PFS:OS relationship to estimate the routine surveillance OS should be included as a scenario for consideration by the Committee.	The ERG welcomes the company's alignment with its preferred OS extrapolation for routine surveillance using Study 19 data for both subgroups. However, the acceptance of Study 19 data for routine surveillance, coupled with mature OS data for niraparib from NOVA, reinforces the ERG's view that a PSM is appropriate for the CDF review.
Issue 5: Treatment	No	As per the TA528 submission and as maintained throughout the TA528 process, the Company believe using treatment-specific utilities captures the quality of life benefit observed with niraparib more fully than an approach using treatment	The ERG notes the company are relying on non-significant numerical

specific utilities		agnostic utilities. The numerical difference between niraparib and placebo reported utilities was captured during the NOVA trial, outlined in Table 26 from company submission appendix below. Patients treated with niraparib have a higher quality of life whilst progression-free compared to patients who receive routine surveillance due to lowering symptoms associated with disease and prior chemotherapy such as pain levels.[6] The impact of niraparib on quality of life was specifically noted by patients with ovarian cancer consulted for this CDF appraisal's patient organisation submission; *"It has given me sufficient quality of life to continue to enjoy my "new normal" as a cancer patient.", "It has given me a certain quality of life back, and would really champion that other women have the chance to try it too.", "My quality of life is excellent, and, every day, I feel grateful for Niraparib, the NHS & Oncology Department."*.[7] Further, as discussed in the technical engagement call, the additional benefit of niraparib - that of providing an active treatment in what otherwise would be a watch and wait situation, was not captured due to the double-blind nature of NOVA. The niraparib treatment specific utility values captured in NOVA, even without capturing this additional benefit, show a numerical difference between niraparib and placebo reported utilities. Patients value maintence therapy options as they feel they can take control of their disease and do something proactively to slow progression, which comes through within the patient group submissions multiple times; *"(it was) a relief to have an alternative other than having to waiting for the another round of chemo…The real advantage is the mental health effects. I can relax a little and not be constantly worrying that my cancer is growing or not stable."* [8]This has not been captured in this appraisal and is an unaccounted-for additional benefit of treatment. The use of treatment specific, as opposed to treatment agnostic utilities goes some way to capture the differential advantage, though unfortunately cannot fully capture it.	differences in utility between niraparib and placebo from NOVA, rather than statistically significant differences. The ERG notes the company has not provided the results of the regression model mentioned in their TE response, but these are due before the ACM. As such, the ERG maintains that utilities based on progression status are more appropriate than treatment-specific utilities.

The Company maintain that utility values as reported by niraparib and placebo patients within the NOVA trial should be implemented in the model. It does not make sense to use pooled utility data across treatment arms, when granular treatment specific utility data are available and can provide a more accurate representation of the quality of life impact.

Table 26. Company submission appendix - Health state utility data – NOVA ITT population, NOVA DCO October 2020

State	Utility value (SE, N)
Mapped EQ-5D-3L data from the NOVA trial	
PFD	[redacted]
PD	[redacted]
Treatment specific mapped EQ-5D-3L utilities from the NOVA trial	
Niraparib PFD	[redacted]
Niraparib PD	[redacted]
Placebo PFD	[redacted]
Placebo PD	[redacted]

To further support the use of treatment-specific utilities, a mixed effect linear regression model was performed to investigate differences in quality of life data between treatment arms in the NOVA trial. Results demonstrate that niraparib is associated with statistically significantly improved quality of life compared with routine surveillance (p-value < 0.05). The Company will endeavour to provide more detail on the statistical difference between treatment specific and treatment agnostic utilities in advance of the appraisal committee meeting.

