NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

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Contents:

The following documents are made available to consultees and commentators:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1.	Professional organisation	NCRI-ACP-RCP-RCR	We strongly support NICE approval of niraparib as a potential treatment option for women with relapsed ovarian/fallopian tube and primary peritoneal cancer irrespective of BRCA status. Our experts have answered the consultation questions as follows: 1. Has all of the relevant evidence been taken into account? 2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? 3. Are the recommendations sound and a suitable basis for guidance to the NHS? 4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? **Response to questions 1, 2 and 3** We do not support the proposed amendment currently under consideration (ID1644). We would like to draw attention to the initial results from the NOVA trial, which clearly demonstrated that niraparib maintenance therapy significantly improved progression free survival (PFS) in all patients with platinum-sensitive relapsed ovarian cancer independent of germline BRCA status (estimated	Thank you for your comments. Clinical data from NOVA, the national systemic anti-cancer therapy (SACT) database in addition to other real world evidence sources were considered carefully by the committee in its decision-making. No changes required.

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			median PFS of 11.3 months for all patients randomized to the niraparib arm and 4.7 months for placebo, HR, 0.42; 95% CI, 0.34–0.53). 1 There was a differential magnitude of benefit based on BRCA status (21 m vs 5.5 m (HR 0.27) in germline BRCAm (gBRCAm) patients compared to 9.3 mo vs 3.9 mo (HR 0.45) in non-gBRCAm patients). Although the NOVA study results demonstrated a more robust benefit for patients carrying a gBRCA mutation, there is evidence that patients without a gBRCA mutation also benefit from therapy with niraparib. This is likely because, although BRCA mutations account for the most common deficit in the HRD pathway, aberrations in other homologous recombination (HR) genes also result in sensitivity to niraparib. Despite the increasing use of homologous recombination deficiency (HRD) testing there remain concerns about the accuracy with which these tests distinguish the specific patients in the non-gBRCAm group who benefit from niraparib compared with those who do not. This guidance if implemented in the NHS will therefore result in women who are not carriers of a BRCAm being denied a potentially effective treatment. The long-term results of NOVA presented in 2020 demonstrated that the benefit of maintenance niraparib extended beyond first progression in both cohorts, HR 0.81 (95% CI 0.632–1.050) in non-gBRCAm patients and HR 0.67 (95% CI 0.479–0.948) in gBRCAm patients. There was no observed difference in OS with niraparib in either cohort, although there was a trend to increased survival in gBRCAm with an improvement in niraparib arm of 9.7 mo. However, it is important to note that NOVA was not powered for overall survival (OS) and the results were confounded by cross-over and missing data: 533 patients enrolled, 28% discontinued	

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			from study and data were not available for 25%. Although cross-over was not permitted in the study, due to the availability of PARPi, 46% gBRCAm and 13% non-gBRCAm patients in the placebo group received subsequent PARPi, which further impacted the OS read out. The long-term safety analysis also confirmed that niraparib was an effective and well-tolerated maintenance treatment for patients with relapsed OC independent of BRCA status. Our experts strongly argue in favour of including niraparib for patients, irrespective of BRCA status as delaying progression and extending time to subsequent chemotherapy is a clinically valuable endpoint in itself for patients (21 m vs 5.5 m (HR 0.27) in gBRCAm patients. 9.3 m vs 3.9 m (HR 0.45) in non-gBRCAm patients). A significant concern is the cumulative toxicity of chemotherapy and the development of platinum resistance as this is associated with low response rates to subsequent chemotherapy and poorer survival. Therefore, increasing the progression free interval with maintenance niraparib has significant merit for patients. The lack of a confirmed OS benefit with niraparib, particularly in the BRCAwt group, should be discussed with patients in relation to the benefits in PFS. However overall, the consensus agreement among international clinical experts is that PARPi should still be offered to patients who have not received a first-line PARPi. **Response to Question 4** We can identify no further that require consideration with respect to unlawful discrimination against any group of people on the	Thank you for your comments. No changes required.

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			grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	
2.	Professional organisation	Ovacome Ovarian Cancer Support Charity	We are concerned that this recommendation limits choice and leads to inequities for patients with relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer who are BRCA negative. Those with a cancer diagnosis are protected under the Equalities Act 2010 and reducing the choice of PARPi technology for relapsed ovarian cancer could have a significant impact on this vulnerable group with incurable disease. Currently the choice of PARPi technology available means that if one drug is unsuitable due to drug interactions or adverse side effects, there is another to try. It is vital that those with incurable disease are given wide access to available technologies and the best opportunity to delay recurrence and further chemotherapy treatments. Seven members of our community who are BRCA negative and being treated with niraparib for a recurrence have explained their experience and concerns regarding the preliminary decision*:* *"In February 2019 I began taking Niraparib 3 tablets a day. In this time my scans have shown less and now no disease and my CA125 is now 12. I am in my third year with no side effects. I am thriving on this drug and hope to continue to do so. I can not believe this lifeline could be removed because I do not have a DNA related additional illness."* *"My oncologist in December (2020) said I would be eligible for niraparib. This was such a relief. The only alternative would have been chemo when the tumours grew again, which I know they would at some point. But niraparib gives me hope to have more*	Thank you for your comments. The committee noted the concerns that the recommendation in the appraisal consultation document (ACD) disadvantages people without a BRCA mutation. The committee noted that the people without a BRCA mutation are not a protected group under the Equalities Act and considered that the recommendation is supported by clinical and cost-effectiveness evidence. No changes required.

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			time to continue to enjoy life. As my oncologist pointed out, more chemo is an option but the gaps between chemo will get shorter and less effective. Niraparib has given me hope. […] I am on my second round of niraparib now and have minimal side effects. […] I dare not think about how long Niraparib will work but it has given me an alternative to just waiting to have more chemo, knowing that eventually chemo will stop working." *"Nov 2019 my scan showed it was back near my liver. More surgery followed by 6 more cycles chemo then Niraparib. Luckily Niraparib appears to be working for me (so far). I feel sad to think this may not be an option for others in the future."* *"In May 2019, I was allowed to commence Niraparib […] Since then I have had 3 monthly CT scans. My Prognostic Indicator, at that time, was classed at Stage B, i.e. Unstable/Advanced disease with prognosis in months! […] I have had no problems at all [since lowering dosage], my CA125 remains stable at 7, and my latest CT scan, in April this year (2021), was clear - even the remaining 'spotting' had disappeared! […] When I was first diagnosed, my husband and I thought we had very little time left together. However, Niraparib has already given us time to move to a smaller, more manageable house and garden, close to our family, and amenities. I feel well and energetic, and prior to Covid 19, we entertained friends and family, and I have been delighted to be able to help out with childcare. We have also had several short breaks and camping holidays. 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. However, I also feel incredibly sad that women like me (& especially those with young families) will no longer qualify to have this treatment, which has the possibility of extending their lives for years."* *"I was diagnosed in March 2016; usual frontline treatment and*	

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			surgery. Recurred in 2017, further surgery and chemo. Commenced on Niraparib in June 2018 and still on it. Usual side effects, insomnia etc. My latest scan in late August (2021) was clear, I am BRCA negative. Do not know my HRD status and do not much care, treatment would be the same I am sure. It is working for me so far and well worth the side effects which do lessen over time." *"I am BRCA negative, without the HRD deficiency and have been on niraparib 200 mg since late April (2021). Doing ok so far on this dose. I have had 2 recurrences to date. I feel well, constipation is my main issue but manageable. I can get out and about - walk 5k each day, appetite ok, a bit of nausea at the start but that has settled. I am grateful to be offered this drug."* *"I feel lucky as I started Niraparib in August (2021), BRCA negative - at least if it does not work for me I know everything possible has been tried."* *A member of our community who is BRCA negative and on chemotherapy for a recurrence explained their concerns about the preliminary decision:* *"This is a kick in the teeth! I'm currently on chemotherapy for recurrence and was told Niraparib would be the best maintenance for me going forward. This was a relief when I heard it. I am BRCA negative, high grade serous stage 4. Yes, I am concerned, worried and annoyed, alongside the usual worries and concerns whilst on chemotherapy treatment. We are all doing everything to stay alive."*	
3.	Professional organisation	Target Ovarian Cancer	The current recommendation does not consider the paucity of treatment options for relapsed ovarian cancer and the importance of progression free survival for those patients. Current standard treatment involves surgery and chemotherapy,	Thank you for your comments. The committee considered all clinical data from NOVA, the national SACT database in addition to other real world evidence sources carefully in its

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			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 restriction of niraparib to the BRCA positive population will have a negative impact on progression free survival for those without a BRCA mutation. We are concerned that this recommendation will lead to inequality for women without a BRCA mutation. The current recommendation means that for 80 per cent of women with ovarian cancer there will be no access to a maintenance PARP inhibitor from the second line of treatment. There are other options from the second line and the first line of treatment, but all of these are available in the Cancer Drugs Fund not routine commissioning. Accessing niraparib from the second line of treatment offers women without a BRCA mutation valuable progression free survival, increasing their quality of life. A period of progression free survival is vital for: • Delaying the next round of chemotherapy, which increases the chances of responding to platinum meaning women can access treatment for longer. • A longer gap between chemotherapy, allowing women to recover and rebuild their strength in preparation for the next round of chemotherapy. • Increasing the quality of life. Niraparib is taken in tablet	decision-making. No changes required. Concerns that the recommendation in the ACD disadvantages people without a BRCA mutation were discussed by the committee. It noted that people without a BRCA mutation are not a protected group under the Equalities Act and the recommendation in the ACD is supported by clinical and cost-effectiveness evidence. No changes required.

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			form at home without the disruption of chemotherapy. For many women, receiving the news that their cancer has returned can be more devastating than the initial ovarian cancer diagnosis. Improvement in progression free survival gives 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. We recently asked women without a BRCA mutation who had taken niraparib from the second line what it meant to them: '*My life is not defined by good weeks and bad weeks and so far my life has not been disrupted by treatment delays. This allows me to plan time with my family which is a vital investment to prepare them for the future when I have a poor long-term prognosis'* *'I am BRCA negative and have been taking Niraparib for 2 years this month, I took it following chemotherapy for a recurrence in 2019. The cancer responded well to the chemotherapy, and I was given it as a maintenance drug, I had a scan in June 2021 and there was no evidence of disease at all, I was thrilled.'* *'I felt like I had a future again, when I was first diagnosed and treated the "watch and wait for it to come back" was soul destroying. That there was a drug suitable for me gave me hope for the future. I am a young lady still working and healthy in every other way. I felt privileged, nothing is ever guaranteed but this drug seemed like my best option, and I have been doing well for two years now.'* *'My cancer came back in Summer 2020, and I completed second line chemo in March 2021, and I am now on month 7 on Niraparib and my recent scans show that while I have residual disease following treatment, that remains stable.'* The recommendation does not seem to consider the rapidly	

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			changing environment around genomic testing. Since April 2021 HRD testing has been made available for women who are newly diagnosed meaning that there may be women who miss out on maintenance access from the first line (currently available on the Cancer Drugs Fund) but will know they are positive for HRD but BRCA negative. This group may well respond very well to PARP inhibitors but under the current recommendation would not be able to access them.	Thank you for your comment. In the original appraisal for niraparib, 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 decided against making a specific recommendation for this group. HRD testing was not considered in the current appraisal. No changes required.
5.	Clinical expert	Professor of Oncology	**Recommendation:** I disagree with the conclusion of restricting to BRCA mutated tumours. This will be elaborated in subsequent sections. The great need for improvement in outcome is acknowledged in the ACD and there is good evidence to support that niraparib extends progression free survival. Furthermore, the overall survival in the non gBRCA cohort – both arms - is far superior to historic good quality trial data before the era of PARP inhibitors. Removing the possibility of PARP maintenance in this population will significantly affect survival of patients in England, there being no prospect of any maintenance therapy with PARP inhibitor or bevacizumab. Details to follow below. **Why committee made these recommendations:** Para 4. 1st sentence is unclear **3.2 Bullet 1:** A highly significant clinical benefit exists in the non-gBRCA group. It is important to remember that all platinum-combination chemotherapy studies in the last 15 years have produced a median PFS beyond the end of chemotherapy of around 5-6	Thank you for your comment. The sentence has been reworded to make the intended meaning clearer in the relevant section. Thank you for your comments. The relevant section reflects the

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			months. This fits in well with the control arm PFS in NOVA. Thus, the PFS almost doubles the median time to progression and the need for further chemotherapy. This is a highly significant result with real clinical benefit and the only option for women in England as bevacizumab in this setting is not available. **Section 3.3:** Whilst there were no differences in the non-gBRCA OS arms (due to deficiencies in FU and placebo cross-over to PARP inhibitors) the median OS results are not less than 31.5 - 36.5 months. It should be noted that OS data in NOVA are taken from the date of randomisation after chemotherapy. Thus, to compare with historical chemotherapy data an additional 6-7 months should be added. The data from clinical trials undertaken before PARP inhibitors were used (and BRCA testing performed) showed a median OS of around 25 months eg the control arm of the GOG218 bevacizumab study (see publication of Rose PG, et al. Obstet Gynecol 2019;133:245–54; DOI:10.1097/AOG.0000000000003086). It should be noted that some of these patients will have received bevacizumab maintenance during relapse therapy, and that the survival graph (see below) of all patients reported in this publication of the GOG 218 series were counted from first relapse. Rose PG, et al. Obstet Gynecol 2019 The NOVA trial included patients who were treated at 2nd or subsequent relapse. 40% of the NOVA population (219/553 patients) were entered into the trial after 3 lines of chemotherapy or greater (≥ 2 relapse). Although the population is selected for patients who responded to platinum, it is known that globally patients survive for increasingly shorter periods with each line of therapy. This can be shown in the follow up data of patients from	progression free survival results from NOVA for people without a BRCA mutation. No changes required. Thank you for your comments. The committee considered randomised evidence from NOVA and Study 19 in its decision-making as well as data from the SACT database. Results from historical data before PARP inhibiters were used in NHS clinical practice was also considered carefully. No changes required.

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			prospectively conducted clinical trials (Hanker et al Ann Oncol 2012; 23: 2605–2612, doi:10.1093/annonc/mds203). This shows the fall-off in survival with second, third, fourth and subsequent relapse. Noting the date of publication, these are patients in the pre-PARP era and clearly show poor survival; medians of 17.6, 11.3, 8.9 months etc after 1st, 2nd 3rd etc relapse (see image below). During the last decade that covers both publications above, there have been no new cytotoxic chemotherapies introduced into the treatment of ovarian cancer. The only two developments have been bevacizumab for recurrence (not available in England) and PARP inhibitors. Hanker et al 2012 Taking account of the 'better group' of patients who respond to platinum, there are data from study 19 where access to PARP inhibitor in the placebo arm was less accessible than a few years later during NOVA follow-up (Olaparib was licensed in 2014). Here in the BRCAwt group median OS is about 25 months (from randomisation). Thus, the overall survival is around 32 months from the start of relapse therapy- again superior to chemotherapy trials. This BRCAwt population is not entirely comparable to the NOVA non-gBRCA group as the Study 19 BRCAwt group excludes patients with a somatic mutation. Nevertheless, the Study 19 data and NOVA data yield survival outcome much larger than has been seen in pre-PARP inhibitor chemotherapy studies Thus, the penultimate sentence in 3.3 needs further consideration. **3.5 The overall trial population in NOVA is not suitable for decision making:** The appraisal committee's conclusions are to separate the BRCA and non-gBRCA groups. Thus, the appraisal committee are diverging from the EMA's licensing position, namely, to include all patients responding to platinum-based therapy. Administering	Thank you for your comment. The observation that the median overall survival in the placebo arm of study 19 is ~25 months was considered in End-of-Life deliberations for people without a BRCA mutation when considering the short life expectancy of less than 24 months criterion. Thank you for your comments. As outlined in section 3.5 of the ACD, clinical trial evidence supports considering the 2 groups separately because prognosis is different for each subgroup. No changes required.

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			niraparib to the overall population improves PFS for all patients who respond to platinum with the greatest effect seen in patients with gBRCA mutations. The data presented at SGO 2021 show publicly available overall survival for both gBRCA and non-gBRCA. In both groups the outcome far exceed survival seen in the pre-PARP era **3.15 Extension to life by more than 3 months with niraparib for people without a BRCA mutation is uncertain** From the above information, there is good evidence that treatment of non gBRCA patients with maintenance niraparib extends survival by more than 3 months compared with chemotherapy studies in the pre-PARP era. An improvement in survival with the corresponding increase in prevalence of the disease (as shown in the original submission) provides good evidence that patients on PARP inhibitors live longer than in the period before these drugs were available. This extension in life is clinically important. It affects a diminishing number of patients within the NHS for the next few years as PARP inhibitors are now being used more commonly in the first line setting. But, for the patients who are not able to access these drugs in first line and who respond to platinum, niraparib offers a major clinical benefit.	Thank you for your comments. The appraisal committee considered data from a variety of different sources to inform its decision-making on End-of-Life. Section 3.14 of the FAD has been updated to reflect the committee's conclusion that niraparib may extend life by more than 3 months for people without a BRCA mutation.
6.	Company	GSK	Results from any analysis to adjust for treatment-switching in the placebo cohort are not meaningful for decision-making due to missingness of survival and subsequent treatment data collected in the NOVA trial. The Committee asked the Company to consider adjusting for the subsequent poly (ADP-ribose) polymerase (PARP) use in the NOVA trial in Section 3.19 of the Appraisal Consultation Document (ACD). Unfortunately, the interpretations of the overall survival (OS) results from NOVA are limited.	

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			The NOVA trial results were presented at the Society of Gynecologic Cancer (SGO) conference 2021 (please note the ACD, Section 3.3, incorrectly states that the data were presented at the American Society of Clinical Oncology) and adjustment was made using inverse probability of censoring weighting (IPCW); however, the results are not considered meaningful or informative for decision-making.1 Unknown subsequent treatment status and incomplete survival follow-up impacted the interpretability of the results for OS in the trial population due to the observed missingness in the trial data. The abstract presented at the SGO was shared in response to the Evidence Review Group's (ERG's) clarification questions and is provided again for ease of reference in Appendix 1.	Thank you for your comment. Section 3.3 of the final appraisal document (FAD) has been updated to amend for the correct name of the conference.
			Discontinuation from the trial was greater than 80% in both the niraparib and placebo arms of the gBRCAmut 2L+ and non-gBRCAmut 2L+ cohorts. Discontinuations for reasons other than death were notable (155/553, 28%), with early withdrawals limiting: a) retrieval of survival status and b) collection of subsequent therapy data. The extent of the missingness prevents robust analysis being conducted to adjust for the crossover of patients treated with placebo to subsequent PARP inhibitor (PARPi) therapy. a) Retrieval of survival status: per the NOVA study protocol, investigators were required to discontinue patients from the study if requesting unblinding.2 This premature study discontinuation limited the collection of long-term follow-up data such as post-progression therapy and survival status. Since loss of follow-up data could compromise the OS analysis, the study protocol was amended to address this limitation by allowing data entry of last known survival update or death, based on public records. By the final data cut-off (DCO), survival status was not able to be determined for 49% of patients that had discontinued from the trial (76/155), representing:	Thank you for your comments. Section 3.3 of the FAD has been updated to reflect the conclusion that adjusting for cross-over to subsequent treatments is inconclusive and does not resolve the uncertainty in the survival benefit with niraparib for people without a BRCA mutation.

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			• gBRCAmut 2L+ cohort: 14% (19/138) from the niraparib arm; 14% (9/65) from the placebo arm • non-gBRCAmut 2L+ cohort: 14% (33/234) from the niraparib arm; 13% (15/116) from the placebo arm b) Subsequent therapies: while crossover to PARPis was not permitted, receipt of subsequent PARPi could occur post-disease progression or withdrawal from the trial according to the oncologist's clinical judgement. Due to study discontinuation, subsequent PARPi information was incomplete for 25% (138/553) of patients from NOVA. In the gBRCAmut 2L+ cohort, extensive cross-over of placebo arm patients to PARPi was observed (46%) and may exceed more than half of patients, given the extent of missingness of data (31%). This was indicative of evolving clinical practice at the time of NOVA, with the registration of PARPis in the second-line setting since December 2014,3–6 and the inability to restrict placebo patients from discontinuing from NOVA post-progression to seek appropriate medical management. The Company would also like to highlight that the use of the Study 19 placebo OS data as the base case comparator arm, in the place of the NOVA OS placebo data, was considered suitable and sufficient for decision making in the gBRCAmut 2L population. Study 19 placebo OS data was also the ERG preference as the base case comparator arm, in place of NOVA placebo OS data which has a high level of uncertainty; the ERG report states (page 65) that "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...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	

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			comparison is maintained in the model."7 The Company ask the Committee to consider the matching-adjusted indirect comparison (MAIC)-adjusted OS results (see Comment 2 below) to reduce uncertainty given the limitations in the interpretability of a treatment-switching adjustment.	
7.	Company	GSK	A MAIC was conducted to adjust for differences in baseline characteristics between patients enrolled in the NOVA and Study 19 clinical trials, in response to the Committee's request in Sections 3.4, 3.10 and 3.19 of the ACD, which forms the basis of the updated Company base case. An anchored MAIC was recently performed where the placebo arm in each trial served as the 'linked network'. Once the baseline characteristics were balanced between NOVA and Study 19 via the MAIC, the adjusted NOVA data (i.e. NOVA using the weights generated from the MAIC) was compared to Study 19 using weighted statistical analyses. The method and rationale for the MAIC analysis are provided in Appendix 2. In response to the Committee's request in Section 3.4, 3.10 and 3.19 of the ACD, the economic model has been updated to include the MAIC-adjusted niraparib OS coefficients for the non-g*BRCA*mut 2L+ population.[1] The lognormal curve was considered to provide the best clinical and statistical fit; the parametric curve	Thank you for your comments. Section 3.4 has been updated to include the results of the MAIC and the committee's preference for using the MAIC analysis to estimate the relative effectiveness of niraparib compared with routine surveillance.

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			selection methods and revised Company base case results are provided in Appendix 3. Using the MAIC-adjusted niraparib OS data and the lognormal distribution compared with the placebo arm observed from Study 19 and the lognormal distribution, the incremental cost-effectiveness ratio (ICER) reduces from £39,608 per quality-adjusted life year (QALY) gained in the previous Company base case to £37,273 per QALY gained for the non-g*BRCA*mut 2L+ population. This analysis forms the basis of the updated Company base case. Niraparib OS in the non-g*BRCA*mut 2L+ cohort, using the MAIC-adjusted OS data, at 5, 10, 15 and 20 years is estimated to be [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively. This compares closely to OS of [redacted]%, [redacted]%, [redacted]%, [redacted]% at 5, 10, 15 and 20-years when unadjusted niraparib OS data is used to estimate OS using the lognormal curve. As outlined in Appendix 2, close assessment of the reported patients' baseline characteristics in NOVA and Study 19 revealed that the differences between the patient populations are minimal, and that "*the cohorts from the two trials are generally comparable*", as stated in the ERG report. [7] This is reflected in the similarities of the Kaplan Meier curves between the MAIC-adjusted and unadjusted niraparib OS in Figure 4 of Appendix 2. The Company asks the Committee to accept the MAIC-adjusted	

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			results as the updated Company base case and the refreshed ICER of £37,273 per QALY gained for the non-g*BRCA*mut 2L+ population.	
8.	Company	GSK	<u>The comparative effectiveness of niraparib is demonstrated via a range of scenarios to reduce the Committee's uncertainty of their assessment of niraparib OS benefit.</u> UK-based real-world evidence (RWE) from Systemic Anti-Cancer therapy (SACT) and Lord et al. (2020) were explored; results derived from OS data from these sources were presented in response to clarification question B3 from the ERG. A scenario analysis using niraparib OS and time to treatment discontinuation (TTD) data from SACT non-g*BRCA*mut 2L+ cohort, and estimating routine surveillance (RS) PFS from the NOVA hazard ratio (HR) and OS using a PFS:OS 1:1 ratio, generated an ICER of £37,986 per QALY gained; this scenario was provided as part of the technical engagement response following changes made, as requested by the ERG. Using the ERG's SACT base case settings, updated to include the use of treatment-specific utilities (see Comment 4), generates an ICER of £41,238 per QALY gained. The use of RS OS data for a mixed/unknown breast cancer susceptibility gene (*BRCA)* status cohort from Lord et al. (2020) compared with niraparib SACT intention-to-treat (ITT) OS data, as an alternative scenario analysis, generates an ICER of £21,976 per QALY gained, as presented in response to question B3 of the ERG's clarification questions.[8] The Company notes the limitations inherent when using single-arm trial data and provides these results to reduce uncertainty by	Thank you for your comments. The committee considered the results of the scenario analyses and the corresponding critique by the ERG in its decision-making. No changes required.