Issue 6: Dose data for niraparib	**No**	The Company would like to clarify the concept of 'returned dose'. The updated NOVA 2020 dosing data captured the dose returned by patients to the investigator during the trial. The Company agree that *"niraparib doses prescribed are unlikely to be returned to the NHS and reused"*, however the Company understand that the unused dose can be retained by the patients and utilised during subsequent treatment cycles. Dose titration may be used to manage adverse events and as such, it is not uncommon for a patient's dose to be down-titrated in the first few weeks of treatment. The Company have made niraparib available only in 100mg capsules to allow for simple dose adjustments and so that unused capsules can be used in subsequent cycles with minimal wastage. The utilisation of this unused dose is typical of NHS clinical practice, where pharmacists and prescribers will discuss medicines supply with patients before issuing an entirely new supply of medicine. As advised by the ERG during the technical engagement TC, the Company have sought clinical input to validate this statement. The Company have spoken with a number of oncology pharmacists regarding the current dispensing and usage practices for NHS patients. It was flagged that a specific Commissioning for Quality and Innovation (CQUIN) standard has been implemented to support Medicines Optimisation.[9] This standard, implemented across NHSE, is evidence that pharmacists are aiming to reach a standardised approach to monitoring medicines waste and promoting schemes to minimise waste. Furthermore, an oncology pharmacist advised that prescriptions are managed through e-prescribing systems to ensure that patients are screened and any repeat prescriptions delayed until needed based on their previously dispensed, additional, niraparib capsules.	The ERG thanks the company for obtaining opinion from oncology pharmacists about dispensing of drugs. However, the ERG notes that the company's experts stated that they are aiming for a standardised approach to monitoring medicines waste, which the ERG interprets as variation still exists in England. The ERG considers that there will always be some wastage incurred with oral drugs and while 100mg capsules and better dispensing can minimise waste, it will not eliminate it. Therefore, the ERG considers that a conservative approach which includes wastage (based on prescribed dose) gives an upper bound of the mean cost of niraparib.

Issue 7: OS extrapolation for SACT	**No**	**<u>OS for the gBRCAmut 2L subgroup</u>** The Company agrees that the log-logistic and generalised gamma curves represent similar statistical and visual fit to the gBRCAmut 2L SACT OS data. Using the ERG's preferred curve, generalised gamma, [redacted] of patients are alive at 10 years, which is pessimistic for the g*BRCA*mut 2L compared with OS extrapolated from NOVA (DCO October 2020) ([redacted]%) and the OS extrapolated from the olaparib arm of Study 19 ([redacted]%).[10] In summary, the company accepts use of the ERG's preferred curve, generalized gamma, however it should be noted that this is a conservative curve choice for this population. **<u>OS for the non-gBRCAmut 2L subgroup</u>** The Company agrees that the log-logistic and Weibull curves represent similar statistical and visual fit to the non-gBRCAmut 2L+ SACT OS data. In summary, the company accepts use of the ERG's preferred Weibull curve, however it should be noted that this is a conservative curve choice for this population.	The ERG welcomes the company's alignment with its preferred SACT OS extrapolation for both subgroups. However, it should be noted that when SACT OS estimates are compared against NOVA, the baseline characteristics of each population need to also be considered. Patients in NOVA were fitter than SACT patients. As such, shorter OS estimates for the SACT cohort are more likely and this has been validated with one of the ERG's clinical experts.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s)	Does this response contain	Response	ERG response

	and/or page(s)	**new evidence, data or analyses?**		

Additional issue 1: End of Life (EOL) criteria for the non-g*BRCA*mut 2L+ population	**Section 7, Page 102**	**Yes**	During the CDF review kick-off meeting, the Company discussed with NICE the possibility of reintroducing consideration for the EOL criteria to be applied in this review, which was then outlined in the company submission • The non-g*BRCA*mut 2L+ population meets the EOL criteria; new SACT data and published real world evidence (RWE) from Lord et al. 2020 support the assertion that patients treated with routine surveillance has a life expectancy of less than 24 months. • Conversely the g*BRCA*mut 2L population does not meet the EOL criteria. Approximately 80% of patients with advanced OC do not have a g*BRCA* mutation, and as such the non-g*BRCA*mut 2L+ population forms the majority of patients with relapsed OC treated in clinical practice; this highlights the significant unmet need in this group of patients. Regarding the first criterion - *The treatment is indicated for patients with a short life expectancy, normally less than 24 months,* the company believe that all appropriate available data on life expectancy should be presented to the committee	It is for the committee to decide on whether EOL applies for the non-gBRCAmut 2L+ subgroup. However, the ERG notes that the niraparib SACT OS estimate and the Lord *et al.* routine surveillance estimate are based on medians rather than means. As the company has changed their base-case assumption to use Study 19 OS data for routine surveillance, the company's mean OS for routine surveillance is [redacted] years.