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			demonstrating that the ICERs, using a variety of sources, are within a similar range or less than the Company's revised base case.	
9.	Company	GSK	<u>A PFS:OS relationship of 1:1 is conservative and is viewed as the minimum OS benefit obtained with niraparib compared to RS</u> The Committee ask the Company to consider modelling niraparib OS assuming no OS benefit compared to RS (ACD, Section 3.19).[1] The assumption of no survival gain after progression-free survival (PFS) gain is not clinically plausible. From a clinical perspective, by increasing PFS, patients have a higher chance of consideration for retreatment with more effective platinum-based therapies in the next treatment line.[9] This has been observed in clinical trials of maintenance therapy in advanced relapsed ovarian cancer which found that prolongation of PFS led to increased platinum retreatment and increased OS.[10–12] Following analysis of the Study 19 *BRCA* wild type (*BRCA*wt) population, a mean incremental PFS:OS ratio of 1:1.5 was observed based on the restricted mean PFS and OS estimates (olaparib PFS: 8.0 months, placebo PFS 5.6 months, incremental PFS benefit 2.4 months; olaparib OS 37.6 months, placebo OS 34.1 months, incremental OS benefit 3.6 months);[13] this provides further evidence to support the assertion that patients without a g*BRCA* mutation treated with a PARPi are expected to achieve *at least* the same OS compared	Thank you for your comments. Section 3.10 of the FAD has been updated to reflect that a 1:1 progression free survival to overall survival ratio is the likely minimum survival benefit with niraparib compared to routine surveillance. The committee accepted that estimating overall survival for people without a BRCA mutation using data from Study 19 for routine surveillance which results in a survival benefit for people without a BRCA mutation is reasonable.

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			to patients treated with RS. Based on the Study 19 ITT population, a ratio of at least 1:2 was observed in terms of mean PFS to mean OS benefit with olaparib; this could be as high as 1:3 depending on the extrapolation technique.[14] Therefore, we maintain that a 1:1: PFS:OS relationship is conservative and is still an appropriate scenario analysis for consideration by the Committee and any relationship lower than this is not clinically relevant. In addition, this scenario analysis is aligned with the ERG's assumption as stated in the TA528 Final Appraisal Determination (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)*."[15] This was subsequently accepted by the Committee as stated in the TA528 FAD and also reported in the Terms of Engagement, "*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*."[15,16]	
10.	Company	GSK	Treatment-specific utilities provide the most accurate representation of the quality-of-life impact observed in patients treated with niraparib or RS.	Thank you for your comments. Section 3.12 of the FAD has been updated to reflect the committee's acceptance that treatment specific utility values are appropriate for decision-making.

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			The Company welcomes the Committee's acceptance of considering treatment-specific utility values in the economic model (ACD, Section 3.11).[1] As requested and shared immediately prior to the Appraisal Committee Meeting, the results of a linear mixed-effects regression analysis, conducted to assess the statistical difference in the mean utility score of patients in each treatment arm (niraparib and placebo) and health state (progression-free disease and progressed disease) is provided again for ease of reference in Appendix 4. The results provide statistical evidence to support the use of treatment-specific utility values for each health state; the statistical difference between treatment arms is maintained after controlling for health state. In addition, as stated in the ACD, the clinical expert and Cancer Drugs Fund clinical lead noted that utilities may improve on niraparib as it may improve clinical response for people with partial response to prior platinum based chemotherapy.[1]	
11.	Company	GSK	<u>TTD is most appropriately modelled using the log-logistic curve for the non-g*BRCA*mut 2L+ population.</u> The Company maintain that the log-logistic curve is the most appropriate long-term extrapolation for TTD for the non-g*BRCA*mut 2L+ population, and do not accept the ERG's use of	Thank you for your comments. Section 3.11 has been added to the FAD to reflect the committee's conclusion that the extrapolation of time to treatment discontinuation (TTD) is not critical to decision making and modelling TTD using the log-logistic curve for people without a BRCA mutation is reasonable

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			the Gompertz curve for this extrapolation. The log-logistic curve has the best statistical fit, with a lower AIC and BIC than the Gompertz curve (AIC [redacted] versus [redacted], and BIC [redacted] versus [redacted] for the log-logistic and Gompertz curves, respectively) with a meaningful difference of over 3 points.[17] 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-g*BRCA*mut 2L+ via the best fitting lognormal distribution whereby [redacted]% of patients are on treatment at 10 years. The Gompertz curve, however, overestimates the proportion of patients still on treatment with [redacted]% of patients on treatment at 10 years. The Company ask the Committee to accept the log-logistic curve as the most appropriate long-term extrapolation for non-g*BRCA*mut 2L+ TTD based on statistical fit, and that it is a sufficiently conservative curve choice compared with extrapolation of UK real world time on treatment data for this population. Further to this point, the Company ask the Committee to consider the scenario for the non-g*BRCA*mut 2L+ population using the SACT time on treatment, as this represents the actual time on treatment observed from RWE for non-g*BRCA*mut 2L+ patients	

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			treated in the UK while niraparib was available to patients via the CDF. This alternative scenario analysis, generates an ICER of £25,969 per QALY gained; £11,304 less than the refreshed base case ICER of £37,273.	
12.	Company	GSK	Investigator assessed (IA) PFS has been included as a scenario analysis to reduce uncertainty in the independent review committee (IRC) PFS cost-effectiveness estimates from the economic model, as requested by the Committee in Sections 3.2 and 3.19 of the ACD.[1] The Company base case uses IRC assessed PFS collected from the NOVA trial (DCO 2016); this was the primary endpoint of the NOVA trial and was met at the DCO June 2016, therefore no additional data was collected. In response to the Committee's request in Section 3.2 of the ACD, the economic model has been updated to include the IA PFS coefficients following independent parametric analysis for the non-g*BRCA*mut 2L+ population (DCO October 2020).[1] The Committee concluded that *"because hazards were similar regardless of who assessed [PFS], the method of assessment was unlikely to be critical to decision making"*.[1] The Committee notes that *"the clinical expert and Cancer Drugs Fund clinical lead cautioned focusing only on the median results and*	Thank you for your comments. Section 3.2 of the FAD has been updated to show that investigator assessed results were not substantially different from results assessed by independent review committee. The section now reflects that niraparib improves progression-free survival compared with placebo regardless of how it is assessed.

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			explained that the hazard ratios of both IA and IRC assessed progression-free survival were similar".[1] The Company maintain that IRC PFS is most appropriate to use within the economic modelling. As discussed as part of the technical engagement, there are 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 in NOVA as a sensitivity analysis to ensure robustness of the PFS 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. 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. The log-logistic and generalised gamma curves were considered	

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			the most appropriate parametric curves to model IA PFS; the full methodology and parametric curve selection is described in Appendix 5. The log-logistic IA PFS curve is more conservative in its estimates of niraparib patients who are progression free at 5-years ([redacted]%) compared to the generalised gamma estimates ([redacted]%) and the ERGs preferred hazards k=1 curve ([redacted]%) for IRC PFS. The longer term, 20-year estimates of the log-logistic IA PFS curve ([redacted]%) are closer to the ERG's preferred hazards k=1 IRC PFS curve ([redacted]%) compared to the generalised gamma IA PFS curve ([redacted]%). Therefore, the log-logistic curve has a more conservative 20-year estimate ([redacted]%) compared to the generalised gamma ([redacted]%) and is in line with the ERG's preferred IRC PFS base case. The mean time in the progression-free (PF) state for the non-g*BRCA*mut 2L+ population using IA PFS (DCO 2020) extrapolated using the log-logistic distribution is [redacted] years and [redacted] years for niraparib and RS, respectively (or [redacted] years and [redacted] years for niraparib and RS, respectively, after discounting is applied). The mean time in the PF state for the non-g*BRCA*mut 2L+ population using IA PFS (DCO 2020) extrapolated using the generalised gamma distribution is [redacted] years and [redacted] years for niraparib and RS, respectively (or [redacted] years and [redacted] years for niraparib and RS,	

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			respectively after discounting is applied). This compares to the mean time in PF state of [redacted] years and [redacted] years for niraparib and RS, respectively (or [redacted] and [redacted] years for niraparib and RS after discounting is applied) when IRC PFS (DCO 2016) is used. A scenario analysis using extrapolated IA PFS data, using the log-logistic curve (NOVA niraparib and placebo IA PFS), and extrapolated OS trial data (NOVA MAIC-adjusted niraparib OS and Study 19 placebo OS) of niraparib versus routine surveillance for non-g*BRCA*mut 2L+, generates an ICER of £34,777 per QALY gained; this is less than the updated Company base case ICER of £37,273 per QALY gained using IRC PFS (presented in Comment 2). A similar scenario analysis, using extrapolated IA PFS data using the generalised gamma curve, generates an ICER of £37,169 per QALY gained; this is in line with the updated Company base case ICER of £37,273 per QALY gained using IRC PFS (presented in Comment 2). The mid-point of these two ICERs is £35,973; this mid-point ICER provides insight into the cost-effectiveness we may expect to achieve when estimating the true IA PFS curve, which is expected to lie somewhere between the conservative (log-logistic) and optimistic (generalised gamma) IA PFS curves. The Company believe that the scenario analyses presented using IA PFS, which demonstrate equal or improved cost effectiveness compared with the Company base case, reduce	

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			the Committee's uncertainty in the assessment method of progression and, as such, reduce uncertainly in the PFS extrapolations that form the Company base case. The Company maintain that IRC PFS is the most appropriate endpoint to model PFS. IRC PFS was the primary endpoint of the NOVA trial and aligns with the health-state utilities values, captured per IRC-defined progression status, applied in the economic model. The ICERs generated using IRC PFS data and IA PFS data are similar and thereby reduce uncertainty in the method of assessment of progression.	
13.	Company	GSK	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** <u>Using the Lord et al. (2020) study as a real world evidence (RWE) routine surveillance comparator provides highly relevant and important evidence for the Committee's consideration.</u> The Company would like to outline two points within the Lord et. al (2020) evidence, which have been interpreted incorrectly within the context of the ACD document and this appraisal: • Section 3.5 of the ACD states "*This study included patients who had completed at least 2 lines of platinum-based*	Thank you for highlighting these misinterpretations. We have removed the associated text from section 3.5 of the FAD.

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			chemotherapy with evidence of an objective disease response (complete or partial response), similar to people enrolled in NOVA." and that *"the median number of previous lines of therapy in Lord et al. 2020 was 3".*[1] The Company would like to clarify that the index date (from which OS was calculated) for all patients was the date when patients finished their second course of platinum-based chemotherapy (PBC).[18] Patients were excluded from the study if they had received more than two courses of PBC. The 3 median lines of chemotherapy, quoted in the ACD, describes the total number of lines of chemotherapy received by patients in the Lord et al. (2020) study, including their first two lines of PBC and all subsequent lines of chemotherapy received during study follow up.[1] Niraparib patients in the NOVA trial and the SACT cohort were also eligible to receive subsequent chemotherapy. From the SACT analysis, [redacted]% of g*BRCA*mut 2L and [redacted]% of non-g*BRCA*mut 2L+ patients treated with niraparib had received subsequent chemotherapies. Most importantly, the index date from which overall survival is measured, post exactly two lines of prior PBC, is comparable across Lord et al. (2020), NOVA and the niraparib SACT cohort. • Section 3.5 of the ACD also states *"Including people with a*	

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			BRCA mutation who had 3 or more courses of chemotherapy (a population outside the scope of this appraisal) in the routine surveillance arm could overestimate the efficacy of niraparib".[1] The patient population in the Lord et al. (2020) study is not expected to have a poorer prognosis than those in the non-g*BRCA*mut 2L+ population. In fact, given the inclusion of an unknown proportion of patients with a *BRCA* mutation and the exclusion of patients who had received more than two courses of PBC, the patients in the Lord et al. (2020) study are expected to have a better prognosis compared to patients in the NOVA or SACT non-g*BRCA*mut 2L+ population, some of whom will have had more than two lines of PBC. The NOVA niraparib ITT population and SACT niraparib ITT population include non-g*BRCA*mut 2L+ patients who have received 3 prior courses of chemotherapy, therefore, can capture more heavily pre-treated patients. The Company would like to reassert the value of presenting the SACT niraparib OS data compared with Lord et al. (2020) RS OS data in a like for like RWE comparative analysis. 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	Thank you for your comments. The analysis comparing SACT niraparib overall survival data with the overall survival of the routine surveillance arm from Lord et al. (2020) and its corresponding ICER was considered by

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			the survival outcomes presented within the study to be reflective of outcomes of patients treated with RS and seen in current UK clinical practice. The pooled SACT niraparib cohort (g*BRCA*mut 2L and non-g*BRCA*mut 2L+) and the Lord et al. (2020) cohort are both broadly reflective of the patients expected to be treated with niraparib in the relapsed setting in UK clinical practice; this provides a valid real-world scenario as requested in clarification question B3 and B6. As outlined in Comment 1, the use of RS OS data from Lord et al. (2020) compared with niraparib SACT ITT OS data, as an alternative scenario analysis, generates an ICER of £21,976 per QALY gained.	the committee in its deliberations.
14.	Company	GSK	<u>Niraparib dose in the economic model should reflect actual dose</u> The NOVA actual dose data, as correctly outlined in the ACD Section 3.12, is updated dose data from the latest NOVA data-cut.[1] The Company believe that the actual dose data aligns with how niraparib is currently used within NHS practice. The Company agree with the Committee, as stated in the Section 3.12 of the ACD, *"that prescribed niraparib doses are unlikely to be returned to the NHS and reused",* however, the Company understand that the unused dose can be retained by patients and utilised during subsequent treatment cycles. As noted in the ACD in Section 3.13, niraparib is available only in 100mg capsules to allow for simple	Thank you for your comments. Section 3.13 of the FAD has been amended to reflect the committee's acceptance that the 300 mg dose of niraparib may be lower in NHS clinical practice and that actual dose data for niraparib from NOVA is appropriate to use in the economic model.

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			dose adjustments and so that unused capsules can be used in subsequent cycles with minimal wastage.[1] The utilisation of this unused dose aligns with NHS clinical practice and the Commissioning for Quality and Innovation (CQUIN) medicines optimisation standard, where pharmacists and prescribers will discuss medicines supply with patients before issuing an entirely new supply of medicine.[19] The ACD in Section 3.12 states that '*In its original appraisal, the committee preferred to use the prescribed dose as a weighted average'*.[1] The Company would like to clarify that the prescribed dose as a weighted average was the most complete and only dosing information from NOVA available at the time of the original appraisal, and the only dosing data from NOVA submitted by the Company for consideration. Therefore, it is not correct to say the prescribed dose was "*preferred"* as it was the only dosing data available for consideration at that time, and we ask that the Committee amend this statement. The Company would like to clarify that the niraparib dose used in economic model does reflect the dose of niraparib in NOVA. All patients within NOVA were required to start treatment on 300 mg of niraparib, and this starting dose is captured within the weighted average cycle one dose, used in the economic model. This 300	

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			mg starting dose is captured in both the prescribed dose and actual dose data. The NOVA dose data (prescribed or actual) provides the weighted average dose per cycle; the actual dose per cycle incorporates any dose reduction which occurred during that cycle and the prescribed dose assumes no dose reduction mid-cycle. The NOVA dose per cycle therefore aligns exactly with the benefits (survival outcomes) experienced by patients in the NOVA trial. The niraparib Summary of Product Characteristics (SmPC) states that a starting dose of 200 mg for patients weighing less than 58 kg or with hepatic impairment may be considered.[20] Therefore, a proportion of patients may receive a starting dose of 200mg, and the starting dose of 300mg in the economic model for all patients is conservative. The Company ask that it is clarified within the ACD in Section 3.13, that the current economic model provided for decision making does reflect the starting dose of niraparib in NOVA, which aligns with the survival outcomes in NOVA. *"Dose used in the model should reflect the dose of niraparib in the summary of product characteristic (SmPC) and NOVA* ***as per the provided dosing data****"* *"The committee noted that the company produces 100 mg*	

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			capsules to account for this change in clinical practice but also noted that the benefits accrued from niraparib should align with the treatment costs from NOVA, ***as per the current economic model****. It concluded that the dose used in economic model should reflect the dose of niraparib in the SmPC and NOVA* ***as per the provided dosing data****."*	
15.	Company	GSK	<u>Clarification of *BRCA* mutation status terminology</u> The Company ask that consistent terminology is used throughout the ACD and future documentation when referring to *BRCA* mutation status. In Section 1 of the ACD the populations are outlined as *'patients with a BRCA mutation*' and *'patients without a BRCA mutation'*.[1] For consistency and ease of comprehension, the Company requests that the terminologies stated in Section 1 of the ACD should be used throughout the document. The following sections of the ACD currently use inconsistent terminology: • Section 3.2 (referring to the *"mutation-negative group"* and *"mutation-positive group*") • Section 3.5 (referring to *"BRCA-positive and negative subgroups*")	Thank you for highlighting these inconsistencies. The editorial changes requested for referring to people with and without a BRCA mutation consistently throughout the document has been made in all sections of the FAD. All inconsistent terminology has been amended or removed.

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			• Section 3.6 (referring to "*BRCA mutation positive and BRCA mutation negative subgroups"* • Section 3.10 (referring to *"BRCA negative group")*[1] The Company ask that it is made clear throughout the document that the niraparib data used within the economic model are based on the CDF recommendation specific subgroups; i.e. patients with a germline *BRCA* mutation whose disease has responded to 2 courses of platinum-based chemotherapy and patients without a germline *BRCA* mutation whose disease has responded to 2 or more courses of platinum-based chemotherapy, rather than the marketing authorisation population. Germline *BRCA* should be referred to as "g*BRCA"* throughout. • Section 3.6 (please include *"Data from SACT was collected as per CDF recommendation specific subgroups; i.e. patients with a gBRCA mutation whose disease has responded to 2 courses of platinum-based chemotherapy and patients without a gBRCA mutation whose disease has responded to 2 or more courses of platinum-based chemotherapy")* • Section 3.8 (please add "*The company's approach to*	Thank you for your comments. The editorial changes requested have been made to sections 3.6, 3.8 and 3.16.

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			*modelling survival is suitable for people with a gBRCA mutation **whose disease has responded to 2 courses of platinum-based chemotherapy**")* • Section 3.16 (please add *"The estimates for people with a gBRCA mutation **whose disease has responded to 2 courses of platinum-based chemotherapy** are within the range considered a cost-effective use of NHS resources")*[1]	
16.	Company	GSK	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Additional UK-based RWE has been published providing OS data of patients treated with niraparib and RS in UK clinical practice which provide further confidence on the life expectancy of patients in the non-g*BRCA*mut 2L+ population when assessing the end-of-life-criteria in this population. The Committee considered in Section 3.14 of the ACD that the study by Lord et al. (2020), providing published UK-based RWE, *"included patients with a BRCA mutation who had 3 or more courses of chemotherapy and were likely to have a poorer prognosis than people in earlier stages of treatment."*[1] The Company would like to clarify that the index date (from which OS was calculated) for all patients was the date when patients finished	Thank you for your comment. The committee noted that patient population in the Lord et al. (2020) study is not expected to have a poorer prognosis than those in the non-g*BRCA*mut 2L+ population. The text from section 3.14 of the ACD has been removed from the FAD.

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			their second course of PBC.[18] Patients were excluded from the study if they had received more than two courses of PBC and therefore the patient population in the Lord et al. (2020) study is not expected to have a poorer prognosis than those in the non-g*BRCA*mut 2L+ population. The Lord et al. (2020) data captured survival outcomes for 233 patients, across 13 UK hospitals, with a median follow up of 23.8 months.[18] The study author 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 a highly clinically relevant real world routine surveillance comparator. The median overall survival in the study was 19.3 months (95% CI ± 2.4) for the all-comers population; therefore it is highly likely that a cohort of non-g*BRCA*mut 2L+ patients who had received two or more lines of PBC would have lower OS than 19.3 months. Observed data from SACT provide a median life expectancy for patients treated with niraparib of [redacted] months (95% CI [redacted]) in the non-gBRCAmut 2L+ cohort; it is expected that patients treated with RS would have a lower life expectancy.[21] Use of RWE to inform the Committee's decision-making is aligned	Thank you for your comments. Data from all sources such as the SACT database, Lord et al., Study 19 and economic model outputs were carefully considered by the committee and used to inform its deliberations around whether niraparib met the criteria to be considered an end-of-life therapy for people without a BRCA mutation.

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			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 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*".[22] A life extension of three months for patients treated with niraparib is demonstrated through comparative analyses. [redacted] years (revised base case MAIC-adjusted NOVA 2020 niraparib OS data and Study 19 placebo), [redacted] years (NOVA 2020 niraparib OS data and Study 19 placebo), [redacted] years (1:1 PFS:OS), [redacted] years (SACT scenario), 1.11 years (Lord et al. (2020) scenario). The Company ask the Committee to revisit the evidence supporting the use of niraparib as an end-of-life therapy for the non-g*BRCA*mut 2L+ population.	Thank you for your comments. Undiscounted life years were used to inform the committee discussion of extension to life with niraparib for people without a BRCA mutation,
17.	Company	GSK	<u>There is a high unmet need for effective oral maintenance treatments, particularly for patients who do not possess a *BRCA* mutation for whom treatment options are extremely limited.</u>	Thank you for your comments. The unmet need in people without a BRCA mutation and lack of oral maintenance treatment options available via routine commissioning if disease relapses for this group was acknowledged by committee and considered in its

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			Ovarian cancer (OC) is responsible for one woman's death every three hours in England.[23,24] Around 70% of OC 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.[25,26] Approximately 80% of patients with OC do not have a g*BRCA* mutation.[27] Data from the NOVA trial and RWE indicate that patients without a g*BRCA* mutation have the potential to respond well to PARPi maintenance treatment, and can experience sustained benefit as long- term responders. Therefore, the prospect of having no oral maintenance treatment options once their disease relapses, if the provisional recommendations are enacted, will result in a high unmet need, as well as inequality in access across the UK. [27] The Committee notes in Section 3.1 of the ACD that only olaparib is available via routine commissioning and later in the treatment pathway; restricted to patients with a *BRCA* mutation who have received three or more courses of PBC.[1] The Company ask the Committee to note that the majority of patients with advanced OC do not possess a *BRCA* mutation (80%) and therefore currently have no oral maintenance treatment options available via routine commissioning in the relapsed setting.[27] This specific unmet need	decision-making. It was agreed that there is an urgent need for a treatment option that is be a cost-effective use of NHS resources.

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			for patients without a *BRCA* mutation was highlighted in the patient access group response to technical engagement as key messages "*There are currently no maintenance treatments available in routine commissioning for women who do not have a BRCA mutation.", "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."* As concluded by the Committee, there is a high unmet need for an oral maintenance treatment for all patients with OC, particularly patients who do not possess a *BRCA* mutation. The number of patients eligible for treatment with niraparib in the relapsed setting is likely to decrease over the coming years, as a greater proportion of patients receive PARPi treatment in the first-line setting. However, there will remain a small but important group of patients who do not receive a PARPi in the first-line setting, receiving therapy with another mechanism of action or routine surveillance, for whom niraparib will remain a critical treatment option. The Company ask the Committee to consider the unmet need for the majority of patients (80%) with OC, who do not possess a	

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			g*BRCA* mutation, when considering a recommendation for niraparib treatment in this group of patients.	
18.	Web comment	British Gynaecological Cancer Society	***Has all of the relevant evidence been taken into account?*** The evidence taken into account acknowledges that there is a substantial PFS benefit and that there is an uncertainty if there is an overall survival benefit. The current clinical practice has changed and most women get Niraparib or another PARP inhibitor in the first line setting . There is an increasingly small proportion of women who were not offered PARP inhibitor in the first line setting and the current approach will significantly disadvantage this group of women. Within the next few years the need for second line Niraparib in BRCA negative patients will become substantially smaller and in view of that the CDF funding should continue to support women who have not had the opportunity to take a PARP inhibitor in the first line setting. ***Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?*** Yes ***Are the recommendations sound and a suitable basis for guidance to the NHS?*** As explained above , the recommendation to stop Niraparib for BRCA negative women in view of an immature data and considering the fact that the number of women who need it will gradually decrease (as they will receive niraparib in the first line setting) does not form a suitable basis for guidance to the NHS and significantly disadvantages women with BRCA negative ovarian cancer. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation,**	Thank you for your comments. Clinical experts at the appraisal meeting highlighted the potential increase of PARP inhibitors in 1st line setting and noted that as PARP inhibitors won't be used more than once in the treatment pathway, the number of people who would have treatment in a relapsed disease setting may be smaller in future clinical practice (see section 3.1) Thank you for your comments. The recommendation for niraparib in people without a BRCA mutation is based on both clinical and cost-effectiveness evidence.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			age, gender reassignment, pregnancy and maternity? No	
19.	Web comment	British Gynaecological Cancer Society	While I am content that funding for platinum-sensitive, relapsed disease is to be continued in those with a BRCA mutation after a response to the 2nd course of platinum-based chemotherapy it should be noted that the majority of otherwise eligible patients in this category may now have received a PARP inhibitor as maintenance in the 1st line setting and PARP inhibitor re-challenge is not permitted so this group is very much smaller than when first reviewed.	Thank you for your comments. Clinical experts at the appraisal meeting highlighted the potential increase of PARP inhibitors in 1st line setting and noted that as PARP inhibitors won't be used more than once in the treatment pathway, the number of people who would have treatment in a relapsed disease setting may be smaller in future clinical practice (see section 3.1)
			I am very concerned that, despite the fact the committee concluded that there was a serious ""unmet need for maintenance treatment especially in those WITHOUT a BRCA mutation"", these new recommendations mean that this group would be seriously disadvantaged. They comprise about 75% of the ovarian cancer cases in the UK and are the group that are less likely to have been given a PARP inhibitor first line. There is currently a clinical trial (MONITOR-UK) recruiting ""real world"" patients in the UK receiving maintenance Niraparib following response to platinum-based chemotherapy including in the 2nd line setting and regardless of BRCA mutation status which will provide valuable data within the next few years and I would urge the committee to continue funding in the otherwise very-disadvantaged non-BRCA cohort. ***Has all of the relevant evidence been taken into account?*** All current evidence has been reviewed. ***Are the summaries of clinical and cost effectiveness***	The unmet need in people without a BRCA mutation and lack of oral maintenance treatment options available via routine commissioning if disease relapses for this group was acknowledged by committee and considered in its decision-making. It was agreed that there is an urgent need for a treatment option that is be a cost-effective use of NHS resources.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			reasonable interpretations of the evidence? I am not satisfied that the clinical effectiveness and benefit interpretations are reasonable. ***Are the recommendations sound and a suitable basis for guidance to the NHS?*** The recommendations are sound in the small minority of patients with a BRCA mutation (approximately 25%) but will significantly disadvantage those without a BRCA mutation who already have a poorer prognosis and less benefit from standard cytotoxic therapies. ***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?*** Not specifically however the prevalence of germline BRCA mutations is much higher in some ethnic/ religious groups than in others.	Thank you for your comments. No changes required.
20.	Web comment	Medicines and Prescribing Team, NICE	For clarification, it would be helpful if the dose was put in the context of the overall dosage i.e. this is taken daily. Suggest changing text to... ""The prescribed dosage used in NOVA as specified in the SmPC for niraparib is 300 mg daily. The clinical expert explained that some clinicians favour starting treatment with a lower dosage of 200 mg daily of niraparib in clinical practice."" I presume that is what is meant as the licensed dose is daily (see SPC)?	Thank you for your comment. Section 3.13 has been updated to include the word “daily” when referring to the dose used in the economic model.

NICE National Institute for Health and Care Excellence

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

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	GSK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

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Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Has all of the relevant evidence been taken into account?
1	Results from any analysis to adjust for treatment-switching in the placebo cohort are not meaningful for decision-making due to missingness of survival and subsequent treatment data collected in the NOVA trial. The Committee asked the Company to consider adjusting for the subsequent poly (ADP-ribose) polymerase (PARP) use in the NOVA trial in Section 3.19 of the Appraisal Consultation Document (ACD). Unfortunately, the interpretations of the overall survival (OS) results from NOVA are limited. The NOVA trial results were presented at the Society of Gynecologic Cancer (SGO) conference 2021 (please note the ACD, Section 3.3, incorrectly states that the data were presented at the American Society of Clinical Oncology) and adjustment was made using inverse probability of censoring weighting (IPCW); however, the results are not considered meaningful or informative for decision-making.[1] Unknown subsequent treatment status and incomplete survival follow-up impacted the interpretability of the results for OS in the trial population due to the observed missingness in the trial data. The abstract presented at the SGO was shared in response to the Evidence Review Group's (ERG's) clarification questions and is provided again for ease of reference in Appendix 1. Discontinuation from the trial was greater than 80% in both the niraparib and placebo arms of the g*BRCA*mut 2L+ and non-g*BRCA*mut 2L+ cohorts. Discontinuations for reasons other than death were notable (155/553, 28%), with early withdrawals limiting: a) retrieval of survival status and b) collection of subsequent therapy data. The extent of the missingness prevents robust analysis being conducted to adjust for the crossover of patients treated with placebo to subsequent PARP inhibitor (PARPi) therapy.

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	a) Retrieval of survival status: per the NOVA study protocol, investigators were required to discontinue patients from the study if requesting unblinding.[2] This premature study discontinuation limited the collection of long-term follow-up data such as post-progression therapy and survival status. Since loss of follow-up data could compromise the OS analysis, the study protocol was amended to address this limitation by allowing data entry of last known survival update or death, based on public records. By the final data cut-off (DCO), survival status was not able to be determined for 49% of patients that had discontinued from the trial (76/155), representing: • g*BRCA*mut 2L+ cohort: 14% (19/138) from the niraparib arm; 14% (9/65) from the placebo arm • non-g*BRCA*mut 2L+ cohort: 14% (33/234) from the niraparib arm; 13% (15/116) from the placebo arm b) Subsequent therapies: while crossover to PARPis was not permitted, receipt of subsequent PARPi could occur post-disease progression or withdrawal from the trial according to the oncologist's clinical judgement. Due to study discontinuation, subsequent PARPi information was incomplete for 25% (138/553) of patients from NOVA. In the g*BRCA*mut 2L+ cohort, extensive cross-over of placebo arm patients to PARPi was observed (46%) and may exceed more than half of patients, given the extent of missingness of data (31%). This was indicative of evolving clinical practice at the time of NOVA, with the registration of PARPis in the second-line setting since December 2014,[3–6] and the inability to restrict placebo patients from discontinuing from NOVA post-progression to seek appropriate medical management. The Company would also like to highlight that the use of the Study 19 placebo OS data as the base case comparator arm, in the place of the NOVA OS placebo data, was considered suitable and sufficient for decision making in the g*BRCA*mut 2L population. Study 19 placebo OS data was also the ERG preference as the base case comparator arm, in place of NOVA placebo OS data which has a high level of uncertainty; the ERG report states (page 65) that *"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...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."*[7]

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	The Company ask the Committee to consider the matching-adjusted indirect comparison (MAIC)-adjusted OS results (see Comment 2 below) to reduce uncertainty given the limitations in the interpretability of a treatment-switching adjustment.
2	A MAIC was conducted to adjust for differences in baseline characteristics between patients enrolled in the NOVA and Study 19 clinical trials, in response to the Committee's request in Sections 3.4, 3.10 and 3.19 of the ACD, which forms the basis of the updated Company base case. An anchored MAIC was recently performed where the placebo arm in each trial served as the 'linked network'. Once the baseline characteristics were balanced between NOVA and Study 19 via the MAIC, the adjusted NOVA data (i.e. NOVA using the weights generated from the MAIC) was compared to Study 19 using weighted statistical analyses. The method and rationale for the MAIC analysis are provided in Appendix 2. In response to the Committee's request in Section 3.4, 3.10 and 3.19 of the ACD, the economic model has been updated to include the MAIC-adjusted niraparib OS coefficients for the non-g*BRCA*mut 2L+ population.[1] The lognormal curve was considered to provide the best clinical and statistical fit; the parametric curve selection methods and revised Company base case results are provided in Appendix 3. Using the MAIC-adjusted niraparib OS data and the lognormal distribution compared with the placebo arm observed from Study 19 and the lognormal distribution, the incremental cost-effectiveness ratio (ICER) reduces from £39,608 per quality-adjusted life year (QALY) gained in the previous Company base case to £37,273 per QALY gained for the non-g*BRCA*mut 2L+ population. This analysis forms the basis of the updated Company base case. Niraparib OS in the non-g*BRCA*mut 2L+ cohort, using the MAIC-adjusted OS data, at 5, 10, 15 and 20 years is estimated to be [redacted]%, [redacted] %, [redacted] % and [redacted]%, respectively. This compares closely to OS of [redacted]%, [redacted]%, [redacted]%, [redacted]% at 5, 10, 15 and 20-years when unadjusted niraparib OS data is used to estimate OS using the lognormal curve. As outlined in Appendix 2, close assessment of the reported patients' baseline characteristics in NOVA and Study 19 revealed that the differences between the patient populations are minimal, and that "*the cohorts from the two trials are generally comparable*", as stated in the ERG report. [7] This is reflected in the similarities of the Kaplan Meier curves between the MAIC-adjusted and unadjusted niraparib OS in Figure 4 of Appendix 2.

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	The Company asks the Committee to accept the MAIC-adjusted results as the updated Company base case and the refreshed ICER of £37,273 per QALY gained for the non-g*BRCA*mut 2L+ population.
3	The comparative effectiveness of niraparib is demonstrated via a range of scenarios to reduce the Committee's uncertainty of their assessment of niraparib OS benefit. UK-based real-world evidence (RWE) from Systemic Anti-Cancer therapy (SACT) and Lord et al. (2020) were explored; results derived from OS data from these sources were presented in response to clarification question B3 from the ERG. A scenario analysis using niraparib OS and time to treatment discontinuation (TTD) data from SACT non-g*BRCA*mut 2L+ cohort, and estimating routine surveillance (RS) PFS from the NOVA hazard ratio (HR) and OS using a PFS:OS 1:1 ratio, generated an ICER of £37,986 per QALY gained; this scenario was provided as part of the technical engagement response following changes made, as requested by the ERG. Using the ERG's SACT base case settings, updated to include the use of treatment-specific utilities (see Comment 4), generates an ICER of £41,238 per QALY gained. The use of RS OS data for a mixed/unknown breast cancer susceptibility gene (*BRCA)* status cohort from Lord et al. (2020) compared with niraparib SACT intention-to-treat (ITT) OS data, as an alternative scenario analysis, generates an ICER of £21,976 per QALY gained, as presented in response to question B3 of the ERG's clarification questions.[8] The Company notes the limitations inherent when using single-arm trial data and provides these results to reduce uncertainty by demonstrating that the ICERs, using a variety of sources, are within a similar range or less than the Company's revised base case.
4	A PFS:OS relationship of 1:1 is conservative and is viewed as the minimum OS benefit obtained with niraparib compared to RS The Committee ask the Company to consider modelling niraparib OS assuming no OS benefit compared to RS (ACD, Section 3.19).[1] The assumption of no survival gain after progression-free survival (PFS) gain is not clinically plausible. From a clinical perspective, by increasing PFS, patients have a higher chance of consideration for retreatment with more effective platinum-based therapies in the next treatment line.[9] This has been observed in clinical trials of maintenance therapy in advanced relapsed ovarian cancer which found that prolongation of PFS led to increased platinum retreatment and increased OS.[10–12] Following analysis of the Study 19 *BRCA* wild type (*BRCA*wt) population, a mean incremental PFS:OS ratio of 1:1.5 was observed based on

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	the restricted mean PFS and OS estimates (olaparib PFS: 8.0 months, placebo PFS 5.6 months, incremental PFS benefit 2.4 months; olaparib OS 37.6 months, placebo OS 34.1 months, incremental OS benefit 3.6 months);[13] this provides further evidence to support the assertion that patients without a g*BRCA* mutation treated with a PARPi are expected to achieve *at least* the same OS compared to patients treated with RS. Based on the Study 19 ITT population, a ratio of at least 1:2 was observed in terms of mean PFS to mean OS benefit with olaparib; this could be as high as 1:3 depending on the extrapolation technique.[14] Therefore, we maintain that a 1:1: PFS:OS relationship is conservative and is still an appropriate scenario analysis for consideration by the Committee and any relationship lower than this is not clinically relevant. In addition, this scenario analysis is aligned with the ERG's assumption as stated in the TA528 Final Appraisal Determination (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)*."[15] This was subsequently accepted by the Committee as stated in the TA528 FAD and also reported in the Terms of Engagement, "*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*."[15,16]
5	Treatment-specific utilities provide the most accurate representation of the quality of life impact observed in patients treated with niraparib or RS. The Company welcomes the Committee's acceptance of considering treatment-specific utility values in the economic model (ACD, Section 3.11).[1] As requested and shared immediately prior to the Appraisal Committee Meeting, the results of a linear mixed-effects regression analysis, conducted to assess the statistical difference in the mean utility score of patients in each treatment arm (niraparib and placebo) and health state (progression-free disease and progressed disease) is provided again for ease of reference in Appendix 4. The results provide statistical evidence to support the use of treatment-specific utility values for each health state; the statistical difference between treatment arms is maintained after controlling for health state. In addition, as stated in the ACD, the clinical expert and Cancer Drugs Fund clinical lead noted that utilities may improve on niraparib as it may improve clinical response for people with partial response to prior platinum based chemotherapy.[1]
6	TTD is most appropriately modelled using the log-logistic curve for the non-g*BRCA*mut 2L+ population.

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	The Company maintain that the log-logistic curve is the most appropriate long-term extrapolation for TTD for the non-g*BRCA*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 than the Gompertz curve (AIC [redacted] versus [redacted], and BIC [redacted] versus [redacted] for the log-logistic and Gompertz curves, respectively) with a meaningful difference of over 3 points.[17] 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-g*BRCA*mut 2L+ via the best fitting lognormal distribution whereby [redacted]% of patients are on treatment at 10 years. The Gompertz curve, however, overestimates the proportion of patients still on treatment with [redacted]% of patients on treatment at 10 years. The Company ask the Committee to accept the log-logistic curve as the most appropriate long-term extrapolation for non-g*BRCA*mut 2L+ TTD based on statistical fit, and that it is a sufficiently conservative curve choice compared with extrapolation of UK real world time on treatment data for this population. Further to this point, the Company ask the Committee to consider the scenario for the non-g*BRCA*mut 2L+ population using the SACT time on treatment, as this represents the actual time on treatment observed from RWE for non-g*BRCA*mut 2L+ patients treated in the UK while niraparib was available to patients via the CDF. This alternative scenario analysis, generates an ICER of £25,969 per QALY gained; £11,304 less than the refreshed base case ICER of £37,273.
7	Investigator assessed (IA) PFS has been included as a scenario analysis to reduce uncertainty in the independent review committee (IRC) PFS cost-effectiveness estimates from the economic model, as requested by the Committee in Sections 3.2 and 3.19 of the ACD.[1] The Company base case uses IRC assessed PFS collected from the NOVA trial (DCO 2016); this was the primary endpoint of the NOVA trial and was met at the DCO June 2016, therefore no additional data was collected. In response to the Committee's request in Section 3.2 of the ACD, the economic model has been updated to include the IA PFS coefficients following independent parametric analysis for the non-g*BRCA*mut 2L+ population (DCO October 2020).[1] The Committee concluded that *"because hazards were similar regardless of who assessed [PFS], the method of assessment was unlikely to be critical to decision making"*.[1] The Committee notes that *"the clinical expert and Cancer Drugs Fund clinical lead cautioned focusing only on the median results and*

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	explained that the hazard ratios of both IA and IRC assessed progression-free survival were similar".[1] The Company maintain that IRC PFS is most appropriate to use within the economic modelling. As discussed as part of the technical engagement, there are 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 in NOVA as a sensitivity analysis to ensure robustness of the PFS 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. 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. The log-logistic and generalised gamma curves were considered the most appropriate parametric curves to model IA PFS; the full methodology and parametric curve selection is described in Appendix 5. The log-logistic IA PFS curve is more conservative in its estimates of niraparib patients who are progression free at 5-years ([redacted]%) compared to the generalised gamma estimates ([redacted]%) and the ERGs preferred hazards k=1 curve ([redacted]%) for IRC PFS. The longer term, 20-year estimates of the log-logistic IA PFS curve ([redacted]%) are closer to the ERG's preferred hazards k=1 IRC PFS curve ([redacted]%) compared to the generalised gamma IA PFS curve ([redacted]%). Therefore, the log-logistic curve has a more conservative 20-year estimate ([redacted]%) compared to the generalised gamma ([redacted]%) and is in line with the ERG's preferred IRC PFS base case. The mean time in the progression-free (PF) state for the non-g*BRCA*mut 2L+ population using IA PFS (DCO 2020) extrapolated using the log-logistic distribution is [redacted] years and [redacted] years for niraparib and RS, respectively (or [redacted] years and [redacted] years for niraparib and RS, respectively, after discounting is applied). The mean time in the PF state for the non-g*BRCA*mut 2L+ population using IA PFS (DCO 2020) extrapolated using the generalised gamma distribution is [redacted] years and [redacted] years for niraparib and RS, respectively (or [redacted] years and [redacted] years for niraparib and RS, respectively after discounting is applied). This compares to the mean time in PF state of [redacted]

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	years and [redacted] years for niraparib and RS, respectively (or [redacted] and [redacted] years for niraparib and RS after discounting is applied) when IRC PFS (DCO 2016) is used. A scenario analysis using extrapolated IA PFS data, using the log-logistic curve (NOVA niraparib and placebo IA PFS), and extrapolated OS trial data (NOVA MAIC-adjusted niraparib OS and Study 19 placebo OS) of niraparib versus routine surveillance for non-g*BRCA*mut 2L+, generates an ICER of £34,777 per QALY gained; this is less than the updated Company base case ICER of £37,273 per QALY gained using IRC PFS (presented in Comment 2). A similar scenario analysis, using extrapolated IA PFS data using the generalised gamma curve, generates an ICER of £37,169 per QALY gained; this is in line with the updated Company base case ICER of £37,273 per QALY gained using IRC PFS (presented in Comment 2). The mid-point of these two ICERs is £35,973; this mid-point ICER provides insight into the cost-effectiveness we may expect to achieve when estimating the true IA PFS curve, which is expected to lie somewhere between the conservative (log-logistic) and optimistic (generalised gamma) IA PFS curves. The Company believe that the scenario analyses presented using IA PFS, which demonstrate equal or improved cost effectiveness compared with the Company base case, reduce the Committee's uncertainty in the assessment method of progression and, as such, reduce uncertainly in the PFS extrapolations that form the Company base case. The Company maintain that IRC PFS is the most appropriate endpoint to model PFS. IRC PFS was the primary endpoint of the NOVA trial and aligns with the health-state utilities values, captured per IRC-defined progression status, applied in the economic model. The ICERs generated using IRC PFS data and IA PFS data are similar and thereby reduce uncertainty in the method of assessment of progression.
	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
8	Using the Lord et al. (2020) study as a real world evidence (RWE) routine surveillance comparator provides highly relevant and important evidence for the Committee's consideration. The Company would like to outline two points within the Lord et. al (2020) evidence, which have been interpreted incorrectly within the context of the ACD document and this appraisal: • Section 3.5 of the ACD states "*This study included patients who had completed at least 2 lines of platinum-based chemotherapy with evidence of an objective disease response (complete or partial response), similar to people enrolled in NOVA."* and that *"the median number of previous lines of therapy in Lord et al. 2020 was 3".*[1] The Company would like

	to clarify that the index date (from which OS was calculated) for all patients was the date when patients finished their second course of platinum-based chemotherapy (PBC).[18] Patients were excluded from the study if they had received more than two courses of PBC. The 3 median lines of chemotherapy, quoted in the ACD, describes the total number of lines of chemotherapy received by patients in the Lord et al. (2020) study, including their first two lines of PBC and all subsequent lines of chemotherapy received during study follow up.[1] Niraparib patients in the NOVA trial and the SACT cohort were also eligible to receive subsequent chemotherapy. From the SACT analysis, [redacted]% of g*BRCA*mut 2L and [redacted]% of non-g*BRCA*mut 2L+ patients treated with niraparib had received subsequent chemotherapies. Most importantly, the index date from which overall survival is measured, post exactly two lines of prior PBC, is comparable across Lord et al. (2020), NOVA and the niraparib SACT cohort. • Section 3.5 of the ACD also states *"Including people with a BRCA mutation who had 3 or more courses of chemotherapy (a population outside the scope of this appraisal) in the routine surveillance arm could overestimate the efficacy of niraparib".*[1] The patient population in the Lord et al. (2020) study is not expected to have a poorer prognosis than those in the non-g*BRCA*mut 2L+ population. In fact, given the inclusion of an unknown proportion of patients with a *BRCA* mutation and the exclusion of patients who had received more than two courses of PBC, the patients in the Lord et al. (2020) study are expected to have a better prognosis compared to patients in the NOVA or SACT non-g*BRCA*mut 2L+ population, some of whom will have had more than two lines of PBC. The NOVA niraparib ITT population and SACT niraparib ITT population include non-g*BRCA*mut 2L+ patients who have received 3 prior courses of chemotherapy, therefore, can capture more heavily pre-treated patients. The Company would like to reassert the value of presenting the SACT niraparib OS data compared with Lord et al. (2020) RS OS data in a like for like RWE comparative analysis. 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 RS and seen in current UK clinical practice. The pooled SACT niraparib cohort (g*BRCA*mut 2L and non-g*BRCA*mut 2L+) and the Lord et al. (2020) cohort are both broadly reflective of the patients expected to be treated with niraparib in the relapsed setting in UK clinical practice; this provides a valid real-world scenario as requested in clarification question B3 and B6. As outlined in Comment 1, the use of RS OS data from Lord et

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	al. (2020) compared with niraparib SACT ITT OS data, as an alternative scenario analysis, generates an ICER of £21,976 per QALY gained.
9	Niraparib dose in the economic model should reflect actual dose The NOVA actual dose data, as correctly outlined in the ACD Section 3.12, is updated dose data from the latest NOVA data-cut.[1] The Company believe that the actual dose data aligns with how niraparib is currently used within NHS practice. The Company agree with the Committee, as stated in the Section 3.12 of the ACD, *"that prescribed niraparib doses are unlikely to be returned to the NHS and reused",* however, the Company understand that the unused dose can be retained by patients and utilised during subsequent treatment cycles. As noted in the ACD in Section 3.13, niraparib is 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.[1] The utilisation of this unused dose aligns with NHS clinical practice and the Commissioning for Quality and Innovation (CQUIN) medicines optimisation standard, where pharmacists and prescribers will discuss medicines supply with patients before issuing an entirely new supply of medicine.[19] The ACD in Section 3.12 states that '*In its original appraisal, the committee preferred to use the prescribed dose as a weighted average'.*[1] The Company would like to clarify that the prescribed dose as a weighted average was the most complete and only dosing information from NOVA available at the time of the original appraisal, and the only dosing data from NOVA submitted by the Company for consideration. Therefore, it is not correct to say the prescribed dose was "*preferred"* as it was the only dosing data available for consideration at that time, and we ask that the Committee amend this statement. The Company would like to clarify that the niraparib dose used in economic model does reflect the dose of niraparib in NOVA. All patients within NOVA were required to start treatment on 300 mg of niraparib, and this starting dose is captured within the weighted average cycle one dose, used in the economic model. This 300 mg starting dose is captured in both the prescribed dose and actual dose data. The NOVA dose data (prescribed or actual) provides the weighted average dose per cycle; the actual dose per cycle incorporates any dose reduction which occurred during that cycle and the prescribed dose assumes no dose reduction mid-cycle. The NOVA dose per cycle therefore aligns exactly with the benefits (survival outcomes) experienced by patients in the NOVA trial. The niraparib Summary of Product Characteristics (SmPC) states that a starting dose of 200 mg for patients weighing less than 58 kg or with hepatic impairment may be considered.[20]

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

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	Therefore, a proportion of patients may receive a starting dose of 200mg, and the starting dose of 300mg in the economic model for all patients is conservative. The Company ask that it is clarified within the ACD in Section 3.13, that the current economic model provided for decision making does reflect the starting dose of niraparib in NOVA, which aligns with the survival outcomes in NOVA. *"Dose used in the model should reflect the dose of niraparib in the summary of product characteristic (SmPC) and NOVA **as per the provided dosing data**"* *"The committee noted that the company produces 100 mg capsules to account for this change in clinical practice but also noted that the benefits accrued from niraparib should align with the treatment costs from NOVA, **as per the current economic model**. It concluded that the dose used in economic model should reflect the dose of niraparib in the SmPC and NOVA **as per the provided dosing data**."*
10	Clarification of *BRCA* mutation status terminology The Company ask that consistent terminology is used throughout the ACD and future documentation when referring to *BRCA* mutation status. In Section 1 of the ACD the populations are outlined as *'patients with a BRCA mutation*' and *'patients without a BRCA mutation'.*[1] For consistency and ease of comprehension, the Company requests that the terminologies stated in Section 1 of the ACD should be used throughout the document. The following sections of the ACD currently use inconsistent terminology: • Section 3.2 (referring to the *"mutation-negative group"* and *"mutation-positive group*") • Section 3.5 (referring to *"BRCA-positive and negative subgroups*") • Section 3.6 (referring to "*BRCA mutation positive and BRCA mutation negative subgroups"* • Section 3.10 (referring to *"BRCA negative group")*[1] The Company ask that it is made clear throughout the document that the niraparib data used within the economic model are based on the CDF recommendation specific subgroups; i.e. patients with a germline *BRCA* mutation whose disease has responded to 2 courses of platinum-