for consideration. The ERG report presents only some of the mean routine surveillance values. Further, published OS outcomes for non-gBRCAmut 2L+ population routine surveillance and placebo patients are also relevant to decision making. Most importantly, UK specific real-world survival outcomes data for the non-gBRCAmut 2L+ population have become available since TA528 and should be outlined to the Committee to aid decision making.

The following relevant life expectancy estimates, from both the published literature, and from the economic model using both the NOVA and the real-world evidence, are currently not outlined in Section 7, End of Life, of the ERG report.

Life expectancy	**Data source**	**Notes**
Medians		
22.6 months[11] (95% CI 21.3 – 24.7) months	SACT non-g*BRCA*mut 2L+ niraparib arm median OS	Population is treated with niraparib; highly likely routine surveillance patients will have lower OS.
19.3 months (95% CI ± 2.4)[12]	Lord et al. 2020 ITT routine surveillance arm median OS	Population is all-comers and therefore contains gBRCAmut patients and non-gBRCAmut patients; likely a non-gBRCAmut only population will have lower OS.
Means*		

			[redacted]	CEM SACT non-gBRCAmut 2L+ routine surveillance mean OS, using 1:1 PFS:OS ratio to estimate OS	Using 1:1 PFS:OS ratio to estimate OS. Estimated real world routine surveillance calculated using the NOVA PFS HR applied to the estimated niraparib PFS SACT curve, and used as the PFS:OS ratio anchor.

*all means undiscounted

Regarding the second criterion - *There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment* - Yes, mean OS estimated in the updated company base-case for the non-gBRCAmut 2L+ population, based on the NOVA 2020 niraparib OS data and Study 19 placebo OS data, is [redacted] and [redacted] years respectively; the difference in terms of life extension in this scenario is [redacted] years.

In scenario analysis, using the PFS:OS 1:1 to relationship to estimate routine surveillance OS, the mean OS is [redacted] and [redacted] years for niraparib and RS, respectively. Therefore, the difference in terms of life extension is [redacted] years. Both indicate that there is an additional 3-month OS gain for patients treated with niraparib.

			Furthermore, the RWE scenarios included in the submission also demonstrate the additional 3-month OS gain for patients treated with niraparib. The non-gBRCAmut 2L+ population, based on the SACT niraparib OS data and using the PFS:OS 1:1 to relationship to estimate real world routine surveillance OS, is [redacted] and [redacted] years for niraparib and RS respectively; the difference in terms of life extension in this scenario is [redacted] years. Mean OS estimated in the company SACT scenario analysis for the combined ITT population, based on the SACT ITT niraparib OS data and the Lord et al routine surveillance OS, is [redacted] and [redacted] years respectively; the difference in terms of life extension in this scenario is [redacted] years.	