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

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	based chemotherapy and patients without a germline *BRCA* mutation whose disease has responded to 2 or more courses of platinum-based chemotherapy, rather than the marketing authorisation population. Germline *BRCA* should be referred to as "g*BRCA"* throughout. • Section 3.6 (please include *"Data from SACT was collected as per CDF recommendation specific subgroups; i.e. patients with a gBRCA mutation whose disease has responded to 2 courses of platinum-based chemotherapy and patients without a gBRCA mutation whose disease has responded to 2 or more courses of platinum-based chemotherapy")* • Section 3.8 (please add "*The company's approach to modelling survival is suitable for people with a gBRCA mutation* ***whose disease has responded to 2 courses of platinum-based chemotherapy****")* • Section 3.16 (please add *"The estimates for people with a gBRCA mutation* ***whose disease has responded to 2 courses of platinum-based chemotherapy*** *are within the range considered a cost-effective use of NHS resources")*[1]
	Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
11	Additional UK-based RWE has been published providing OS data of patients treated with niraparib and RS in UK clinical practice which provide further confidence on the life expectancy of patients in the non-g*BRCA*mut 2L+ population when assessing the end-of-life-criteria in this population. The Committee considered in Section 3.14 of the ACD that the study by Lord et al. (2020), providing published UK-based RWE, *"included patients with a BRCA mutation who had 3 or more courses of chemotherapy and were likely to have a poorer prognosis than people in earlier stages of treatment."*[1] The Company would like to clarify that the index date (from which OS was calculated) for all patients was the date when patients finished their second course of PBC.[18] Patients were excluded from the study if they had received more than two courses of PBC and therefore the patient population in the Lord et al. (2020) study is not expected to have a poorer prognosis than those in the non-g*BRCA*mut 2L+ population. The Lord et al. (2020) data captured survival outcomes for 233 patients, across 13 UK hospitals, with a median follow up of 23.8 months.[18] The study author 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 a highly clinically relevant real world routine surveillance comparator. The median overall survival in the study was 19.3

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	months (95% CI ± 2.4) for the all-comers population; therefore it is highly likely that a cohort of non-g*BRCA*mut 2L+ patients who had received two or more lines of PBC would have lower OS than 19.3 months. Observed data from SACT provide a median life expectancy for patients treated with niraparib of [redacted] months (95% CI [redacted]) in the non-gBRCAmut 2L+ cohort; it is expected that patients treated with RS would have a lower life expectancy.[21] 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 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*".[22] A life extension of three months for patients treated with niraparib is demonstrated through comparative analyses. [redacted] years (revised base case MAIC-adjusted NOVA 2020 niraparib OS data and Study 19 placebo), [redacted] years (NOVA 2020 niraparib OS data and Study 19 placebo), [redacted] years (1:1 PFS:OS), [redacted] years (SACT scenario), 1.11 years (Lord et al. (2020) scenario). The Company ask the Committee to revisit the evidence supporting the use of niraparib as an end-of-life therapy for the non-g*BRCA*mut 2L+ population.
12	<u>There is a high unmet need for effective oral maintenance treatments, particularly for patients who do not possess a *BRCA* mutation for whom treatment options are extremely limited.</u> Ovarian cancer (OC) is responsible for one woman's death every three hours in England.[23,24] Around 70% of OC 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.[25,26] Approximately 80% of patients with OC do not have a g*BRCA* mutation.[27] Data from the NOVA trial and RWE indicate that patients without a g*BRCA* mutation have the potential to respond well to PARPi maintenance treatment, and can experience sustained benefit as long- term responders. Therefore, the prospect of having no oral maintenance treatment options once their disease relapses, if the provisional recommendations are enacted, will result in a high unmet need, as well as inequality in access across the UK. [27]

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	The Committee notes in Section 3.1 of the ACD that only olaparib is available via routine commissioning and later in the treatment pathway; restricted to patients with a *BRCA* mutation who have received three or more courses of PBC.[1] The Company ask the Committee to note that the majority of patients with advanced OC do not possess a *BRCA* mutation (80%) and therefore currently have no oral maintenance treatment options available via routine commissioning in the relapsed setting.[27] This specific unmet need for patients without a *BRCA* mutation was highlighted in the patient access group response to technical engagement as key messages "*There are currently no maintenance treatments available in routine commissioning for women who do not have a BRCA mutation.", "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."* As concluded by the Committee, there is a high unmet need for an oral maintenance treatment for all patients with OC, particularly patients who do not possess a *BRCA* mutation. The number of patients eligible for treatment with niraparib in the relapsed setting is likely to decrease over the coming years, as a greater proportion of patients receive PARPi treatment in the first-line setting. However, there will remain a small but important group of patients who do not receive a PARPi in the first-line setting, receiving therapy with another mechanism of action or routine surveillance, for whom niraparib will remain a critical treatment option. The Company ask the Committee to consider the unmet need for the majority of patients (80%) with OC, who do not possess a g*BRCA* mutation, when considering a recommendation for niraparib treatment in this group of patients.

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.

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

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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Comments received during our consultations 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.

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NOVA long-term safety & secondary endpoints SGO 2021 presentation vignette

NCT01847274

Niraparib▼ is 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.
- as 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.

Adverse events should be reported. Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard (UK) or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to GSK: please call 0800 221 441

NOVA NIRAPARIB TRIAL

Long-term safety and secondary efficacy endpoints in the ENGOT-OV16/NOVA phase 3 trial of niraparib in recurrent ovarian cancer

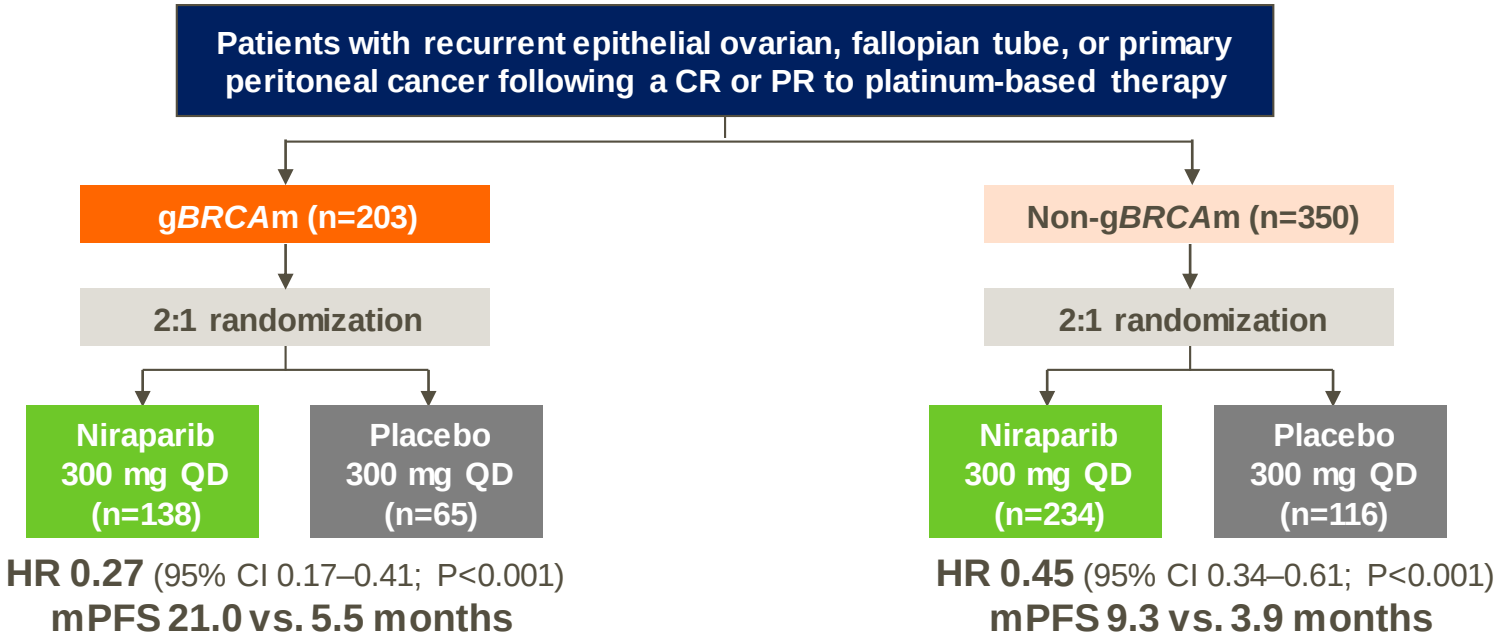
Ursula A. Matulonis, Jørn Herrstedt, Amit Oza, Sven Mahner, Andrés Redondo, Dominique Berton, Jonathan S. Berek, Bente Lund, Frederik Marme, Antonio González-Martín, Anna V. Tinker, Jonathan Ledermann, Benedict Benigno, Gabriel Lindahl, Nicoletta Colombo, Yong Li, Divya Gupta, Bradley J. Monk, Mansoor R. Mirza

Presented at the Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer

March 19–25, 2021 (virtual)

Primary PFS endpoint: ENGOT-OV16/NOVA study

- NOVA (NCT01847274) was a randomized, double-blind, placebo-controlled phase 3 trial of niraparib maintenance treatment for patients with platinum-sensitive recurrent OC
- Niraparib demonstrated statistically significant improvement in PFS in g*BRCA*m and non-g*BRCA*m cohorts[1]

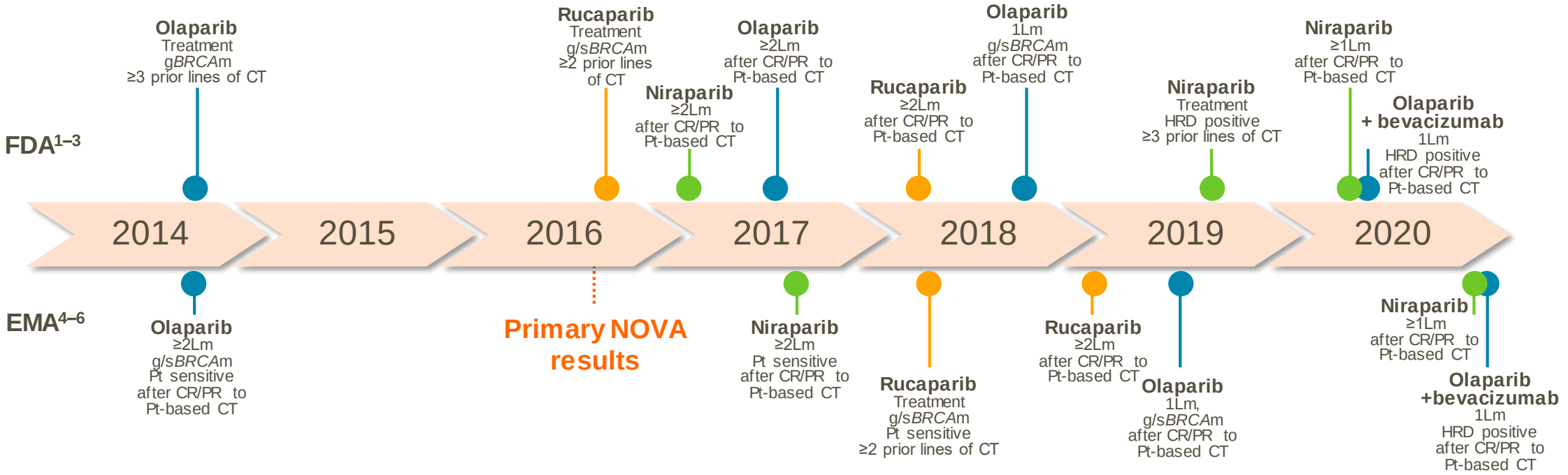


- Secondary endpoints included safety and exploratory long-term efficacy such as PFS2 and OS, which were not statistically powered

Primary data cutoff date was June 20, 2016 (median duration of follow-up was 16.9 months).
CR, complete response; g*BRCA*m, germline *BRCA* mutant; HR, hazard ratio; mPFS, median progression-free survival; OC, ovarian cancer; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival 2; PR, partial response; QD, once daily. 1. Mirza MR, et al. N Engl J Med 2016;375:2154–64.
Matulonis UA, et al. presented at SGO 2021, March 19–25, 2021 (virtual).

Approvals of PARPi for advanced OC

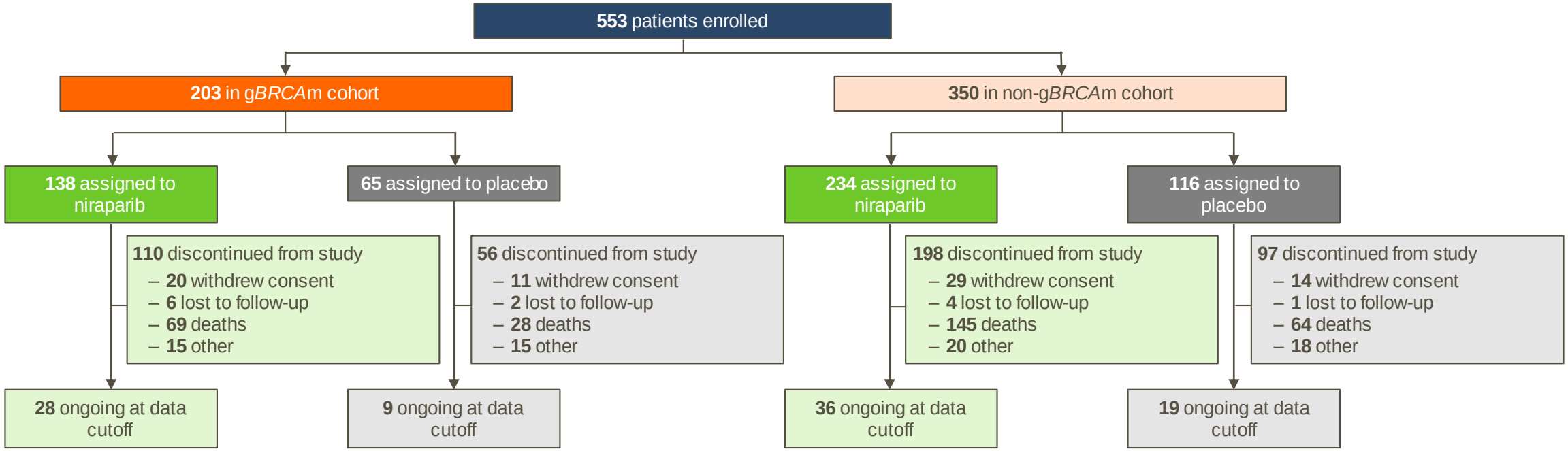
- **PARPi have changed the treatment paradigm for the management of advanced OC**



- **A high proportion of patients were withdrawn from the NOVA study after primary results in 2016 and post-commercial availability of PARPi**

1Lm, first-line maintenance; 2Lm, second-line maintenance; CR, complete response; CT, chemotherapy; EMA, European Medicines Agency; FDA, Food & Drug Administration; g*BRCA*m, germline *BRCA* mutant; HGS, high-grade serous; HRD, homologous recombination deficiency; PARPi, poly (ADP-ribose) polymerase inhibitor; OC, ovarian cancer; PR, partial response; Pt, platinum; s*BRCA*m, somatic *BRCA* mutant. 1. ZEJULA® (niraparib): US prescribing information (Apr 2020), Research Triangle Park, NC 27709, GlaxoSmithKline; 2 LYNPARZA® (olaparib): US prescribing information (Dec 2020), Wilmington, DE 19850, AstraZeneca Pharmaceuticals LP; 3. RUBRACA® (rucaparib): US prescribing information (Oct 2020), Boulder, CO 80301, Clovis Oncology, Inc.; 4. ZEJULA® (niraparib): EPAR – Product information – Summary of product characteristics (Nov 2020); 5. LYNPARZA® (olaparib): EPAR – Product information – Summary of product characteristics (Nov 2020); 6. RUBRACA® (rucaparib): EPAR – Product information – Summary of product characteristics (Jan 2021).
Matulonis UA, et al. presented at SGO 2021, March 19–25, 2021 (virtual).

Patient disposition and survival status



- **In the overall population, 28% (155/553) discontinued from the study for reasons other than death**
  - Imbalances were observed because of the small sample size in each cohort
  - Early withdrawal of consent limited the collection of survival and subsequent therapy data
- **By final data lock, survival status could not be retrieved for 49% (76/155) of patients:**
  - g*BRCA*m cohort: 14% (19/138) in niraparib group, 14% (9/65) in placebo group
  - Non-g*BRCA*m cohort: 14% (33/234) in niraparib group, 13% (15/116) in placebo group

Final data cutoff date was October 1, 2020 (average duration of follow-up for OS was 67 months).
g*BRCA*m, germline *BRCA* mutant.
Matulonis UA, et al. presented at SGO 2021, March 19–25, 2021 (virtual).

Assessment of missing subsequent PARPi therapy

- Crossover to PARPi on study was not permitted; however, patients could receive subsequent PARPi after disease progression or withdrawal from the study per oncologist's clinical judgement
- Because of study discontinuation, post-progression therapy information was not available for 25% (138/553) of patients

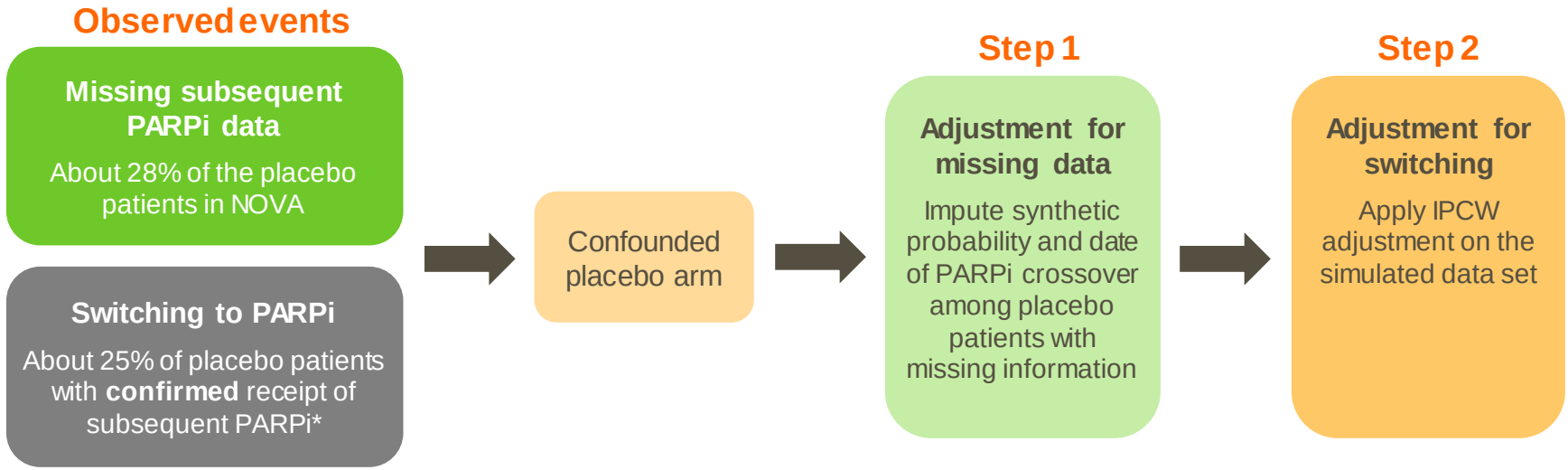
	g*BRCA*m		Non-g*BRCA*m	
Subsequent PARPi treatment received on NOVA, n (%)	**Niraparib (n=138)**	**Placebo (n=65)**	**Niraparib (n=234)**	**Placebo (n=116)**
Yes	34 (25)	30 (46)	15 (6)	15 (13)
No	68 (49)	15 (23)	168 (72)	70 (60)
Missing information	36 (26)	20 (31)	51 (22)	31 (27)

- Both the small sample size and the missing data challenge survival analyses and interpretation

g*BRCA*m, germline *BRCA* mutant; PARPi, poly (ADP-ribose) polymerase inhibitor.
Matulonis UA, et al. presented at SGO 2021, March 19–25, 2021 (virtual).

OS sensitivity analyses

- **Adjusted OS analysis was conducted after missing subsequent PARPi therapy data were imputed**
- **An inverse probability of censoring weighted (IPCW) methodology[1,2] was applied to adjust for subsequent PARPi therapy use**



- **Restricted mean survival time (RMST) analysis was conducted when non-proportional hazards were observed**

*46% in the g*BRCA*m cohort and 13% in the non-g*BRCA*m cohort.
IPCW, inverse probability of censoring weighted; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; RMST, restricted mean survival time.
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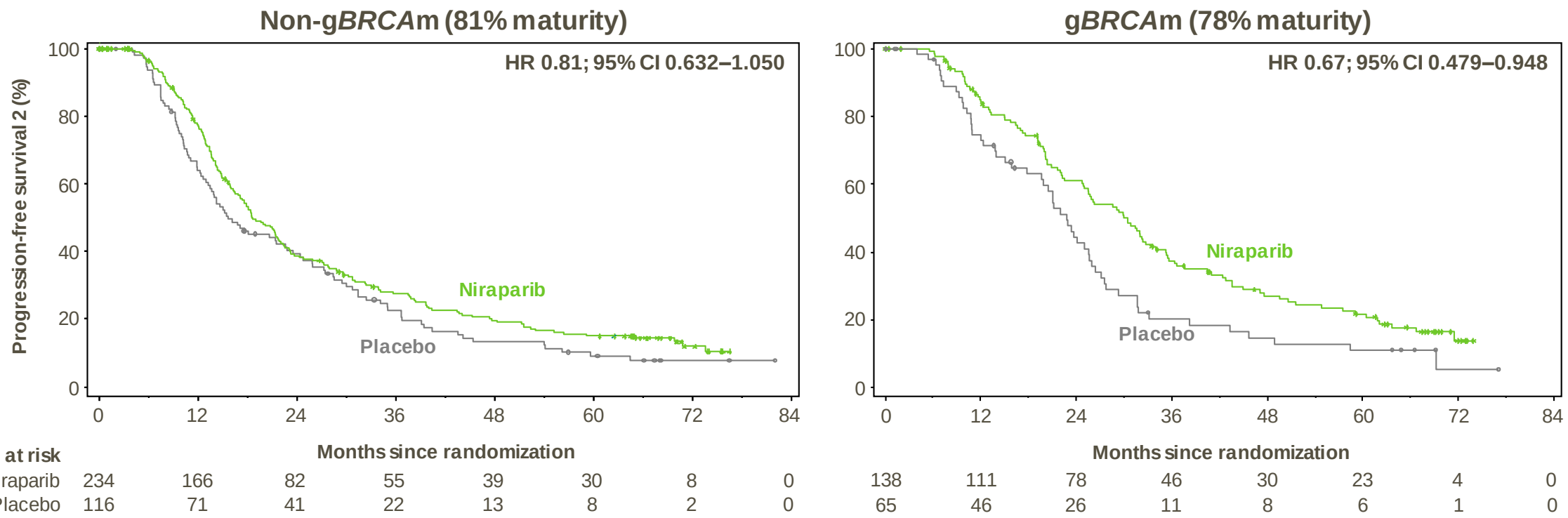
Matulonis UA, et al. presented at SGO 2021, March 19–25, 2021 (virtual).

PFS2: non-g*BRCA*m and g*BRCA*m cohorts

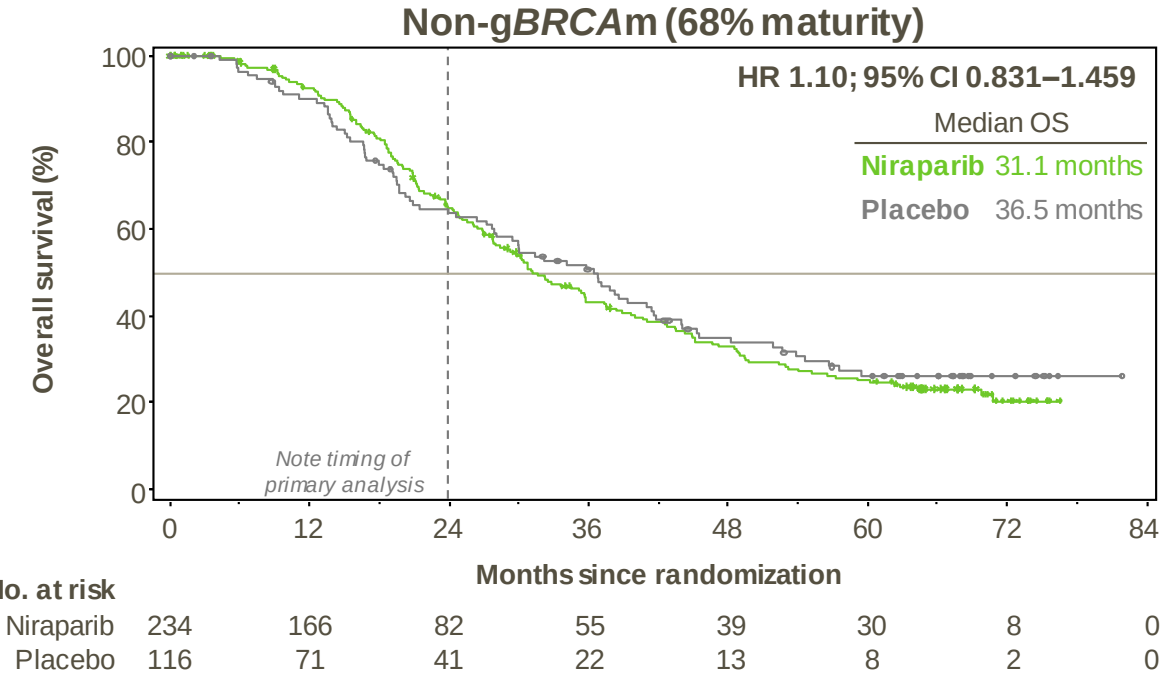
- According to updated analysis, the benefit of niraparib extended beyond first progression

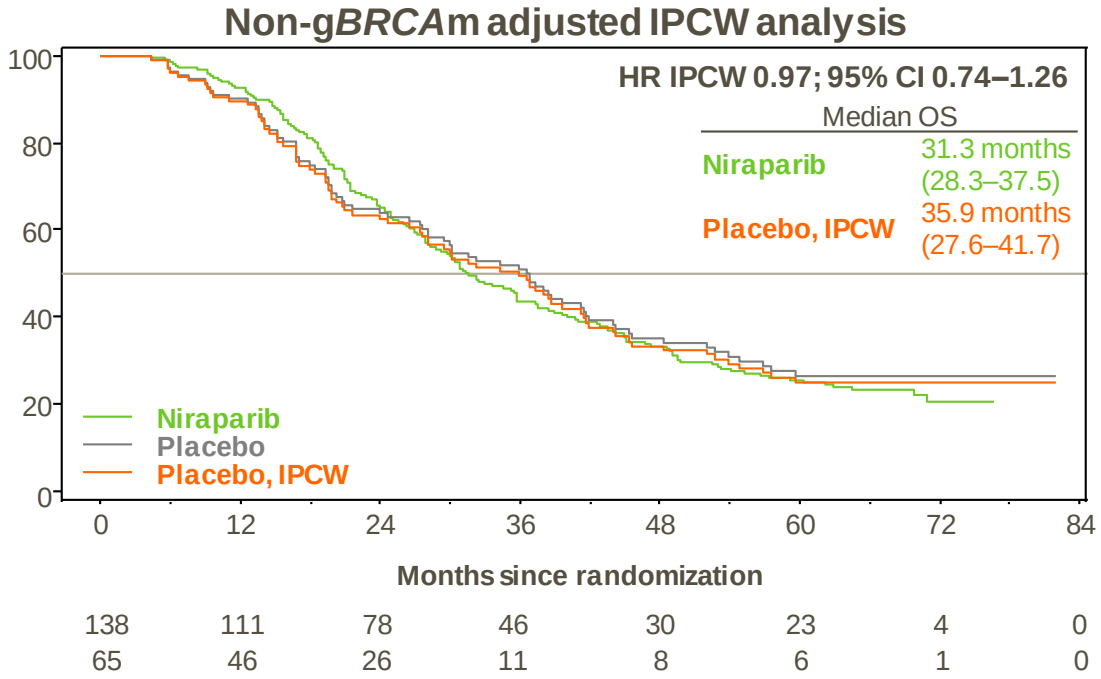


Final data cutoff date was October 1, 2020 (average duration of follow-up for OS was 67 months). PFS2 was measured from the time of randomization to progression on subsequent chemotherapy.
CI, confidence interval; g*BRCA*m, germline *BRCA* mutant; HR, hazard ratio; OS, overall survival; PFS2, progression-free survival 2
Matulonis UA, et al. presented at SGO 2021, March 19–25, 2021 (virtual)

OS: non-g*BRCA*m cohort

- At the time of the final analysis, average follow-up time was 5.6 years
- Based on adjusted analysis for subsequent PARPi therapy, no difference in survival was observed





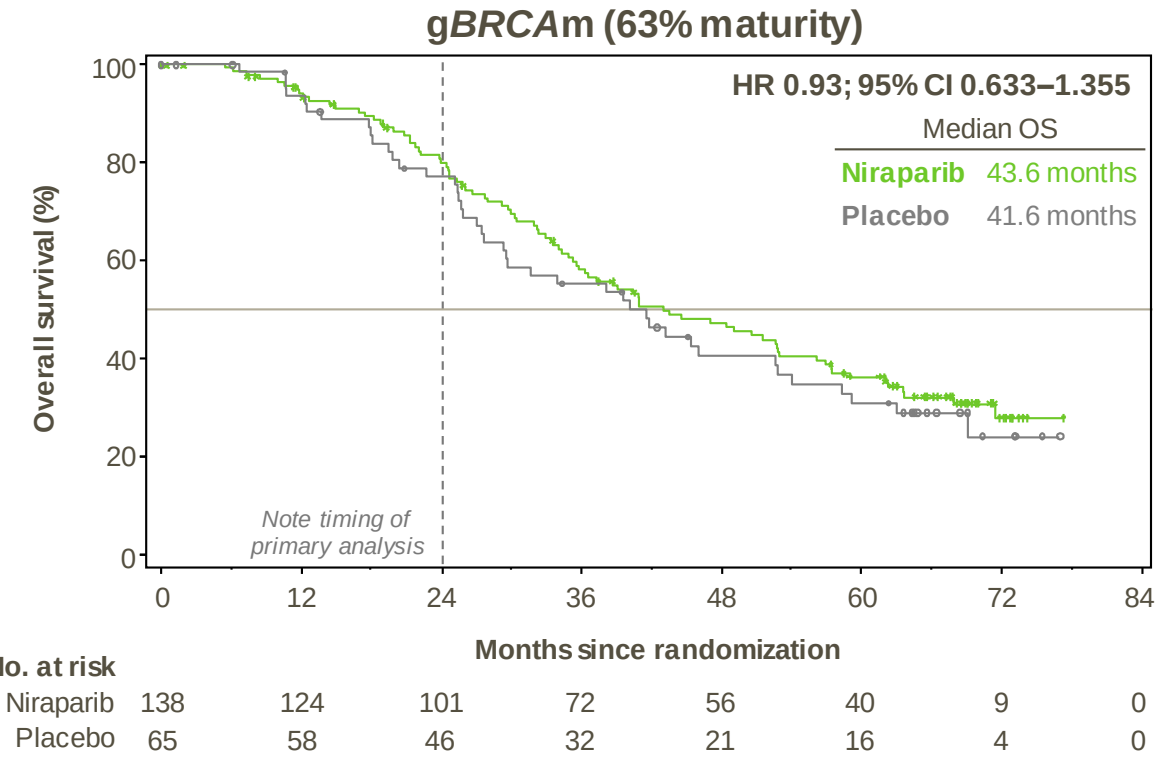
No. at risk																
Niraparib	234	166	82	55	39	30	8	0	138	111	78	46	30	23	4	0
Placebo	116	71	41	22	13	8	2	0	65	46	26	11	8	6	1	0

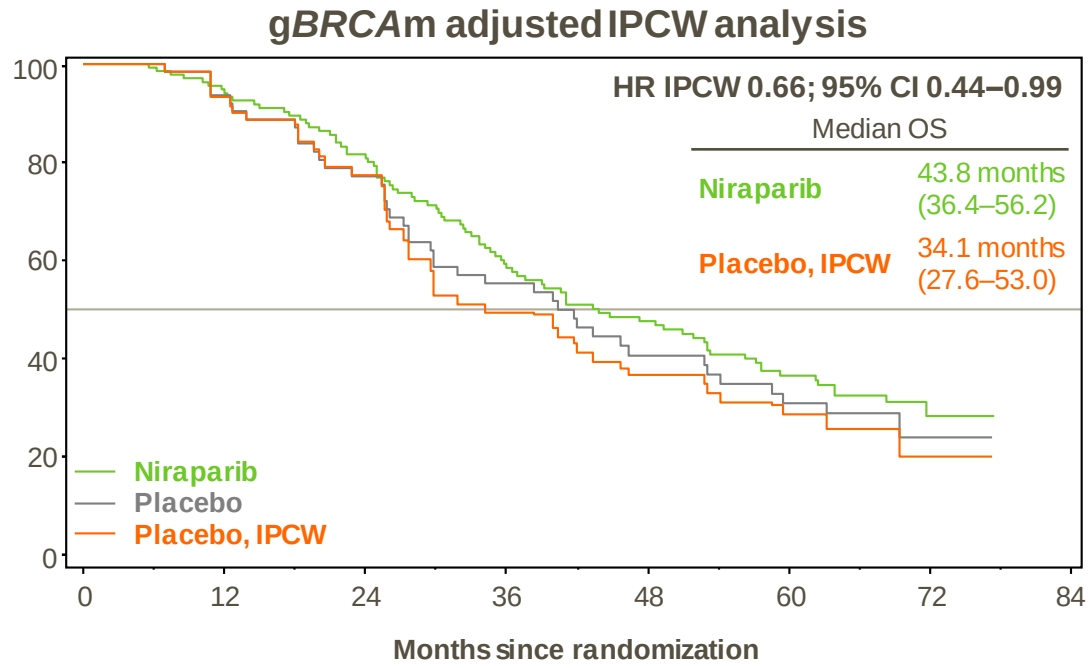
- Given evidence of non-proportional hazards, RMST analysis was conducted in the ITT population to estimate the difference in restricted mean values (area under the curve)
  - Up to 24 months: 20.6 months in placebo cohort vs 21.3 months in niraparib cohort (Δ of 0.7; 95% CI −0.5–1.9)
  - Up to 72 months: 39.1 months in placebo cohort vs 38.5 months in niraparib cohort (Δ of −0.7; 95% CI −6.0–4.7)

Final data cutoff date was October 1, 2020.
CI, confidence interval; g*BRCA*m, germline *BRCA* mutant; HR, hazard ratio; IPCW, inverse probability of censoring weighted; ITT, intention-to-treat; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; RMST, restricted mean survival time.
Matulonis UA, et al. presented at SGO 2021, March 19–25, 2021 (virtual).

OS: g*BRCA*m cohort

- At the time of the final analysis, average follow-up time was 5.6 years
- Adjusted analysis indicated a trend for improved survival with niraparib maintenance, with an HR of 0.66 and increased median OS of 9.7 months





Final data cutoff date was October 1, 2020.
CI, confidence interval; g*BRCA*m, germline *BRCA* mutant; HR, hazard ratio; IPCW, inverse probability of censoring weighted; OS, overall survival.
Matulonis UA, et al. presented at SGO 2021, March 19–25, 2021 (virtual).

Long-term safety: Grade ≥3 adverse events

- **Hematologic TEAEs primarily occurred in the first year of niraparib treatment**
- **Incidence of grade ≥3 thrombocytopenia decreased from 33.8% to 2.8%, anemia decreased from 25.6% to 0.7%, and neutropenia decreased from 19.3% to 2.1% from year 1 to years 2–3**
- **49 (13%) patients remained on niraparib vs. 9 (5%) on placebo for more than 3 years**

Adverse event, n (%)	Niraparib arm				Placebo arm			
	Overall (N=367)	Year 1 (n=367)	Years 2–3 (n=143)	Year 3+ (n=49)	Overall (N=179)	Year 1 (n=179)	Years 2–3 (n=31)	Year 3+ (n=9)
Thrombocytopenia*	131 (35.7)	124 (33.8)	4 (2.8)	6 (12.2)	1 (0.6)	1 (0.6)	0	0
Anemia†	99 (27.0)	94 (25.6)	1 (0.7)	5 (10.2)	0	0	0	0
Neutropenia‡	76 (20.7)	71 (19.3)	3 (2.1)	4 (8.2)	3 (1.7)	3 (1.7)	0	0
Hypertension	36 (9.8)	32 (8.7)	7 (4.9)	4 (8.2)	4 (2.2)	4 (2.2)	0	0
Fatigue§	31 (8.4)	30 (8.2)	0	1 (2.0)	1 (0.6)	1 (0.6)	0	0
GI disorders**	30 (8.2)	24 (6.5)	4 (2.8)	2 (4.1)	9 (5.0)	8 (4.5)	1 (3.2)	0

Final data cutoff date was October 1, 2020 (average duration of follow-up for OS was 67 months). *Thrombocytopenia includes reports of thrombocytopenia and decreased platelet count. †Anemia includes reports of anemia and decreased hemoglobin count. ‡ Neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia. §Fatigue includes reports of fatigue, asthenia, and malaise. **GI disorders includes constipation, diarrhea, nausea, vomiting, and abdominal pain. GI, gastrointestinal; OS, overall survival; TEAE, treatment-emergent adverse event.

Matulonis UA, et al. presented at SGO 2021, March 19–25, 2021 (virtual).

Summary of MDS/AML

- **At the time of the primary analysis, incidence of MDS/AML was 1.4% (5/367) in the niraparib arm vs. 1.1% (2/179) in the placebo arm[1]**
- **With long-term follow-up and administration of subsequent therapies, 3.5% (13/367) of patients in the niraparib arm vs. 1.7% (3/179) in the placebo arm developed MDS/AML**

	Niraparib arm			Placebo arm		
Adverse event, n (%)	**All (N=367)**	**g*BRCA*m (n=136)**	**Non-g*BRCA*m (n=231)**	**All (N=179)**	**g*BRCA*m (n=65)**	**Non-g*BRCA*m (n=114)**
MDS/AML all	**13* (3.5)**	9 (6.6)	4 (1.7)	**3 (1.7)**	2 (3.1)	1 (0.9)
TEAE (treatment)	9 (2.5)	7 (5.1)	2 (0.9)	0	0	0
TEAE (follow-up)	4 (1.1)	2 (1.5)	2 (0.9)	3 (1.7)	2 (3.1)	1 (0.9)

Final data cutoff date was October 1, 2020 (average duration of follow-up for OS was 67 months). *A total of 16 events of MDS/AML were reported in 13 patients treated with niraparib: 1 patient had MDS then AML; 1 patient had MDS grade 1, then MDS grade 4, then AML. AML, acute myeloid leukemia; g*BRCA*m, germline *BRCA* mutant; MDS, myelodysplastic syndromes; OS, overall survival; TEAE, treatment-emergent adverse event.

1. Mirza MR, et al. N Engl J Med 2016;375:2154–64.
Matulonis UA, et al. presented at SGO 2021, March 19–25, 2021 (virtual).

Final NOVA analysis in platinum-sensitive recurrent OC

- **Clinical benefit of niraparib was demonstrated in the primary PFS analysis in non-g*BRCA*m (HR 0.45) and g*BRCA*m patients (HR 0.27)**
- **Final PFS2 analysis indicated that the benefit of niraparib maintenance therapy extended beyond first progression**
- **OS interpretation is limited:**
  - OS was a secondary endpoint, not statistically powered
  - Analysis was challenged by the high rate of subsequent PARPi use and missing data
  - No difference in survival was observed in patients with non-g*BRCA*m OC
  - Trend toward improved survival was observed in patients with g*BRCA*m OC, based on the adjusted analyses, with an increased survival of 9.7 months
- **Long-term safety analysis supported use of niraparib for maintenance treatment**
  - Number of hematologic adverse events decreased after the first year of maintenance

g*BRCA*m, germline *BRCA* mutant; HR, hazard ratio; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS2, progression-free survival 2.
Matulonis UA, et al. presented at SGO 2021, March 19–25, 2021 (virtual).

Appendix 2. Matching adjusted indirect comparison using NOVA and Study 19 clinical trials

1 Executive Summary

Background: Ovarian cancer (OC) is a rare type of cancer with no viable cure. It is the deadliest of all gynaecological cancers, and the 5th leading cause of cancer death in women. Most cases are diagnosed at an advanced stage (i.e. stage III or IV), and >50% of patients with advanced disease die within 5 years of diagnosis. The overall 5-year mortality rate for OC is almost twice as high as that of breast cancer.

ENGOT-OV16/NOVA (ClinicalTrials.gov identifier: NCT01847274) is a Phase 3, randomized, double-blind, placebo-controlled (routine surveillance [RS]), multicenter study of niraparib maintenance treatment in patients with platinum-sensitive, recurrent ovarian cancer following receipt of two or more platinum-based chemotherapy regimens. In this trial, patients were categorized according to the presence or absence of a germline *BRCA* mutation—g*BRCA*mut 2L+ and non-g*BRCA*mut 2L+ cohorts. As per the primary efficacy analyses, a clinically significant improvement in PFS (per blinded independent central review (BICR)) across the g*BRCA*mut 2L+ (hazard ratio-HR = 0.27, 95% CI: 0.17, 0.41) and non-g*BRCA*mut 2L+ cohorts (HR = 0.45, 95% CI: 0.34, 0.61) was demonstrated for the comparison of niraparib vs placebo.

Most recently, the longer-term results of NOVA were made available (DCO: October 2020).[1] While no difference in OS was observed, interpretation of OS data in the g*BRCA*mut 2L+ and non-g*BRCA*mut 2L+ cohorts was challenged by the high rate of subsequent PARPi use and missing data. In the overall ITT population, 28% (155/553) discontinued from the study for reasons other than death and by final data lock, survival status could not be retrieved for 49% (76/155) of these patients:

- g*BRCA*mut 2L+ cohort: 14% (19/138) in niraparib group, 14% (9/65) in placebo group
- non-g*BRCA*mut 2L+ cohort: 14% (33/234) in niraparib group, 13% (15/116) in placebo group

Although planned cross-over from placebo to niraparib after progression was not part of the NOVA study protocol, 46% of placebo patients switched to a poly (ADP-ribose) polymerase inhibitor (PARPi) after progression and an additional 31% had missing information on subsequent PARPi use during follow-up. The non-g*BRCA*mut 2L+ analysis comparing OS for niraparib vs. placebo indicated an HR=1.10 (0.83, 1.46).

The efficacy of olaparib, another PARPi agent used as maintenance treatment in platinum-sensitive, relapsed ovarian cancer patients, was assessed in Study 19. Study 19 included patients receiving at least two platinum-based chemotherapy regimens and were in complete or partial response to their most recent regimen. In Study 19, known *BRCA*mut status was not required, however, it was retrospectively established using germline or tumor testing.

The results from Study 19 indicated an OS advantage in the *BRCA*mut population for olaparib vs placebo. The median OS for olaparib was estimated at 34.9 (95 % CI 29.2, 54.6) months and 30.2 (23.1, 40.7) months for placebo. The estimated HR was 0.62 (0.42, 0.93) for olaparib compared to placebo. Similarly, in the non-*BRCA*mut population the median OS for olaparib was estimated at 24.5 (19.8, 35.0) months and 26.6 (23.1, 32.5) for placebo and the estimated HR was 0.84 (0.57, 1.25).

After adjusting (using post-hoc OS analysis) for placebo patients in the *BRCA*mut group that received subsequent PARPi therapy via other study, the OS HR between olaparib and placebo was estimated at 0.49 (0.28, 0.85).

A matching adjusted indirect treatment comparison (MAIC) was conducted to adjust for between-trial differences in the baseline characteristics of NOVA vs. Study 19 to inform estimates of relative effectiveness of niraparib compared with placebo (routine surveillance).

Methods: An MAIC was conducted to adjust for between-trial differences in baseline characteristics of NOVA vs Study 19. The anchored version of the MAIC was performed where the placebo arm in each comparator trial served as the 'linked network'. Once the baseline characteristics were balanced between NOVA and Study 19 via the MAIC, the adjusted NOVA (i.e NOVA using the weights generated from the MAIC) was compared to Study 19 using weighted statistical analyses. More specifically, the relative indirect efficacy of niraparib compared to placebo was assessed using: (i) weighted hazard ratios (HRs) and 95% confidence intervals (CIs); (ii) weighted Kaplan-Meier (KM) curves.

Results: The estimated OS HR for niraparib vs placebo, before and after MAIC adjustment, was 1.10 (0.83, 1.46) and [redacted] in the non-g*BRCA*mut 2L+ population (NOVA vs Study 19).

Discussion: Overall, MAIC results suggest that there is [redacted] when adjusted for between-trial differences in the baseline characteristics of NOVA vs. Study 19. It is important to acknowledge a few limitations regarding the MAIC analyses, as with any ITC, differences in the methodology for trial's analysis, outcome measurement and populations of the included trials must be carefully considered. MAICs are not randomized comparisons and cannot be interpreted as such. They are essentially observational findings across trials and may suffer from biases inherent to observational studies (for example confounding).

Conclusion: An MAIC was conducted to adjust for potential differences in baseline characteristics, between the NOVA and Study 19 trials for non-g*BRCA*mut 2L+. MAIC results suggested that there is [redacted] niraparib vs. placebo following this adjustment.

2 Background & Objectives

2.1 Ovarian Cancer

Ovarian cancer (OC) is a rare type of cancer with no viable cure. It is the deadliest of all gynecological cancers, and the fifth leading cause of cancer death in women. Most cases are diagnosed at an advanced stage (i.e. stage III or IV), and >50% of patients with advanced disease die within 5 years of diagnosis. The overall 5-year mortality rate for OC is almost twice as high as that of breast cancer.[3, 4]

The cornerstone of drug treatment in the first-line advanced disease setting is platinum (cisplatin or carboplatin) plus a taxane (paclitaxel or docetaxel), with or without bevacizumab. First-line treatment regimens result in high response rates, but most patients with advanced disease will experience a recurrence within 2 years. Relapse rates for epithelial OC can be as high as 85% for patients diagnosed at stage III or IV.[5-7]

Most patients who recur are treated with a round of platinum-based chemotherapy. However, the effectiveness of additional chemotherapy diminishes over time, and the disease tends to recur rapidly after treatment completion, requiring further chemotherapy. Duration of progression-free survival (PFS) decreases with each subsequent line of chemotherapy. Risk of cumulative toxicities also increases with each line of treatment. Once the PFS decreases to <6 months after platinum-based chemotherapy, the disease is considered platinum-resistant, and patients have a poor prognosis with a median overall survival (OS) of about 12 months. Maintenance therapy may be used to extend the time between chemotherapy treatments and prolong PFS. The objective of maintenance therapy is to delay progression of disease by either killing residual cancer cells or by preventing cell turnover by inhibitory signaling or through immunological control.

Given the high rate of OC relapse and the negative impact on patients' health-related quality of life (HRQoL),[8] an effective maintenance treatment is one that both delays disease progression and does so without added HRQoL impact by means of drug toxicity.

2.2 NOVA Trial

ENGOT-OV16/NOVA (ClinicalTrials.gov identifier: NCT01847274) is a Phase 3, randomized, double-blind, placebo-controlled (routine surveillance [RS]), multicenter study of niraparib maintenance treatment in patients with platinum-sensitive, recurrent ovarian cancer following receipt of two or more platinum-based chemotherapy regimens. Patients in the NOVA trial were required to have had platinum-sensitive disease—complete or partial response and disease progression—more than 6 months after their penultimate platinum-based chemotherapy.[9,1] In this trial, patients were categorized according to the presence or absence of a germline *BRCA* mutation—g*BRCA*mut 2L+ and non-g*BRCA*mut 2L+ cohorts. Results demonstrated that niraparib treatment significantly extended median PFS in both the cohorts: g*BRCA*mut 2L+ (21.0 months v 5.5 months; P, 0.001) and non-g*BRCA*mut

2L+ (9.3 months v 3.9 months; P, 0.001). [10] The trial results also demonstrated that quality of life (QoL) remained stable during treatment and the pre-progression period. No significant differences in QoL were observed between the treatment arms.[10]

Most recently, the longer-term results of NOVA were made available (DCO: October 2020). While no difference in OS was observed, interpretation of OS data in the g*BRCA*mut 2L+and non-g*BRCA*mut 2L+cohorts is challenged by the high rate of subsequent PARPi use and missing data. In the overall ITT population, 28% (155/553) discontinued from the study for reasons other than death and by final data lock, survival status could not be retrieved for 49% (76/155) of these patients:

- g*BRCA*mut 2L+ cohort: 14% (19/138) in niraparib group, 14% (9/65) in placebo group
- Non-g*BRCA*mut 2L+ cohort: 14% (33/234) in niraparib group, 13% (15/116) in placebo group

Although planned cross-over from placebo to niraparib after progression was not part of the NOVA study protocol, 46% of placebo patients switched to a poly (ADP-ribose) polymerase inhibitor (PARPi) after progression and an additional 31% had missing information on subsequent PARPi use during follow-up.

2.3 Study 19 Trial

Study 19 was a randomized, placebo-controlled, Phase II trial enrolling 265 patients receiving at least two platinum-based chemotherapy regimens and were in complete or partial response to their most recent regimen. Patients were randomized to olaparib (capsules; 400 mg bid) or placebo. Known *BRCA*mut status was not required for enrollment in Study 19, however it was retrospectively established using germline or tumor testing. The results from Study 19 indicated an OS advantage in the *BRCA*mut population for olaparib vs placebo. The median OS for olaparib was estimated at 34.9 (95 % CI 29.2, 54.6) months and 30.2 (23.1, 40.7) months for placebo. The estimated HR was 0.62 (0.42, 0.93) for olaparib compared to placebo in the *BRCA*mut population. Similarly, in the non-*BRCA*mut population the median OS for olaparib was estimated at 24.5 (19.8, 35.0) months and 26.6 (23.1, 32.5) for placebo and the estimated HR was 0.84 (0.57, 1.25). [11] After adjusting (using post-hoc OS analysis) for placebo patients in the *BRCA*mut group that received subsequent PARPi therapy via other study, the OS HR between olaparib and placebo was estimated at 0.49 (0.28, 0.85). [11]This post-hoc analysis simply excluded patients in Study 19 who received subsequent PARPi therapy. Such simple methods, unlike IPCW or RPSFT, can be highly prone to selection bias because switching is likely to be associated with prognosis.[12]

2.4 Objective

The objective was to conduct an MAIC using the NOVA and Study 19 clinical trial data.