Additional issue 2: ITT population and comparison versus Lord et al. 2020	**Section 2.3 Critique of company's adherence to committees preferred assumptions from the Terms of Engagement; page 31** **Section 3.12; page 38** Section 3.32; *Lord et al. 2020,* page 54	**No**	The Company would like to reassert the value of presenting the ITT comparison versus Lord et al to the Committee, particularly the latterly submitted analysis, in which SACT niraparib data were compared with Lord et al routine surveillance in a like for like analysis. The company would like to additionally clarify that the intention of presenting evidence for the pooled intention-to-treat (ITT) population is not to change the scope or decision problem of this re-appraisal. As outlined during the clarification process, the pooled ITT population analysis provides an additional helpful analysis to contextualise the NOVA 2020 data and this re-submission, as well as providing an insightful additional comparison compared with Lord et al. 2020. It is the understanding of GSK that even if these data are presented, a Committee decision can still be taken based on the original populations. Analysis in the ITT population is informative as it allows OS outcomes of patients treated with niraparib to be compared to published, UK-based, RWE OS outcomes of patients on routine surveillance as seen in the Lord et al. 2020 publication. The Lord et al. 2020 publication is not split into BRCA subgroups, and therefore can	The CDF ToE states that, "*The committee concluded that those with and without BRCA mutation after 2 courses of platinum-based chemotherapy could only be recommended within the Cancer Drugs Fund. This is the population that should be considered within the Cancer Drugs Fund review*". Furthermore, the committee for TA528 considered, "*that niraparib could not be considered plausibly cost-effective compared with olaparib in people with BRCA mutation who have had 3 or more courses of chemotherapy*". The ITT population in NOVA includes gBRCAmut patients who have had 3 or more lines of chemotherapy. Furthermore, the median number of lines of chemotherapy for the population in the Lord *et al.* study was 3 (a range of 2 to 9 lines) and 22% received more than 4 lines and no distinction was available for BRCA status. In comparison, the SACT gBRCA cohort was limited to 2 lines of prior chemotherapy. In addition, only age and ECOG status were reported for the SACT cohorts, which shows that these cohorts had a better performance status than the patients included in Lord *et al.* Due to the limited reporting there could be many more

			only be compared versus an overall, all comers, recurrent OC population. Real-world scenarios have been included in the company clarification response [Company clarification response B3 and B6, and Section 4.1.8 of the ERG report], as requested by the ERG, *"it is useful for the committee to see a "real world" base case using SACT data for niraparib. An alternative to the above approach which yields similar results would also be considered appropriate."* The Company have endeavoured to fully respond to question B3 by providing a comparison using niraparib SACT ITT outcomes to Lord et al. 2020 outcomes; an analysis which utilises and compares UK RWE vs UK RWE data. Lord et al. 2020 is an important piece of UK specific RWE on the survival outcomes experienced in relapsed advanced OC. As outlined in company CDF re-submission Appendix A.22 a clinical expert and author of Lord et al. 2020 who was consulted with considered the survival outcomes presented within the study to be reflective of outcomes of patients treated with routine surveillance and seen in current UK clinical practice and the study therefore provides an excellent real world routine surveillance comparator.	differences between the populations that would affect the robustness of any naïve comparison between the two. As such, the company's ITT analyses (NOVA and SACT) are very uncertain and do not reflect the final scope of the CDF review.

			The ERG highlighted the uncertainty that the current SACT analysis '*relies heavily on assumptions that simulate a SACT-like routine surveillance arm*". Using the Lord et al. 2020 study as an RWE routine surveillance comparator, removes this uncertainty and provides highly relevant and important evidence, that the Committee should be given the opportunity to consider. Furthermore, the 2L population currently covered by the NICE guidance is in fact a broad ITT population, who can be treated with niraparib irrespective of biomarker. The Lord et al. 2020 study and therefore the pooled ITT population is relevant and central to this re-appraisal.	

<table>
<tr>
<td>Additional issue 3: Scenario analysis</td>
<td>Section 5.1.2.3, page 87</td>
<td>Yes</td>
<td>The company request that the various scenario analyses conducted in the company submission, to assess alternate model settings and structural uncertainty of the base case analysis, be presented to the committee. The scenario analysis tables from the company submission and ERG report, are presented below, using the updated company basecase:

Adapted from Table 10 of company submission. Key scenario analyses – Pooled ITT
<table>
<tr><th></th><th>Basecase</th><th>Scenario</th><th>ICER</th></tr>
<tr><td>Basecase</td><td></td><td></td><td>35,579</td></tr>
<tr><td>1</td><td>Extrapolated trial data from Study 19 for RS OS</td><td>Extrapolated trial data from Lord et al. 2020 for RS OS</td><td>23,147</td></tr>
<tr><td>2</td><td>Extrapolated trial data from Study 19 for RS OS</td><td>1:1 PFS:OS ratio for RS OS</td><td>25,875</td></tr>
<tr><td>3</td><td>Niraparib TTD data sourced from NOVA 2020</td><td>Niraparib TTD data sourced from SACT</td><td>21,782</td></tr>
<tr><td>4</td><td>Extrapolated trial data from Study 19 for RS OS and niraparib TTD data sourced from NOVA 2020</td><td>Extrapolated trial data from Lord et al. 2020 for RS OS and niraparib TTD data from SACT</td><td>14,238</td></tr>
</table>
</td>
<td>This is not new evidence (tables for the gBRCAmut 2L and non-gBRCAmut 2L+ subgroups are presented in the ERG report).</td>
</tr>
</table>

			5	Extrapolated trial data from Study 19 for RS OS and niraparib TTD data from NOVA 2020	1:1 PFS:OS ratio for RS OS and niraparib TTD data from SACT	15,893

The revised base-case for the pooled ITT population uses extrapolated RS OS data from Study 19.

Adapted from Table 11 of company submission and Table 1 ERG report. Key scenario analyses – gBRCAmut 2L subgroup

	Parameter	Base case	Scenario	ICER (£/QALY)
0	**Base case**			22,185
1	Overall survival for RS	21,838	PFS:OS ratio of 1:1	21,838
2	Time to maintenance treatment discontinuation for niraparib	20,769	**B2 ERG clarification question** Niraparib TTD data sourced from SACT - gBRCAmut 2L	20,769
3	-	20,445	Scenario 1 and 2	20,769
4	Progression-free survival	22,205 21,900	PFS extrapolated using the	20,445

			lognormal curve	
5			PFS extrapolated using the normal k=1 flexible curve	22,205
6	Utilities	23,686	**B8 ERG clarification question** Non-treatment specific health state utilities	21,900
7	Niraparib dose	25,663	**B9 ERG clarification question** Planned niraparib dose NOVA 2016	23,686

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention to treat; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; RS, routine surveillance; SACT, Systemic Anti-Cancer Therapy; TTD, time to maintenance treatment discontinuation.

Adapted from Table 12 of company submission and Table 22 ERG report. Key scenario analyses – non-gBRCAmut 2L+ subgroup

	Parameter	**Base case**	**Scenario**	**ICER (£/QALY)**

			0	**Base case**			39,608
			1	Overall survival for RS	36,449	PFS:OS ratio of 1:1	36,449
			2	Time to maintenance treatment discontinuation for niraparib	26,299	**B2 ERG clarification question** Niraparib TTD data sourced from SACT - non-gBRCAmut 2L+	26,299
			3	-	24,204	Scenario 1 and 2	24,204
			4	Utilities	44,716	**B8 ERG clarification question** Non-treatment specific health state utilities	44,716
			5	Niraparib dose	Actual niraparib dose NOVA 2020	**B9 ERG clarification question** Planned niraparib	42,601

						dose NOVA 2016	
			Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention to treat; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; RS, routine surveillance; SACT, Systemic Anti-Cancer Therapy; TTD, time to maintenance treatment discontinuation.				

Additional issue 4: Non-gBCRAmut 2L+ TTD	**Section 4.1.4.3**	**No**	**The company maintain that the log-logistic curve is the most appropriate long-term extrapolation for the non-g*BCRA*mut 2L+ population, and do not accept the ERG's use of the Gompertz curve for this extrapolation.** **The log-logistic curve has the best statistical fit, with a lower AIC and BIC that the Gompertz curve (AIC [redacted] versus [redacted], and BIC [redacted] versus [redacted] for the log-logistic and Gompertz curves respectively).** **The log-logistic is also the more clinically plausible curve; the log-logistic curve estimated [redacted]% of niraparib patients on treatment at 10 years. This aligns with the modelling of SACT non-gBRCAmut 2L+ via the best fitting lognormal distribution whereby [redacted]% of patients are on treatment at 10 years. The Gompertz however overestimates with [redacted]% of patients on treatment at 10 years.** **In summary, the log-logistic curve is the most appropriate long-term extrapolation for non-gBRCAmut 2L+ based on statistical fit and is a conservative curve choice compared with extrapolation of UK real world time on treatment data for this population.**	As outlined in the ERG report, the Gompertz extrapolation captures the tail of the observed KM data from NOVA better that the company's log-logistic extrapolation. However, the ERG reiterates that TTD estimates need to align with PFS estimates, given that the SmPC advises that treatment should be stopped upon progression. As such, the longer TTD estimates, while fitting the observed data better, may help to align with the IRC PFS (but doesn't resolve the issue of disconnected PFS and TTD). Furthermore, comparison of TTD from NOVA and SACT may be inappropriate, as NOVA patients were fitter than SACT patients and so are likely to be on treatment for longer.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