3 Methods

3.1 Overview

To achieve the above objective, the following core analyses were implemented:

1. Adjust for between-trial differences in baseline characteristics between NOVA vs Study 19, using an MAIC[13]

2. Estimate the indirect relative treatment effect between treatments (after adjusting for trials' differences) using:
    a. Cox proportional hazard models
    b. Comparison of weighted KM curves

3.2 Study Settings

3.2.1 Study Design

This study was a post-hoc analysis of data from the NOVA (ClinicalTrial.gov number NCT01847274), a double-blind, randomized, phase 3 placebo-controlled (2:1 niraparib: placebo) study in patients categorized according to the presence or absence of a germline *BRCA* mutation (g*BRCA* mutated cohort and g*BRCA* non-mutated cohort). The study assessed the efficacy of niraparib as maintenance treatment, as measured by the primary end-point PFS.[1]

Eligible patients in the NOVA trial were at least 18 years of age and had histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with predominantly high-grade serous histologic features. Additionally, all patients had shown sensitivity to platinum-based treatment and had received at least two such regimens.[1]

Definitions of study end points used in the current analysis were consistent with those in the NOVA trial. The primary end point for this trial was PFS assessed by BICR (Blinded Independent Central Review), defined as the time from the date of treatment randomization to the earliest date of disease progression or death. The secondary outcomes considered in this analysis included OS. [1]

3.2.2 Data Source/Data Collection

All analyses were conducted using the full analysis set (FAS) for the NOVA study and digitized[a] individual patient-level data (IPD) from Study 19 provided by GSK for the comparison of niraparib and olaparib.

3.2.3 Study Population

The study population for the data analysis was the non-gBRCAmut 2L+ subgroup population of the relevant clinical trials.

3.2.4 Outcomes/Endpoints Variables

The endpoint of interest was OS. In line with the objective, analyses provided measures of relative treatment effect (i.e. weighted HRs and weighted KM curves), to estimate the indirect relative treatment effect of niraparib vs. placebo, after balancing for potential differences in baseline characteristics in NOVA vs Study 19.

3.2.5 Covariates/Control Variables

An MAIC analysis was conducted to balance the between trial differences in baseline characteristics that are known effect modifiers as well as relevant prognostic factors between NOVA and Study 19 trials. [16] The covariates of interest are presented in **Table 1** below.

[a] using the methods introduced by Guyot et al. (2012).14. Guyot P, Ades A, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC medical research methodology*. 2012;12(1):1-13.

Table 1. Characteristics of the Patients at Baseline in NOVA[1] and STUDY19[17]

	NOVA - Study Non-g*BRCA*mut 2L+		Study19 non-*BRCA*mut 2L+	
Characteristic	Niraparib	Placebo	Olaparib	Placebo
N patients	234	116	57	61
Age (median)	63	60.5	62	63
Ovary	82.05	82.76	87.72	80.33
Fallopian tube or primary peritoneal	17.95	16.38	12.28	19.67
Serous	91.02	93.10	NR	NR
Endometroid	0.43	0.86	NR	NR
Other	3.85	1.72	NR	NR
Missing	0	0	NR	NR
*BRCA*1	2.14	1.72	NR	NR
*BRCA*2	2.14	1.72	NR	NR
0	68.38	67.24	NR	NR
1	31.62	32.76	NR	NR
CR	50.00	51.72	35.08	40.98
PR	50.00	48.27	64.91	59.02
2	74.36	75.65	56.14	57.38
3	20.08	13.91	24.56	22.95
4	3.42	6.96	10.53	14.75
≥5	2.14	3.48	8.77	4.92
>6-12 months	38.46	37.93	40.35	39.34
≥12 months	61.54	62.07	59.65	60.65
Yes	26.49	25.86	NR	NR
No	73.50	74.14	NR	NR

CR: Complete Response; NR: Not reported; PR: Partial Response

3.2.6 Sample Size / Power Calculations

The sample size for all the analyses were based on the sample size of the relevant clinical trials.

Table 2. Studies' sample size.

Study	Treatment arm	Total patients – non-g*BRCA*mut 2L+
NOVA[1]	niraparib	234
	placebo	116
Study 19[17]	olaparib	57[$]
	placebo	61[$]

[$] authors noted that data was not available for all randomized patients.

As reported by Matulonis et al 2021, the NOVA study was not powered for OS. Additional power/sample size calculations or precision calculations were not performed for this MAIC.

3.3 Adjustment for baseline characteristics differences between trial: matching-adjusted indirect comparison (MAIC)

The premise of MAIC is to adjust for between-trial baseline characteristics differences. MAIC can be used to evaluate an "anchored" indirect comparison, where there is a common comparator arm in each trial, or an "unanchored" indirect comparison, where there is a disconnected treatment network or single-arm studies.[13] When a common treatment comparator or 'linked network' is available, only the "anchored" form of the MAIC should be used to perform indirect comparison, and all effect modifiers should be adjusted to ensure balance and reduce bias. In this analysis, we conducted an anchored indirect comparison using placebo as the common comparator arm across trials.

MAIC is a non-parametric likelihood reweighting method that allows a propensity score logistic regression model to be estimated without IPD in one of the treatment arms.[18]

3.3.1 Rationale for MAIC

An MAIC was conducted to adjust for between-trial differences in the baseline characteristics of NOVA vs. Study 19 to inform estimates of relative effectiveness of niraparib compared with placebo. Standard methods for an indirect treatment comparison (ITC) and network meta-analysis (NMA), proposed by Bucher et al.[19] and Dias et al.[20] are based on aggregate data. The key assumption behind these methods is that there is no difference between trials in the distribution of effect-modifying variables.

Given the observed differences in patient baseline characteristics in NOVA compared to Study 19 (see **Table 1**), it was deemed necessary to consider a population-adjusted method such as an MAIC to adjust for the differences in patients' baseline characteristic prior to comparing the relative efficacy of these maintenance treatments. When differences are observed between trials in patients' characteristics, it is important to first adjust for such differences in order to provide a fair comparison between of those trials. Please refer to the technical support document (TSD) 18 for the UK National Institute for Health and Care Excellence (NICE) for more extensive discussions on the rationale for MAIC.[13]

3.3.2 Outcomes analyzed for the MAIC

The MAIC was performed to adjust the OS curves in NOVA after balancing for differences in the patients' baseline characteristics in Study 19.

3.3.3 Analysis Dataset

To perform the MAIC, IPD from the NOVA trial as well as OS from the published KM curves from Study 19 were digitized. The corresponding IPDs were recreated using the methods introduced by Guyot et al. (2012).[14] The KM curves for OS in NOVA and Study 19 are shown in **Figure 1**. Individual data for patients treated with niraparib and placebo in the NOVA trial were assigned statistical weights that adjust for over- or under-representation relative to observed baseline values in Study 19. These MAIC weights were then incorporated in combination with the analyses for treatment switching adjustment for the placebo arm in NOVA. Please refer to section **3.3.4** for details on the weights.

Figure 1. Kaplan-Meier curves of OS for the non-g*BRCA*mut 2L+ population in NOVA and Study 19

3.3.4 Identification of Treatment Effect Modifiers

Two criteria were considered to identify treatment effect modifier variables to adjust for in the MAIC. The first criterion was based on GSK's clinical experts' opinion regarding baseline characteristics believed to be potential effect modifiers, i.e. covariates that can alter the effect of treatment on outcomes, so that the treatment is more or less effective in different subgroups formed by the levels of the effect modifier. Since the NOVA trial was to be adjusted to match the baseline characteristics of the Study 19 trial, where only aggregated data was available, the second criterion for selection was to consider only the effect modifiers available for the Study 19 trial **(Table 1).** For the NOVA vs Study 19 comparison, due to lack of available data for covariates reported in both NOVA and Study 19, only one set of covariates were considered that included all covariates that were reported in both NOVA and Study 19 **(Table 3)**. It is important not to overmatch by including irrelevant baseline characteristics variables as it would lead to inflating the standard-errors.[21]

Table 3. Matching covariates in the MAIC analysis of NOVA vs Study 19

Parameters	NOVA vs. Study 19
Primary tumor location	[redacted]
Histology	[redacted]
Response to previous platinum therapy	[redacted]

Parameters	NOVA vs. Study 19
Platinum free interval	[redacted]
Prior use of bevacizumab	[redacted]
g*BRCA*mut by Myriad testing	[redacted]
ECOG performance	[redacted]
Number of previous platinum regimens	[redacted]

Y= yes the covariate was included in that scenario; N= no the covariate wasn't included in that scenario

3.3.5 Estimation of Weights for the MAIC

To make an adjusted comparison between NOVA and Study 19, individuals in the NOVA study were assigned statistical weights that adjusted for their over- or under-representation relative to the treatment effect modifiers observed in Study 19. Following weighting, average baseline characteristics were then balanced for the niraparib-treated patients (in NOVA study) and the olaparib-treated patients (Study 19) as well as in the placebo arms in the two studies being compared. Weighting and balancing are described further below.

Weights were derived using an MAIC, a form of propensity score weighting. The propensity score logistic regression model estimated the odds of being enrolled into the NOVA or the Study 19 trial. In accordance with the NICE DSU guideline, a method of moments was used to allow a propensity score logistic regression model to be estimated, without patient-level data for the comparative evidence source(s), i.e. for olaparib (Study 19).[13] The model was estimated based on IPD available from the NOVA trial and published summary data available from the Study 19 trials.

Following estimation of the weights, it was necessary to explore their distribution. Re-scaled weights were explored via the use of histograms to determine whether specific patient(s) or groups of patients (based on covariate values) were over- or underrepresented in the analysis. The use of scaled weights aids with interpretation; a scaled weight of > 1 means that an individual carries more weight in the re-weighted sample than in the original sample, and a scaled weight of < 1 means that an individual carries less weight.

- Calculation of rescaled weights

$$Rescaled\ weight_i = \frac{weight_i}{\sum_{i=1}^{n} weight_i} \times N$$

Where N is the total number of patients in the NOVA trial, n is the number of patients in a treatment arm (e.g. in niraparib or placebo arm) and i is the i-th individual.

The robustness of the analyses was also considered by approximating the effective sample size (ESS). For a weighted estimate, the ESS is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate. A small ESS, relative to the original sample size, is an indication that the weights are highly variable due to a lack of population overlap, and that the estimate may be unstable and biased. It is therefore imperative that the ESS is calculated and reported so that the analysis results can be interpreted accordingly. [22]

- Calculation of the effective sample size

$$ESS = \frac{(\sum_{i=1}^{n} weight_i)^2}{\sum_{i=1}^{n} weight_i^2}$$

Where n is the number of patients in a treatment arm (e.g. in niraparib or placebo arm) and i is the i-th individual.

3.4 Estimation of the indirect relative treatment effect after conducting the MAIC analysis

After the matching procedure was conducted and the weights were derived, survival outcomes in NOVA and Study 19 were compared between balanced treatment groups using analyses that incorporated the derived weights. Specifically, two different approaches were used to estimate the indirect relative efficacy of treatments: (i) weighted HR; (ii) weighted KM curves.

3.5 Model Validation

Internal validity - quality control was maintained continuously throughout the project by working closely together with GSK. After the analyses were finalized, an independent reviewer checked the codes line by line for programming errors for the purposes of quality control.

4 MAIC Results

All the results presented here in the main report use the base case scenario (Table 3) for matching adjustment, and the OS outcomes for the NOVA and Study 19 trials.

4.1 Adjusting for trial between-trial differences in baseline characteristics using an MAIC: NOVA vs Study 19 – non-g*BRCA*mut 2L+

The estimated weights distribution in NOVA after matching the baseline characteristics of the non-g*BRCA*mut 2L+ subgroup patients in Study 19 are shown in **Figure** 2 and

Figure 3**.** The estimated ESS are given in Table 4 and shows that the baseline characteristics are balanced between the two studies after reweighting of NOVA.

Figure 2. Patients' weights distribution in niraparib – non-g*BRCA*mut 2L+

Figure 3. Patients' weights distribution in placebo NOVA – non-g*BRCA*mut 2L+

Table 4. Estimated effective sample size in reweighted NOVA-non-g*BRCA*mut 2L+

Treatment arm	Original sample	ESS
Niraparib	234	[redacted]
Placebo	116	[redacted]

ESS= effective sample size

Table 5. Balanced baseline characteristics between NOVA and Study 19 after NOVA reweighting

Parameters	Niraparib before reweighting	NOVA-placebo before reweighting	Niraparib after reweighting	NOVA-placebo after reweighting	Olaparib	Study 19-placebo
Primary tumor location (ovary) %	82.05	82.76	[redacted]	[redacted]	87.72	80.33
Response to previous platinum therapy (CR), %	50.00	51.72	[redacted]	[redacted]	35.08	40.98
Platinum free interval (>6-12mo), %	38.46	37.93	[redacted]	[redacted]	40.35	39.34
Number of prior platinum (2), %	74.36	75.65	[redacted]	[redacted]	56.14	57.38

4.2 Matching adjusted indirect relative efficacy

4.2.1 Hazard ratios (HRs) estimates - NOVA vs Study 19: non-g*BRCA*-mut 2L+ population

In the non-g*BRCA*mut 2L+ subgroup, we estimated an HR of [redacted] for niraparib vs. placebo using the re-weighted NOVA trial. Similarly, an HR of [redacted] was estimated between olaparib and placebo in Study 19. The estimated HRs for the NOVA vs Study 19 comparison in the non-g*BRCA*mut 2L+ are presented in **Table 6.**

Table 6. HRs comparison in NOVA and Study 19 –OS outcomes-non-g*BRCA*mut 2L+

Treatment comparison	HR (95% CI) estimates
Niraparib vs placebo before MAIC	[redacted]
Niraparib vs placebo after MAIC	[redacted]
Olaparib vs placebo	[redacted]

Figure 4Error! Reference source not found. Error! Reference source not found. shows the OS KM curves for niraparib and placebo before and after the MAIC adjustment in the non-g*BRCA*mut 2L+ group, along with the Study 19 KM curves.

Figure 4: KM curves before and after MAIC adjustment for non-g*BRCA*mut 2L+

5 Discussions

An MAIC was conducted to adjust for between-trial differences in the baseline characteristics of NOVA vs. Study 19 to inform estimates of relative effectiveness of niraparib compared with placebo. Standard methods for ITC such as the Bucher method and the NMA rely on the key assumption that there is no difference between the compared trials in the distribution of their effect-modifying variables. Close assessment of the reported patients' baseline characteristics in NOVA and Study 19 revealed that there are subtle differences **(Table 1)** between the patient populations that would be important to control for when comparing NOVA to Study 19. Therefore, a population-adjusted method such as MAIC was considered to compare NOVA to Study 19.

The anchored version of the MAIC was performed where the placebo arm in each comparator trial served as the 'linked network'. Once the baseline characteristics were balanced between NOVA and Study 19 via the MAIC, the adjusted NOVA (i.e NOVA using the weights generated from the MAIC) was compared to Study 19 using weighted statistical analyses. More specifically, the relative indirect efficacy of treatments using: (i) a weighted HRs; (ii) weighted KM curves.

Limitations

It is important to acknowledge the limitations of the analyses. First, regarding the MAIC, as with any ITC, differences in the methodology for trial's analysis, outcome measurement and populations of the included trials must be carefully considered. MAICs are not randomized comparisons and cannot be interpreted as such. They are essentially observational findings across trials and may suffer from biases inherent in observational studies (for example confounding). Beside the methodological limitations, it should be noted that the extent of the missingness in NOVA prevents robust analysis being conducted to adjust for the crossover of patients treated with placebo to subsequent PARPi therapy.

Conclusion

An MAIC was conducted to adjust for potential differences in baseline characteristics, between the NOVA and Study 19 trials for non-g*BRCA*mut 2L+. MAIC results suggested that there is [redacted] following this adjustment.

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Appendix 3. Extrapolated trial data MAIC-adjusted NOVA/Study 19

1. Parametric curve selection in the non-gBRCAmut 2L+ population

Niraparib overall survival (OS) data from ENGOT-OV16/NOVA (data cut off [DCO] October 2020) was adjusted to the population of Study 19 using a matching-adjusted indirect comparison (MAIC). Please refer to Appendix 2 for details regarding the methodology and analyses performed.

Table 1 summarises the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) scores for each survival distribution when fitted to the MAIC-adjusted niraparib OS data from ENGOT-OV16/NOVA and the routine surveillance OS data from Study 19. The Kaplan-Meier and parametric distributions for niraparib and routine surveillance are presented in Figure 1 and Figure 2.

The lognormal curve was considered the most plausible curve based on statistical and visual fit. The statistical goodness of fit measures in Table 1 shows that the lognormal distribution was best fit for niraparib and routine surveillance. Upon visual inspection of Figure 1 and Figure 2, it can be observed that the lognormal distribution fits the data reasonably well.

OS curves using the lognormal distribution for niraparib and routine surveillance are presented in Figure 3. Using the lognormal distribution, niraparib and routine surveillance mean OS was calculated as the area under the curve (AUC) using the trapezium rule as [redacted] and [redacted] years, respectively, and [redacted] and [redacted] years after applying discounting. Niraparib mean OS has increased compared to the unadjusted niraparib OS data ([redacted] or [redacted] years after applying discounting).

Table 1: Goodness of fit statistics for the non-gBRCAmut 2L+ niraparib MAIC-adjusted (Study 19) OS parametric distributions, ENGOT-OV16/NOVA (DCO October 2020) and routine surveillance (RS) OS, Study 19 (DCO May 2016)

OS[1,2]				
Curve	**Niraparib**		**RS**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	524.33	526.45
Weibull	[redacted]	[redacted]	511.25	515.47
Gompertz	[redacted]	[redacted]	520.18	524.40
Log-logistic	[redacted]	[redacted]	503.48	507.70
Lognormal	[redacted]	[redacted]	**503.04**	**507.26**
Generalised gamma	[redacted]	[redacted]	504.89	511.23

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; gBRCAmut, Germline breast cancer susceptibility gene mutation; TTD, time to treatment discontinuation. Lower AIC/BIC indicates better fit. **Best fitting curve.**

Figure 1: Kaplan-Meier and parametric distributions for niraparib OS adjusted to the population of Study 19 using a MAIC OS for non-gBRCAmut 2L+, ENGOT-OV16/NOVA DCO October 2020

Abbreviations: DCO, data cut-off; gBRCAmut, Germline breast cancer susceptibility gene mutation; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival

Figure 2: Kaplan-Meier and parametric distributions for routine surveillance OS for non-gBRCAmut 2L+, Study 19 (BRCAwt, final DCO May 2016)

Abbreviations: DCO, data cut-off; BRCAwt, wild type breast cancer susceptibility gene; KM, Kaplan-Meier; OS, overall survival

Figure 3: Kaplan-Meier and lognormal distribution for niraparib (ENGOT-OV16/NOVA DCO October 2020, adjusted to the population of Study 19 using a MAIC), and routine surveillance OS (Study 19 DCO May 2016) for non-g*BRCA*mut 2L+

Abbreviations: DCO, data cut-off; gBRCA, germline breast cancer susceptibility gene mutation; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival.

A.1. Results

The Company base case has been updated since the Appraisal Consultation Document (ACD) to reflect the MAIC analysis results for the non-g*BRCA*mut 2L+ population, using MAIC-adjusted niraparib OS from ENGOT-OV16/NOVA (DCO: October 2020) and routine surveillance OS from Study 19; the revised base case results are presented in Table 2. Niraparib was associated with [redacted] incremental QALYs, and £[redacted] incremental costs per patient, compared with routine surveillance. The corresponding ICER was £37,273 per QALY gained, which is lower than the ICER estimated using the unadjusted niraparib OS data from ENGOT-OV16/NOVA due to an increase in mean survival following adjustment to the Study 19 population.

Table 2: Revised Company base case results (updated following ACD) using extrapolated OS trial data – NOVA (MAIC-adjusted)/Study 19 of niraparib versus routine surveillance for non-gBRCAmut 2L+

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline (QALYs)
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**37,273**

Abbreviations: ACD, appraisal consultation document; gBRCA, germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; LYG, life years gained; MAIC, matching-adjusted indirect comparison; QALY, quality-adjusted life year.

Appendix 4. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (CDF review TA528) [ID1644]

Analysis of health state utility values from the NOVA clinical trial

Prepared in response to NICE technical engagement, August 2021

Health-related quality of life data (EQ-5D-5L) were collected as part of the NOVA clinical trial (data cut-off October 2020); EQ-5D-5L data were mapped to the UK EQ-5D-3L valuation set using the 'cross-walk' algorithm published by van Hout et al which used a UK tariff developed from a UK general population, and mean utility scores were obtained.[1] Statistical tests were conducted to assess the statistical difference in the mean utility score of patients in each treatment arm (niraparib and routine surveillance [RS]) and health state (progression-free disease [PFD] and progressed disease [PD]).

A linear mixed-effect model is considered the most appropriate model to test for a statistically significant difference between treatment- and health state-specific utility scores as the model allows for repeated measures and does not assume normality. A linear mixed-effect model was developed in R using the 'lme4' and tested using the 'stats' package, and the methods were validated with an external statistics expert; the model was developed using treatment and health state as independent variables and patient ID as a random effect.[2,3] The model suggests a statistically significant difference between treatment arms (niraparib and RS) and health state (PFD and PD) with p-values of [redacted] and <[redacted], respectively, providing statistical evidence to support the use of treatment-specific utility values for each health state; the statistical difference between treatment arms is maintained after controlling for health state. The results are presented in Table 1.

Results from the linear mixed-effect model are supported by an additional analysis using a two-way repeated measures ANOVA model. A two-way repeated measures ANOVA model is used as the data is assumed to be normally distributed based on the sample size (>30) using the central limit theorem, accepting the known limitations of this assumption.[4] The two-way repeated measures ANOVA model was developed using treatment and health state as independent variables; both variables were statistically significant in the model with p-values of [redacted] and [redacted] for treatment and health states, respectively. The results are presented in Table 2.

In addition to the statistically significant difference between the treatment arms after controlling for health state, the clinical evidence presented in the NICE technical engagement response form explains that using treatment-specific utilities captures the quality-of-life benefit of niraparib as an active treatment compared to RS. Patients treated with niraparib have a higher quality of life whilst progression-free compared to patients who receive RS due to lowering symptoms associated with disease and prior chemotherapy such as pain levels.[5]

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*.".[6]

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 as part of the NOVA trial, even without capturing this additional benefit, show a numerical difference between niraparib and placebo reported utilities. Patients value maintenance 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*."[7] 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. The use of pooled utility data across treatment arms is not advisable when granular treatment-specific utility data are available and can provide a more accurate representation of the quality-of-life impact. Based upon the clinical and statistical evidence, utility values as reported by niraparib and placebo patients within the NOVA trial should be implemented in the economic model for each health state.

Table 1: Linear mixed-effects model results

Model Description	p-value (* = p-value <0.05)
Treatment and health state as fixed effects and patient ID as a random effect	Treatment = [redacted] * Health state = <[redacted]*

Abbreviations: ID – identification number

Table 2: Two-way repeated measures ANOVA model results

Model Description	p-value (* = p-value <0.05)
Treatment and health state as fixed effects and patient ID as a random effect	Treatment = [redacted]* Health state = [redacted]*

Abbreviations: ID – identification number

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Appendix 5. IA PFS, ENGOT-OV16/NOVA (DCO October 2020)

A.1. Introduction

The Company base case uses independent review committee (IRC) assessed progression-free survival data (PFS) collected from the NOVA trial (data cut off [DCO] June 2016); this was the primary endpoint of the NOVA trial and was met at the DCO June 2016, therefore no additional data has been collected. In response to the Committee's request in Section 3.2 of the Appraisal Committee Document (ACD), the economic model has been updated to include the investigator assessed (IA) PFS coefficients following independent parametric analysis for the non-g*BRCA*mut 2L+ population (DCO October 2020).[1] The Committee concluded that "because hazards were similar regardless of who assessed [PFS], the method of assessment was unlikely to be critical to decision making".[1] The Committee notes that "the clinical expert and Cancer Drugs Fund clinical lead cautioned focusing only on the median results and explained that the hazard ratios of both IA and IRC assessed progression-free survival were similar".

The inclusion of IA PFS as a scenario analysis has been included to reduce uncertainty in the IRC PFS estimates from the economic model, as requested by the Committee in Sections 3.2 and 3.19 of the ACD. However, the Company maintain that IRC PFS is the most appropriate for use within the economic modelling. As discussed as part of the technical engagement, there are 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 in NOVA as a sensitivity analysis to ensure robustness of the PFS 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. 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.

A.2. Curve selection

IA PFS Kaplan-Meier (KM) data for niraparib and routine surveillance are presented in Figure 1 for non-g*BRCA*mut 2L+.

Figure 1: Niraparib and routine surveillance investigator assessed (IA) PFS Kaplan-Meier curve for non-g*BRCA*mut 2L+. NOVA (DCO October 2020)

Abbreviations: DCO, data cut-off; g*BRCA*, germline breast cancer susceptibility gene; KM, Kaplan-Meier; IA, investigator-assessed; PFS, progression-free survival; RS, routine surveillance

Table 1 summarises the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) scores for each independent parametric survival distribution. The KM and independent parametric distributions for niraparib and routine surveillance are presented in Figure 2 and Figure 3, respectively. Table 2 details the proportion of patients who are progression-free at key timepoints for all six standard parametric curves.