gBCRAmut 2L

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER	ERG response

Issue 2: Extrapolation of PFS - gBRCAmut 2L	**Company curve choice for gBRCAmut 2L PFS curve was lognormal.**	**Updated curve choice for gBRCAmut 2L PFS is hazard k=1 spline.**	**Base-case: £21,838** (+£2,363 impact)	The ERG has been able to verify this result.
Issue 4: OS for routine surveillance	**Mean OS for the routine surveillance arm in the company's base case analysis was estimated using a PFS:OS relationship of 1:1**	**OS based on Study 19 for routine surveillance (lognormal)**	**Base-case: £22,205** (+£2,730 impact)	The ERG has been able to verify this result.
Company's preferred base case following technical engagement	**Base-case incremental QALYs:** [redacted] ([redacted] impact)	**Base-case incremental costs: £41,895** (-£743 impact)	**Base-case: £22,185** (+£2,710 impact)	The ERG has been able to verify this result. As the company has only accepted two of the ERG assumptions and presented no new compelling evidence for the remaining issues, the ERG's base case ICER presented in the ERG report remains unchanged.

Non-gBCRAmut 2L+

Key issue(s) in the ERG report that	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER	ERG response

the change relates to				
Issue 4: OS for routine surveillance	**Mean OS for the routine surveillance arm in the company's base case analysis was estimated using a PFS:OS relationship of 1:1**	**OS based on Study 19 for routine surveillance (lognormal)**	**Base-case: £39,608 (+£3,159 impact)**	The ERG has been able to verify this result.
Company's preferred base case following technical engagement	**Base-case incremental QALYs:** [redacted] [redacted] impact)	**Base-case incremental costs:** [redacted] [redacted] impact)	**Base-case: £39,608 (+£3,159 impact)**	The ERG has been able to verify this result. As the company has only accepted one of the ERG assumptions and presented no new compelling evidence for the remaining issues, the ERG's base case ICER presented in the ERG report remains unchanged.

g*BRCA*mut 2L: SACT analysis

Key issue(s) in the ERG report that	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER	ERG response

the change relates to				
Issue 7: OS extrapolation for SACT	**Company curve choice for g*BRCA*mut 2L OS curve was log-logistic.**	**Updated curve choice for g*BRCA*mut 2L OS is generalised gamma.**	**Scenario analysis: £18,312** (+£382 impact)	The ERG has been able to verify this result.
Company's preferred base case following technical engagement	**Scenario analysis incremental QALYs:** [redacted] [redacted]	**Scenario analysis incremental costs:** [redacted] [redacted]	**Scenario analysis: £18,312** **(+£382 impact)**	The ERG has been able to verify this result. As the company has only accepted one of the ERG assumptions and presented no new compelling evidence for the remaining issues, the ERG's base case ICER presented in the ERG report remains unchanged.

Non-gBCRAmut 2L+: SACT analysis

Key issue(s) in the ERG report that	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER	ERG response

the change relates to				
Issue 7: OS extrapolation for SACT	**Company curve choice for non-g*BRCA*mut 2L+ OS curve was loglogistic.**	**Updated curve choice non-g*BRCA*mut 2L+ OS is Weibull.**	Scenario analysis: £37,986 **(+£2,640 impact)**	The ERG has been able to verify this result.
Company's preferred base case following technical engagement	**Scenario analysis incremental QALYs:** [redacted] [redacted] **impact)**	**Scenario analysis incremental costs:** [redacted] [redacted] **impact)**	**Scenario analysis: £37,986** **(+£2,640 impact)**	The ERG has been able to verify this result. As the company has only accepted one of the ERG assumptions and presented no new compelling evidence for the remaining issues, the ERG's base case ICER presented in the ERG report remains unchanged.

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