The statistical goodness of fit measures in Table 1 suggest that the generalised gamma curve is the best statistical fit to the observed IA PFS data for niraparib and routine surveillance, as it has the lowest AIC and BIC scores, and the log-logistic is the second-best

statistical fit to the observed IA PFS data. The log-logistic and generalised gamma distributions were selected as the most appropriate distribution for scenario analysis based on statistical fit, clinical plausibility and visual fit.

The log-logistic IA PFS curve is more conservative in its estimates of niraparib patients who are progression-free at 5 years ([redacted]%) compared to the generalised gamma estimates ([redacted]%) and the Evidence Review Group's (ERG's) preferred hazards k=1 curve ([redacted]%) for IRC PFS. The longer term, 20-year estimates of the log-logistic IA PFS curve ([redacted]%) are closer to the ERG's preferred hazards k=1 IRC PFS curve ([redacted]%) compared to the generalised gamma IA PFS curve ([redacted]%). Therefore, the log-logistic curve has a more conservative 20-year estimate ([redacted]%) compared to the generalised gamma ([redacted]%) and is in line with the ERG's preferred IRC PFS base case.

As stated in the Terms of Engagement, the ERG thought it "clinically implausible" that patients would be alive, without progression, at 10 years.[2] Therefore, the proportion of niraparib patients who are progression free at 10 years ([redacted]%) using the log-logistic IA PFS curve is deemed clinically plausible and sufficiently conservative compared to the generalised gamma curve ([redacted]%). In addition, using the log-logistic PFS IA curve, [redacted]% are modelled as progression-free at 20 years, such that the cap applied at 20 years in the model is only applied to a very limited proportion of patients. Using the generalised gamma IA PFS curve, at 20 years, [redacted]% are modelled as progression-free and capped within the model.

The proportion of patients treated with placebo who remain progression-free, per IA, at 1-year using the log-logistic distribution ([redacted]%) is considered clinically plausible in comparison to the 1-year estimates for placebo from Study 19 for *BRCA*wt patients (13%).[3] The log-logistic 1-year IA progression-free estimate ([redacted]%) was more conservative compared to the generalised gamma ([redacted]%).

The log-logistic IA PFS curve has a reasonably good visual fit to the observed KM data between 0 and 24 months. The log-logistic curve IA PFS curve has a poorer visual fit to the KM data from the 24-month time point. Between years 1 and 3, the generalised gamma IA PFS curve deviates from the observed KM data and overestimates the proportion of patients who remain progression-free compared to the observed KM curve and the log-logistic curve, shown in Figure 2 and Figure 3, particularly for the niraparib distributions. The generalised gamma IA PFS curve has a good visual fit to the KM data beyond 36 months. The routine surveillance KM curve, presented in Figure 1, details the number of patients at risk over the observed follow-up period; the numbers at risk over time shows that a very small number of patients remain progression free between 18 months and 42 months ([redacted] patients [[redacted]%]

and [redacted] patients [redacted%], respectively). This is also seen in the niraparib KM curve between 18 months and 42 months ([redacted] patients [redacted%] and [redacted] patients [redacted%], respectively). The small number of patients at risk who remain progression-free drives the extended, plateaued KM curve which is not considered to be reflective of clinical practice. As such, while the long, fat tail of the generalised gamma curve may align more closely with the tail of the KM curve, it is unlikely to be reflective of the cohort of non-g*BRCA*mut 2L+ patients treated in clinical practice. Therefore, upon visual inspection of the parametric curves against the KM curve, both the log-logistic and generalised gamma curve have imperfect fit for the niraparib and routine surveillance IA PFS data.

The proportion of patients estimated to be progression-free, per IA, after 20 years using the log-logistic distribution is [redacted]% of niraparib patients and [redacted]% of routine surveillance patients. Applying a 20-year cap (patients could not be progression-free after 20 years) and ensuring PFS is less than OS for niraparib and routine surveillance (

Figure 4), niraparib and routine surveillance mean PFS was calculated as the AUC using the trapezium rule as [redacted] and [redacted] years, respectively. After discounting these equate to [redacted] years and [redacted] years, respectively.

The proportion of patients estimated to be progression-free, per IA, after 20 years using the generalised gamma distribution is [redacted]% of niraparib patients and [redacted]% of routine surveillance patients. Applying a 20-year cap (patients could not be progression-free after 20 years) and ensuring PFS is less than OS for niraparib and routine surveillance (Figure 5), Niraparib and routine surveillance mean PFS was calculated as the AUC using the trapezium rule as [redacted] and [redacted] years, respectively. After discounting these equate to [redacted] years and [redacted] years, respectively.

PFS IA is capped by OS and time to treatment discontinuation (TTD) in the presented scenario analyses, as per the company base-case, and in line with the ERG suggestion in Clarification Question B7.

Table 1: Goodness of fit statistics for the non-g*BRCA*mut 2L+ niraparib and routine surveillance IA PFS parametric distributions, ENGOT-OV16/NOVA (DCO October 2020)

Curve	Niraparib		Routine surveillance	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion; DCO – data cut off; gBRCA – germline breast cancer susceptibility gene; IA – investigator assessed; PFS – progression-free survival. **Selected curves.**

Table 2: Proportion surviving and progression-free (investigator assessed) at key time points for the parametric models for niraparib and routine surveillance non-g*BRCA*mut 2L+, NOVA (DCO October 2020)

Year	Exponential	Weibull	Gompertz	Log-logistic	Lognormal	Generalised gamma
Niraparib						
5	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
10	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
15	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
20	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Routine surveillance						
1	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
20	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DCO – data cut off; gBRCA – germline breast cancer susceptibility gene. **Selected curves.**

Figure 2: Kaplan-Meier and parametric distributions for niraparib IA PFS non-g*BRCA*mut 2L+, ENGOT-OV16/NOVA (DCO October 2020)

Abbreviations: DCO, data cut-off; g*BRCA*, germline breast cancer susceptibility gene; KM, Kaplan-Meier; IA, investigator-assessed; PFS, progression-free survival

Figure 3: Kaplan-Meier and parametric distributions for routine surveillance IA PFS non-g*BRCA*mut 2L+, ENGOT-OV16/NOVA (DCO October 2020)

Abbreviations: g*BRCA*, germline breast cancer susceptibility gene; DCO, data cut-off; IA, investigator-assessed; KM, Kaplan-Meier.

Figure 4: Kaplan-Meier and log-logistic distribution for niraparib and routine surveillance IA PFS with a 20-year cap applied and ensuring that PFS is less than OS in the non-g*BRCA*mut 2L+ population, ENGOT-OV16/NOVA (DCO October 2020)

Abbreviations: g*BRCA*, germline breast cancer susceptibility gene; DCO, data cut-off; IA, investigator-assessed; KM, Kaplan-Meier; OS, overall survival.

Figure 5. Kaplan-Meier and generalised gamma distribution for niraparib and routine surveillance IA PFS with a 20-year cap applied and ensuring that PFS is less than OS in the non-g*BRCA*mut 2L+ population, ENGOT-OV16/NOVA (DCO October 2020)

A.3. Scenario analysis results using IA PFS

A.3.1. IA PFS scenario analysis using previous company ACM base-case

Previous company base-case deterministic results using the extrapolated trial data (NOVA/Study 19) of niraparib versus routine surveillance for non-g*BRCA*mut 2L+ and IA PFS (NOVA [DCO October 2020]) are presented in Table 3. A scenario analysis using the extrapolated IA PFS data, using the log-logistic curve (NOVA niraparib and placebo IA PFS), and the extrapolated OS trial data (NOVA niraparib OS and Study 19 placebo OS) of niraparib versus routine surveillance for non-g*BRCA*mut 2L+, generates an ICER of £37,035 per QALY gained; this is less than the previous Company base case ICER of £39,608 per QALY gained using IRC PFS. A similar scenario analysis, using extrapolated IA PFS data using the generalised gamma curve, generates an ICER of £39,527 per QALY gained; this is in line with the previous Company base case ICER of £39,608 per QALY gained using IRC PFS. The mid-point of these two ICERs is £38,281; this mid-point ICER provides insight into the cost-effectiveness we may expect to achieve when estimating the true IA PFS curve, which is expected to lie somewhere between the conservative (log-logistic) and optimistic (generalised gamma) IA PFS curves.

Table 3: A.3.1. IA PFS scenario analysis using previous company ACM base-case deterministic results of niraparib versus routine surveillance for non-g*BRCA*mut 2L+

Technologies		Total			Incremental			ICER (£)
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline (QALYs)
Log-logistic curve	RS	[redacted]	[redacted]	[redacted]	-	-	-	-
	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,035
Generalised gamma curve	RS	[redacted]	[redacted]	[redacted]	-	-	-	-
	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	39,527
Mid-point ICER								38,281

Abbreviations: ACM, appraisal committee meeting; g*BRCA*, germline breast cancer susceptibility gene mutation; IA, investigator assessed; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PFS, progression-free survival; QALY, quality-adjusted life year; RS: routine surveillance

A.3.2. IA PFS scenario analysis using updated company base-case

Updated company base-case deterministic results using the extrapolated trial data (NOVA [MAIC-adjusted]/Study 19) of niraparib versus routine surveillance for non-g*BRCA*mut 2L+ and IA PFS (NOVA [DCO October 2020]) are presented in Table 4.

A scenario analysis using extrapolated IA PFS data, using the log-logistic curve (NOVA niraparib and placebo IA PFS), and extrapolated OS trial data (NOVA MAIC-adjusted niraparib OS and Study 19 placebo OS) of niraparib versus routine surveillance for non-g*BRCA*mut 2L+, generates an ICER of £34,777 per QALY gained; this is less than the updated Company base case ICER of £37,273 per QALY gained using IRC PFS (presented in Comment 2 of the ACD stakeholder comments form). A similar scenario analysis, using extrapolated IA PFS data using the generalised gamma curve, generates an ICER of £37,169 per QALY gained; this is in line with the updated Company base case ICER of £37,273 per QALY gained using IRC PFS (presented in Comment 2 of the ACD stakeholder comments form). The mid-point of these two ICERs is £35,973; this mid-point ICER provides insight into the cost-effectiveness we may expect to achieve when estimating the true IA PFS curve, which is expected to lie somewhere between the conservative (log-logistic) and optimistic (generalised gamma) IA PFS curves. The Company believe that the scenario analyses presented using IA PFS, which demonstrate equal or improved cost effectiveness compared with the Company base case, reduce the Committee's uncertainty in the assessment method of progression and, as such, reduce uncertainly in the PFS extrapolations that form the Company base case.

Table 4: A.3.2. IA PFS scenario analysis using updated company base-case deterministic results of niraparib versus routine surveillance for non-g*BRCA*mut 2L+

Technologies		Total			Incremental			ICER (£)
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline (QALYs)
Log-logistic curve	RS	[redacted]	[redacted]	[redacted]	-	-	-	-
	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	34,777
Generalised gamma curve	RS	[redacted]	[redacted]	[redacted]	-	-	-	-
	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,169
Mid-point ICER								**35,973**

Abbreviations: g*BRCA*, germline breast cancer susceptibility gene mutation; IA, investigator assessed; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PFS, progression-free survival; QALY, quality-adjusted life year; RS: routine surveillance

A.4. References

1. NICE. Appraisal consultation document (ACD) Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer. 2021. at <https://www.nice.org.uk/guidance/gid-ta10782/documents/129-2>
2. NICE. TA528 Niraparib CDF review. Terms of Engagement v1.0. 2021.

3. Ledermann JA, Harter P, Gourley C, *et al.* Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. *The Lancet Oncology* 2016. 17: 1579–1589.

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

Consultation on the appraisal consultation document – deadline for comments 5pm on **Friday 17 September 2021** Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]
Comment	**Comments**

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number	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
General	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to comment as follows.
1	We strongly support NICE approval of niraparib as a potential treatment option for women with relapsed ovarian/fallopian tube and primary peritoneal cancer irrespective of BRCA status. Our experts have answered the consultation questions as follows: 1. Has all of the relevant evidence been taken into account? 2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? 3. Are the recommendations sound and a suitable basis for guidance to the NHS? 4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? **Response to questions 1, 2 and 3** We do not support the proposed amendment currently under consideration (ID1644). We would like to draw attention to the initial results from the NOVA trial, which clearly demonstrated that niraparib maintenance therapy significantly improved progression free survival (PFS) in all patients with platinum-sensitive relapsed ovarian cancer independent of germline BRCA status (estimated median PFS of 11.3 months for all patients randomized to the niraparib arm and 4.7 months for placebo, HR, 0.42; 95% CI, 0.34–0.53). 1 There was a differential magnitude of benefit based on BRCA status (21 m vs 5.5 m (HR 0.27) in germline BRCAm (gBRCAm) patients compared to 9.3 mo vs 3.9 mo (HR 0.45) in non-gBRCAm patients). Although the NOVA study results demonstrated a more robust benefit for patients carrying a gBRCA mutation, there is evidence that patients without a gBRCA mutation also benefit from therapy with niraparib. This is likely because, although BRCA mutations account for the most common deficit in the HRD pathway, aberrations in other homologous recombination (HR) genes also result in sensitivity to niraparib. Despite the increasing use of homologous recombination deficiency (HRD) testing there remain concerns about the accuracy with which these tests distinguish the specific patients in the non-gBRCAm group who benefit from niraparib compared with those who do not. This guidance if implemented in the NHS will therefore result in women who are not carriers of a BRCAm being denied a potentially effective treatment. The long-term results of NOVA presented in 2020 demonstrated that the benefit of maintenance niraparib extended beyond first progression in both cohorts, HR 0.81 (95% CI 0.632–1.050) in non-gBRCAm patients and HR 0.67 (95% CI 0.479–0.948) in gBRCAm patients. There was no observed difference in OS with niraparib in either cohort, although there was a trend to increased survival in

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	gBRCAm with an improvement in niraparib arm of 9.7 mo. However, it is important to note that NOVA was not powered for overall survival (OS) and the results were confounded by cross-over and missing data: 533 patients enrolled, 28% discontinued from study and data were not available for 25%. Although cross-over was not permitted in the study, due to the availability of PARPi, 46% gBRCAm and 13% non-gBRCAm patients in the placebo group received subsequent PARPi, which further impacted the OS read out. The long-term safety analysis also confirmed that niraparib was an effective and well-tolerated maintenance treatment for patients with relapsed OC independent of BRCA status. Our experts strongly argue in favour of including niraparib for patients, irrespective of BRCA status as delaying progression and extending time to subsequent chemotherapy is a clinically valuable endpoint in itself for patients (21 m vs 5.5 m (HR 0.27) in gBRCAm patients. 9.3 m vs 3.9 m (HR 0.45) in non-gBRCAm patients). A significant concern is the cumulative toxicity of chemotherapy and the development of platinum resistance as this is associated with low response rates to subsequent chemotherapy and poorer survival. Therefore, increasing the progression free interval with maintenance niraparib has significant merit for patients. The lack of a confirmed OS benefit with niraparib, particularly in the BRCAwt group, should be discussed with patients in relation to the benefits in PFS. However overall, the consensus agreement among international clinical experts is that PARPi should still be offered to patients who have not received a first-line PARPi. **Response to Question 4** We can identify no further that require consideration with respect to unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? References 1. Matulonis UA, et al. Long-term safety and secondary efficacy endpoints in the ENGOT-OV16/NOVA phase III trial of niraparib in recurrent ovarian cancer. Presented at: Society of Gynecologic Oncology 2021 Virtual Annual Meeting on Women's Cancer; 19–25 March 2021. 2. Mirza MR, et al. N Engl J Med 2016;375:2154–64.

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Ovacome Ovarian Cancer Support Charity**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**N/A**]
Name of commentator person completing form:	■
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number	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are concerned that this recommendation limits choice and leads to inequities for patients with relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer who are BRCA negative.
2	Those with a cancer diagnosis are protected under the Equalities Act 2010 and reducing the choice of PARPi technology for relapsed ovarian cancer could have a significant impact on this vulnerable group with incurable disease.
3	Currently the choice of PARPi technology available means that if one drug is unsuitable due to drug interactions or adverse side effects, there is another to try.
4	It is vital that those with incurable disease are given wide access to available technologies and the best opportunity to delay recurrence and further chemotherapy treatments.
5	**Seven** members of our community who are BRCA negative and being treated with niraparib for a recurrence have explained their experience and concerns regarding the preliminary decision: "In February 2019 I began taking Niraparib 3 tablets a day. In this time my scans have shown less and now no disease and my CA125 is now 12. I am in my third year with no side effects. I am thriving on this drug and hope to continue to do so. I can not believe this lifeline could be removed because I do not have a DNA related additional illness."
6	"My oncologist in December (2020) said I would be eligible for niraparib. This was such a relief. The only alternative would have been chemo when the tumours grew again, which I know they would at some point. But niraparib gives me hope to have more time to continue to enjoy life. As my oncologist pointed out, more chemo is an option but the gaps between chemo will get shorter and less effective. Niraparib has given me hope. […] I am on my second round of niraparib now and have minimal side effects. […] I dare not think about how long Niraparib will work but it has given me an alternative to just waiting to have more chemo, knowing that eventually chemo will stop working."
7	"Nov 2019 my scan showed it was back near my liver. More surgery followed by 6 more cycles chemo then Niraparib. Luckily Niraparib appears to be working for me (so far). I feel sad to think this may not be an option for others in the future."
8	"In May 2019, I was allowed to commence Niraparib […] Since then I have had 3 monthly CT scans. My Prognostic Indicator, at that time, was classed at Stage B, i.e. Unstable/Advanced disease with prognosis in months! […] I have had no problems at all [since lowering dosage], my CA125 remains stable at 7, and my latest CT scan, in April this year (2021), was clear - even the remaining 'spotting' had disappeared! […] When I was first diagnosed, my husband and I thought we had very little time left together. However, Niraparib has already given us time to move to a smaller, more manageable house and garden, close to our family, and amenities. I feel well and energetic, and prior to Covid 19, we entertained friends and family, and I have been delighted to be able to help out with childcare. We have also had several short breaks and camping holidays. 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. However, I also feel incredibly sad that women like me (& especially those with young families) will no longer qualify to have this treatment, which has

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	the possibility of extending their lives for years."
9	"I was diagnosed in March 2016; usual frontline treatment and surgery. Recurred in 2017, further surgery and chemo. Commenced on Niraparib in June 2018 and still on it. Usual side effects, insomnia etc. My latest scan in late August (2021) was clear, I am BRCA negative. Do not know my HRD status and do not much care, treatment would be the same I am sure. It is working for me so far and well worth the side effects which do lessen over time."
10	"I am BRCA negative, without the HRD deficiency and have been on niraparib 200 mg since late April (2021). Doing ok so far on this dose. I have had 2 recurrences to date. I feel well, constipation is my main issue but manageable. I can get out and about - walk 5k each day, appetite ok, a bit of nausea at the start but that has settled. I am grateful to be offered this drug."
11	"I feel lucky as I started Niraparib in August (2021), BRCA negative - at least if it does not work for me I know everything possible has been tried."
12	A member of our community who is BRCA negative and on chemotherapy for a recurrence explained their concerns about the preliminary decision: "This is a kick in the teeth! I'm currently on chemotherapy for recurrence and was told Niraparib would be the best maintenance for me going forward. This was a relief when I heard it. I am BRCA negative, high grade serous stage 4. Yes, I am concerned, worried and annoyed, alongside the usual worries and concerns whilst on chemotherapy treatment. We are all doing everything to stay alive."

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Target Ovarian Cancer
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]
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number	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The current recommendation does not consider the paucity of treatment options for relapsed ovarian cancer and the importance of progression free survival for those patients. Current 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 restriction of niraparib to the BRCA positive population will have a negative impact on progression free survival for those without a BRCA mutation.
2	We are concerned that this recommendation will lead to inequality for women without a BRCA mutation. The current recommendation means that for 80 per cent of women with ovarian cancer there will be no access to a maintenance PARP inhibitor from the second line of treatment. There are other options from the second line and the first line of treatment, but all of these are available in the Cancer Drugs Fund not routine commissioning. Accessing niraparib from the second line of treatment offers women without a BRCA mutation valuable progression free survival, increasing their quality of life. A period of progression free survival is vital for: • Delaying the next round of chemotherapy, which increases the chances of responding to platinum meaning women can access treatment for longer. • A longer gap between chemotherapy, allowing women to recover and rebuild their strength in preparation for the next round of chemotherapy. • Increasing the quality of life. Niraparib is taken in tablet form at home without the disruption of chemotherapy. For many women, receiving the news that their cancer has returned can be more devastating than the initial ovarian cancer diagnosis. Improvement in progression free survival gives 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. We recently asked women without a BRCA mutation who had taken niraparib from the second line what it meant to them: *'My life is not defined by good weeks and bad weeks and so far my life has not been disrupted by treatment delays. This allows me to plan time with my family which is a vital investment to prepare them for the future when I have a poor long-term prognosis'* *'I am BRCA negative and have been taking Niraparib for 2 years this month, I took it following chemotherapy for a recurrence in 2019. The cancer responded well to the chemotherapy, and I was given it as a maintenance drug, I had a scan in June 2021 and there was no evidence of disease at*

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	all, I was thrilled.' *'I felt like I had a future again, when I was first diagnosed and treated the "watch and wait for it to come back" was soul destroying. That there was a drug suitable for me gave me hope for the future. I am a young lady still working and healthy in every other way. I felt privileged, nothing is ever guaranteed but this drug seemed like my best option, and I have been doing well for two years now.'* *'My cancer came back in Summer 2020, and I completed second line chemo in March 2021, and I am now on month 7 on Niraparib and my recent scans show that while I have residual disease following treatment, that remains stable.'*
3	The recommendation does not seem to consider the rapidly changing environment around genomic testing. Since April 2021 HRD testing has been made available for women who are newly diagnosed meaning that there may be women who miss out on maintenance access from the first line (currently available on the Cancer Drugs Fund) but will know they are positive for HRD but BRCA negative. This group may well respond very well to PARP inhibitors but under the current recommendation would not be able to access them.
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Note: We reserve the right to summarise and edit comments received during consultations, or

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not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	**Professor Jonathan A Ledermann BSc MD FRCP FMedSci**
Comment	**Comments**

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number	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Recommendation: I disagree with the conclusion of restricting to BRCA mutated tumours. This will be elaborated in subsequent sections. The great need for improvement in outcome is acknowledged in the ACD and there is good evidence to support that niraparib extends progression free survival. Furthermore, the overall survival in the non gBRCA cohort – both arms - is far superior to historic good quality trial data before the era of PARP inhibitors. Removing the possibility of PARP maintenance in this population will significantly affect survival of patients in England, there being no prospect of any maintenance therapy with PARP inhibitor or bevacizumab. Details to follow below.
2	Why committee made these recommendations: Para 4. 1st sentence is unclear
3	3.2 Bullet 1: A highly significant clinical benefit exists in the non-gBRCA group. It is important to remember that all platinum-combination chemotherapy studies in the last 15 years have produced a median PFS beyond the end of chemotherapy of around 5-6 months. This fits in well with the control arm PFS in NOVA. Thus, the PFS almost doubles the median time to progression and the need for further chemotherapy. This is a highly significant result with real clinical benefit and the only option for women in England as bevacizumab in this setting is not available.
4	Section 3.3: Whilst there were no differences in the non-gBRCA OS arms (due to deficiencies in FU and placebo cross-over to PARP inhibitors) the median OS results are not less than 31.5 - 36.5 months. It should be noted that OS data in NOVA are taken from the date of randomisation after chemotherapy. Thus, to compare with historical chemotherapy data an additional 6-7 months should be added. The data from clinical trials undertaken before PARP inhibitors were used (and BRCA testing performed) showed a median OS of around 25 months eg the control arm of the GOG218 bevacizumab study (see publication of Rose PG, et al. Obstet Gynecol 2019;133:245–54; DOI:10.1097/AOG.0000000000003086). It should be noted that some of these patients will have received bevacizumab maintenance during relapse therapy, and that the survival graph (see below) of all patients reported in this publication of the GOG 218 series were counted from first relapse.

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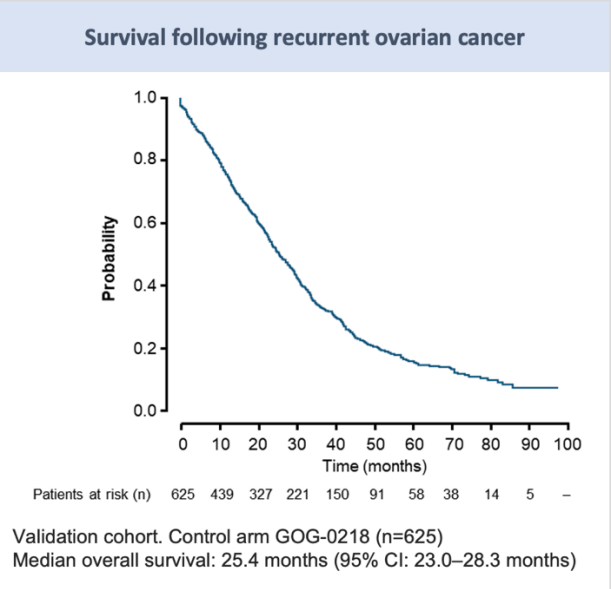

Rose PG, et al. Obstet Gynecol 2019

The NOVA trial included patients who were treated at 2nd or subsequent relapse. 40% of the NOVA population (219/553 patients) were entered into the trial after 3 lines of chemotherapy or greater (≥ 2 relapse). Although the population is selected for patients who responded to platinum, it is known that globally patients survive for increasingly shorter periods with each line of therapy. This can be shown in the follow up data of patients from prospectively conducted clinical trials (Hanker et al Ann Oncol 2012; 23: 2605–2612, doi:10.1093/annonc/mds203). This shows the fall-off in survival with second, third, fourth and subsequent relapse. Noting the date of publication, these are patients in the pre-PARP era and clearly show poor survival; medians of 17.6, 11.3, 8.9 months etc after 1st, 2nd 3rd etc relapse (see image below). During the last decade that covers both publications above, there have been no new cytotoxic chemotherapies introduced into the treatment of ovarian cancer. The only two developments have been bevacizumab for recurrence (not available in England) and PARP inhibitors.

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

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	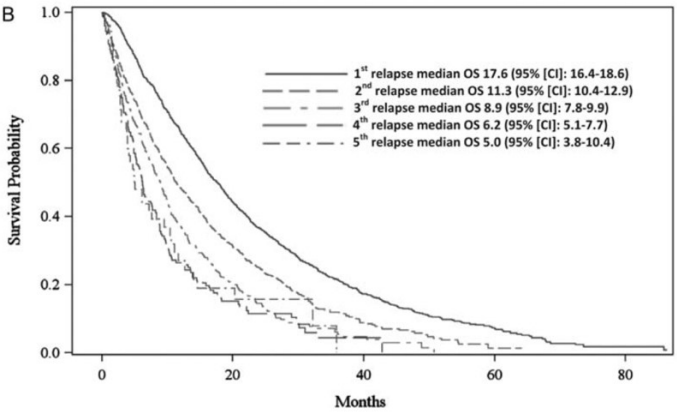 Hanker et al 2012 Taking account of the 'better group' of patients who respond to platinum, there are data from study 19 where access to PARP inhibitor in the placebo arm was less accessible than a few years later during NOVA follow-up (Olaparib was licensed in 2014). Here in the BRCAwt group median OS is about 25 months (from randomisation). Thus, the overall survival is around 32 months from the start of relapse therapy- again superior to chemotherapy trials. This BRCAwt population is not entirely comparable to the NOVA non-gBRCA group as the Study 19 BRCAwt group excludes patients with a somatic mutation. Nevertheless, the Study 19 data and NOVA data yield survival outcome much larger than has been seen in pre-PARP inhibitor chemotherapy studies Thus, the penultimate sentence in 3.3 needs further consideration.
5	3.5 The overall trial population in NOVA is not suitable for decision making: The appraisal committee's conclusions are to separate the BRCA and non-gBRCA groups. Thus, the appraisal committee are diverging from the EMA's licensing position, namely, to include all patients responding to platinum-based therapy. Administering niraparib to the overall population improves PFS for all patients who respond to platinum with the greatest effect seen in patients with gBRCA mutations. The data presented at SGO 2021 show publicly available overall survival for both gBRCA and non-gBRCA. In both groups the outcome far exceed survival seen in the pre-PARP era
6	3.15 Extension to life by more than 3 months with niraparib for people without a BRCA mutation is uncertain From the above information, there is good evidence that treatment of non gBRCA patients with maintenance niraparib extends survival by more than 3 months compared with chemotherapy studies in the pre-PARP era. An improvement in survival with the corresponding increase in prevalence of the disease (as shown in the original submission) provides good evidence that patients on PARP inhibitors live longer than in the period before these drugs were available. This extension in life is clinically important. It affects a diminishing number of patients within the NHS for the next few years as PARP inhibitors are now being used more commonly in the first line setting. But, for the patients who are not able to access these drugs in first line and who respond to platinum, niraparib offers a major clinical benefit.

Insert extra rows as needed

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

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	
Organisation	[redacted]

Comments on the ACD:

Has all of the relevant evidence been taken into account?
The evidence taken into account acknowledges that there is a substantial PFS benefit and that there is an uncertainty if there is an overall survival benefit. The current clinical practice has changed and most women get Niraparib or another PARP inhibitor in the first line setting . There is an increasingly small proportion of women who were not offered PARP inhibitor in the first line setting and the current approach will significantly disadvantage this group of women. Within the next few years the need for second line Niraparib in BRCA negative patients will become substantially smaller and in view of that the CDF funding should continue to support women who have not had the opportunity to take a PARP inhibitor in the first line setting.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Yes

Are the recommendations sound and a suitable basis for guidance to the NHS?
As explained above , the recommendation to stop Niraparib for BRCA negative women in view of an immature data and considering the fact that the number of women who need it will gradually decrease (as they will receive niraparib in the first line setting) does not form a suitable basis for guidance to the NHS and significantly disadvantages women with BRCA negative ovarian cancer.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
No

Name	[redacted]
Role	
Organisation	[redacted]

Comments on the ACD:

While I am content that funding for platinum-sensitive, relapsed disease is to be continued in those with a BRCA mutation after a response to the 2nd course of platinum-based chemotherapy it should be noted that the majority of otherwise

eligible patients in this category may now have received a PARP inhibitor as maintenance in the 1st line setting and PARP inhibitor re-challenge is not permitted so this group is very much smaller than when first reviewed.
I am very concerned that, despite the fact the committee concluded that there was a serious ""unmet need for maintenance treatment especially in those WITHOUT a BRCA mutation"", these new recommendations mean that this group would be seriously disadvantaged. They comprise about 75% of the ovarian cancer cases in the UK and are the group that are less likely to have been given a PARP inhibitor first line.
There is currently a clinical trial (MONITOR-UK) recruiting ""real world"" patients in the UK receiving maintenance Niraparib following response to platinum-based chemotherapy including in the 2nd line setting and regardless of BRCA mutation status which will provide valuable data within the next few years and I would urge the committee to continue funding in the otherwise very-disadvantaged non-BRCA cohort.

Has all of the relevant evidence been taken into account?
All current evidence has been reviewed.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
I am not satisfied that the clinical effectiveness and benefit interpretations are reasonable.

Are the recommendations sound and a suitable basis for guidance to the NHS?
The recommendations are sound in the small minority of patients with a BRCA mutation (approximately 25%) but will significantly disadvantage those without a BRCA mutation who already have a poorer prognosis and less benefit from standard cytotoxic therapies.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Not specifically however the prevalence of germline BRCA mutations is much higher in some ethnic/ religious groups than in others.

Name	[redacted]
Role	
Organisation	[redacted]

Comments on the ACD:

For clarification, it would be helpful if the dose was put in the context of the overall dosage i.e. this is taken daily. Suggest changing text to...
""The prescribed dosage used in NOVA as specified in the SmPC for niraparib is 300 mg daily. The clinical expert explained that some clinicians favour starting treatment with a lower dosage of 200 mg daily of niraparib in clinical practice."" I presume that is what is meant as the licensed dose is daily (see SPC)?

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

ERG response to company ACD comments

September 2021

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/12/19T.

1 Introduction

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the appraisal committee document (ACD). In the ACD, niraparib was recommended as an option for treating relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer in adults. It is recommended only if:

- they have a breast cancer susceptibility cancer (BRCA) mutation and
- have had 2 courses of platinum-based chemotherapy and their disease has responded to the most recent one.

Niraparib was not recommended as a treatment option for patients without the hereditary germline BRCA mutation and who have had 2 lines or more of platinum-based chemotherapy (non-gBRCAmut 2L+ subgroup). As such, the company's response to the ACD focuses on the non-gBRCAmut 2L+ subgroup.

The company's response addressed the following issues raised in the ACD:

- Feasibility of inverse probability of censoring weighting (IPCW) analysis;
- Matched adjusted indirect comparison (MAIC) for NOVA and Study 19 overall survival (OS);
- Relevance of real-world evidence;
- Committee's request to model the niraparib arm assuming no overall survival benefit compared to routine surveillance;
- Treatment-specific utilities;
- Modelling of TTD;
- Scenario exploring investigator-assessed (IA) progression-free survival (PFS);
- Modelling of niraparib dose; and
- End of life.

The ERG's critique of the company's response to each of these issues is discussed in Section 2 and addition ERG analyses are presented in Section 3.

In their ACD response, the company updated their base case post technical engagement for the non-gBRCAmut 2L+ subgroup to include the MAIC analysis of OS and results are presented in Table 1. No further updates were made to the company base case.

Table 1. Company's updated deterministic cost effectiveness results – non-gBRCAmut 2L+ subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Company base case post technical engagement							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	39,608
Updated company base case							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,273

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

2 ERG response to comments

2.1 Adjustment for treatment switching (comment 1)

The Committee asked the company to consider adjusting for the subsequent poly (ADP-ribose) polymerase inhibitor (PARPi) use in NOVA in Section 3.19 of the Appraisal Consultation Document (ACD). The company has presented the results of an adjustment for treatment switching presented at the Society of Gynecologic Cancer (SGO) conference 2021.[1]

Early withdrawal of consent in NOVA limited the collection of survival and subsequent therapy data. By final data lock, survival status could not be retrieved for 14% (33/234) from the niraparib arm and 13% (15/116) from the placebo arm in the non-gBRCAmut 2L+ cohort, and subsequent therapy data was missing for 22% of patients in the niraparib arm and 27% in the placebo arm. Subsequent therapy data that were available, showed that 6% in the niraparib arm and 13% in the placebo arm received subsequent PARPi therapy in this cohort. In comparison, 25% and 46% of patients received subsequent PARPi in the niraparib and placebo arm, respectively, of the gBRCA cohort.

The company reports that missing data among placebo patients were adjusted for by imputing synthetic probabilities and date of PARPi crossover. Adjustment for treatment switching was then made using inverse probability of censoring weighting (IPCW) on the simulated data set. No further details were provided around the imputation of missing data or the crossover adjustment. The choice of using IPCW to adjust for treatment switching may be appropriate as the proportion of patients who received subsequent PARPi in the placebo group was relatively low. Due to the sparce information provided, the ERG cannot comment further on the execution or robustness of these analyses.

The IPCW adjusted analysis for subsequent PARPi therapy showed no statistically significant difference in survival between niraparib and placebo in the non-gBRCAmut 2L+ cohort (OS HR 0.97, 95% CI: 0.74 to 1.26), similar to the unadjusted analysis (OS HR 1.10, 95% CI: 0.831 to 1.459).

The company states that there was evidence of non-proportional hazards (PHs) for OS. A restricted mean survival time (RMST) analysis was therefore conducted in the ITT population. It is unclear if the non-PHs only applied to the ITT population or if there was evidence of non-PHs also for the non-gBRCAmut 2L+ cohort.

The ERG acknowledges the large amount of missing data on subsequent PARPi use (22% and 27% in the niraparib and placebo arm, respectively) but also notes that the available data indicates a relatively modest crossover to subsequent PARPi in the placebo arm (13%) in the non-gBRCAmut 2L+ cohort. If the company's imputation of missing data and IPCW analysis are considered robust, the results of the analysis indicates that crossover may not have much of an impact on survival in the non-gBRCAmut 2L+ cohort and that niraparib does not provide a survival benefit over RS. For the gBRCA cohort in NOVA, the proportion of subsequent PARPi use was substantially higher and more uneven between the treatment arms, meaning that crossover is likely to have a bigger impact.

2.2 Matching adjusted indirect comparison (comment 2)

In the ACD, the committee requested the company to explore analyses that adjust for baseline differences in the NOVA and Study 19 populations using methods outlined in NICE decision support unit technical support document 18, such as a matching-adjusted indirect comparison (MAIC).[2] The company conducted a MAIC and used the results of the analysis to update their base case for the non-gBRCAmut 2L+ subgroup.

The company performed an anchored MAIC where the placebo arm in each of the trials served as the common comparator. However, the aim of the analysis was to adjust the NOVA cohort to be comparable to the patients in the placebo arm of Study 19, and so only the initial adjustment step of the MAIC was done rather than a calculation of the relative efficacy of niraparib and olaparib.

Potential treatment effect modifiers to adjust for were identified based on clinical expert input and limited by patient characteristics reported for Study 19. The covariates chosen for matching in the MAIC were primary tumour location, response to previous platinum therapy, platinum-free interval and number of previous platinum regimens received. The ERG's clinical expert advised that the covariates chosen by the company's experts are associated with the incidence of HRD and BRCA mutations. Although patients with a gBRCA mutation are excluded from the non-gBRCAmut NOVA cohort, it will include some people with a somatic BRCA mutation, and the cohorts from both trials will include people with homologous recombinant deficiency (HRD), which is associated with a better response to PARPi therapy. The covariates chosen by the company are therefore likely treatment effect modifiers, although not necessarily independent of each other. It is important to note that the inclusion of patients with a somatic BRCA mutation in the non-gBRCAmut cohort in NOVA will introduce bias in favour of niraparib from NOVA over routine surveillance from Study 19 in both the adjusted and naïve comparison.

The company states that the MAIC weights were incorporated in combination with the analyses for treatment switching adjustment for the placebo arm in NOVA (reported in comment 1, Section 2.1). The ERG notes that if the company considers the adjustment for treatment switching to produce a reliable estimate of the survival in NOVA then the MAIC with Study 19 would not be required. The ERG also assumes that crossover adjusted data for Study 19, where around 5% of patients in the placebo arm received subsequent PARPi therapy, were not available for this analysis.

The NOVA patients re-weighted to the Study 19 population characteristics were presented as HRs and KM-curves. Baseline characteristics before re-weighting were balanced within the NOVA cohort but for two covariates there were imbalances between the olaparib and placebo arm of the Study 19 cohort. This is likely due to the *post-hoc* nature of the BRCAwt subgroup. The company re-weighted the niraparib arm in NOVA to match the characteristics of the olaparib arm in Study 19 and similarly the placebo arm in NOVA was matched to the placebo arm in Study 19. The effective sample size (ESS) for niraparib and placebo were relatively high, indicating a good overlap between the NOVA and Study 19 populations. Adjusted baseline characteristics were well balanced between niraparib and olaparib and between the two placebo arms but due to the imbalances between arms in Study 19, this created a similar imbalance between niraparib and placebo. To address this the ERG suggests the company adjust both arms of NOVA to match the placebo arm of Study 19.

The adjusted HR ([redacted] was very similar to the original NOVA HR ([redacted]) and the adjusted KM-curves are also very similar to the unadjusted.

Figure 1. KM curves before and after MAIC adjustment for non-gBRCAmut 2L+

The company fitted standard parametric survival distributions to the MAIC-adjusted niraparib OS data from NOVA and routine surveillance Kaplan-Meier data from Study 19. Based on Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics and visual fit of the extrapolations to the OS data, the company selected lognormal distribution for the updated base case. Figure 2 presents the MAIC-adjusted survival curves for niraparib and Study 19 routine surveillance.

Figure 2. MAIC-adjusted OS Kaplan Meier and lognormal distribution for niraparib (NOVA) and routine surveillance OS from Study 19 (BRCAwt) – non-gBRCAmut 2L+ (Figure 3, Appendix 3 of the company ACD response)

Table 2. Comparison of company MAIC and naive overall survival estimates (years)

OS Analysis	Niraparib	Routine surveillance
MAIC-adjusted NOVA niraparib OS data	[redacted]	[redacted]
Naïve comparison of NOVA niraparib and Study 19 routine surveillance	[redacted]	[redacted]

Abbreviations: MAIC, matched adjusted indirect comparison; OS, overall survival.

The ERG considers that the results of the MAIC analysis results in similar, if not slightly optimistic, estimates of OS compared with the naïve comparison of niraparib from NOVA and routine surveillance from Study 19. The ERG is concerned that, niraparib was adjusted to match olaparib

rather than the placebo arm of Study 19, which has introduced imbalances between niraparib and placebo and effectively broken randomisation. In addition, as OS for niraparib is adjusted to Study 19 and OS for routine surveillance is also based on Study 19, the correlation between OS and PFS has been broken as PFS for niraparib and routine surveillance is based on NOVA. Nonetheless, the ERG has explored the use of MAIC-adjusted OS for niraparib as a scenario around the ERG base case in Section 3 for reference.

2.3 Real world evidence scenarios (comment 3)

The company highlights the results of scenario analyses based on Lord *et al.*[3] and the SACT[4] data, previously provided by the company.

The ERG considers that the SACT scenario provides an important illustrative but not robust estimate of the potential benefit of niraparib compared with routine surveillance in clinical practice. The SACT scenario relies 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 ERG considers that the clinical trial data used by the company and the ERG for their base case analyses provide a more robust assessment of niraparib and routine surveillance.

The scenario analysis comparing Lord *et al.* with the SACT ITT population (pooled gBRCAmut 2L and non-gBRCAmut 2L+ cohorts) is not relevant to this ACD response. As stated in the ACD, "*clinical trial evidence suggests considering [people with and without a BRCA mutation] separately because prognosis is different for each subgroup. The committee concluded that the overall trial population is not suitable for decision making and that the subgroups of interest in this appraisal are people with a BRCA mutation who have had 2 lines of platinum-based chemotherapy or people without a BRCA mutation who have had 2 or more lines of platinum-based chemotherapy.*" The Lord *et al*. vs SACT ITT scenario does not provide an accurate estimate of the clinical efficacy or the cost effectiveness of niraparib compared with routine surveillance in the non-gBRCAmut 2L+ population.

To enable a real world evidence (RWE) scenario based on Lord *et al*. that is relevant to the non-gBRCAmut 2L+ population, the ERG suggests comparing Lord *et al*. with the non-gBRCAmut 2L+ SACT cohort. This may be a conservative scenario as Lord *et al.* included people with a gBRCA mutation. Although, the proportion of patients with a gBRCA mutation in Lord *et al*. is unknown as BRCA status was not captured for the majority of patients. In addition, due to the limited reporting of patient

characteristics for the non-gBRCAmut 2L+ SACT cohort, the ability to compare and adjust for any differences between Lord *et al.* and the SACT cohort is very limited.

2.4 No overall survival benefit for niraparib vs routine surveillance (comment 4)

In the ACD, the committee asked the company to explore, "*modelling the niraparib arm assuming no overall survival benefit compared to routine surveillance*". The company did not provide the requested scenario, but instead explained why they believed the request to be clinically implausible. The company considered that, based on an analysis from Study 19, the PFS:OS ratio was at least 1:2 and could be as high as 1:3. The company also quoted an extract from the final appraisal document (FAD) for TA528 which stated that, "*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*".

However, based on the issues discussed in Section 2.1, assuming no OS benefit may not be implausible given the evidence supplied by the company. As such, as the company did not provide an analysis based on the results of crossover adjustment (discussed in Section 2.1), the ERG ran a scenario assuming the routine surveillance OS curve is equal to the niraparib OS curve based on NOVA in lieu of having crossover adjusted data. Table 3 presents the results of the scenario which the ERG addresses the committee's request for scenarios exploring crossover adjustment and no OS benefit for niraparib.

Table 3. No overall survival benefit scenario – non-gBRCAmut 2L+ subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Updated company base case							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,273
No overall survival benefit scenario							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	168,986

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

2.5 Treatment specific utilities (comment 5)

The company supplied the treatment and health state coefficients from a linear mixed-effects regression model to substantiate their assumption that treatment-specific utilities should be used in the economic model. The p-values from the linear mixed-effects regression model for treatment and health state are [redacted] and [redacted], respectively. However, the coefficients from the model have not been supplied, therefore the ERG are unable to assess which has the greatest impact.

In the ACD, the committee stated that, "*it would continue to consider both treatment specific and health-state based utility values for the cost-effectiveness analyses*". The company's updated base case includes treatment-specific utility values. Based on the committee's preference to also consider progression-based utility values, the ERG ran a scenario around the company's updated base case using progression-based utility values and results are presented in Table 4. A scenario around the ERG's base case including treatment specific utilities is presented in Section 3.

Table 4. Progression-based utility scenario (updated company base case) – non-gBRCAmut 2L+ subgroup

Scenario	Interventions	Total		Incremental		ICER (£/QALY)
		Costs (£)	QALYs	Costs (£)	QALYs	
Post-technical engagement ICER – IA PFS scenarios						
Updated base case (MAIC adjusted OS)	Routine surveillance	[redacted]	[redacted]	-	-	-
	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	37,273
Progression-based utility values	Routine surveillance	[redacted]	[redacted]	-	-	-
	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	41,797

Abbreviations: gBRCA, germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; MAIC, matched adjusted indirect comparison; PFS, progression-free survival; OS, overall survival; QALY, quality-adjusted life year.

2.6 Time to treatment discontinuation and (comment 6)

The company has not supplied any new evidence to alter the ERG's view on the modelling of time to treatment discontinuation (TTD) using the Gompertz distribution (as described in the ERG report). The company has requested the committee consider the scenario where SACT TTD data are using

instead of NOVA data for the non-gBRCAmut 2L+ subgroup. The ERG considers that SACT TTD data should only be considered in the SACT specific scenarios. Using SACT TTD data alongside survival outcomes from NOVA substantially underestimates treatment costs that are not linked to the benefits estimated from the trial. This is reflected in the magnitude of the reduction in the company's updated base case ICER (£25,969 vs £37,273). It should be noted that the ERG was unable to validate the company's scenario using SACT TTD data for the updated base case.

2.7 Investigator assessed progression-free survival (comment 7)

As requested in the ACD, the company has supplied a scenario exploring the use of IA PFS for the non-gBRCAmut 2L+ subgroup. For the scenario, the company extrapolated IA PFS KM data from NOVA using standard parametric distributions. Based on AIC/BIC statistics and visual fit of the extrapolations to the IA PFS data, the company selected log-logistic and generalised gamma distributions for the scenario analyses. Figure 3 and

Figure 4 presents the log-logistic and generalised gamma IA PFS curves.

Figure 3. NOVA IA PFS KM data and log-logistic distribution – non-gBRCAmut 2L+ subgroup

Figure 4. NOVA IA PFS KM data and generalised gamma distribution – non-gBRCAmut 2L+ subgroup

The results of the scenarios are presented in Table 5 and are applied to the company's base case post technical engagement and the updated base case. The company considered that the log-logistic distribution represents a conservative estimation of survival and the generalised gamma distribution is more optimistic, thus the midpoint of the two ICERs is likely reflect the cost-effectiveness when estimating a more accurate IA PFS curve.

The ERG notes that this scenario was more relevant for the gBRCAmut 2L subgroup, as sensitivity analysis in NOVA show [redacted] median PFS for patients treated with niraparib when assessed by the IRC compared with IA PFS, and this difference was less pronounced for the non-gBRCAmut 2L+ subgroup. As such, the ERG does not consider the IA PFS scenario as critical to the decision making

for the non-gBRCAmut 2L+ subgroup as it would have been for the gBRCAmut 2L subgroup. This is reflected in the results for the scenario not being substantially different from the company's base case post technical engagement.

Table 5. Investigator assessed PFS scenarios – non-gBRCAmut 2L+ subgroup

Scenario	Interventions	Total		Incremental		ICER (£/QALY)
		Costs (£)	QALYs	Costs (£)	QALYs	
Post-technical engagement ICER – IA PFS scenarios						
Base case	Routine surveillance	[redacted]	[redacted]	-	-	-
	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	39,608
Log-logistic	Routine surveillance	[redacted]	[redacted]	-	-	-
	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	37,035
Generalised gamma	Routine surveillance	[redacted]	[redacted]	-	-	-
	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	39,527
Midpoint						38,281
Updated base case ICER – IA PFS scenarios						
Updated base case (MAIC adjusted OS)	Routine surveillance	[redacted]	[redacted]	-	-	-
	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	37,273
Log-logistic	Routine surveillance	[redacted]	[redacted]	-	-	-
	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	34,777
Generalised gamma	Routine surveillance	[redacted]	[redacted]	-	-	-
	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	37,169
Midpoint						35,973

Abbreviations: gBRCA, germline breast cancer susceptibility gene mutation; IA, investigator assessed; ICER, incremental cost-effectiveness ratio; MAIC, matched adjusted indirect comparison; PFS, progression-free survival; OS, overall survival; QALY, quality-adjusted life year.

2.8 Lord *et al.* 2020 (comment 8)

The company would like to reassert the value of the scenario analysis comparing RWE data for niraparib from SACT[4] and for routine surveillance from Lord *et al.*[3] As mentioned in response to comment 3 (Section 2.3), the scenario comparing Lord *et al.* with SACT ITT data is not relevant to this ACD response, which is focused on resolving the uncertainty around the survival benefit of niraparib in the non-gBRCAmut 2L+ population.

As suggested in response to comment 3, an alternative and more relevant scenario could be to compare Lord *et al*. with the non-gBRCAmut 2L+ SACT cohort. Although, all the limitations of a naïve comparison between the two RWE sources needs to be kept in mind.

The company has helpfully highlighted that Lord *et al.* has been described incorrectly in the ACD and the ERG's response to technical engagement. The index date in Lord *et al.* was the date when patients finished their second course of platinum-based chemotherapy (PBC). That is, all patients in Lord *et al.* had received two courses of PBC, not two or more, but the median number of previous lines of chemotherapy (platinum-based or not) in Lord *et al.* was 3.

2.9 Prescribed niraparib dose (comment 9)

The company has not supplied any new evidence to alter the ERG's view on using prescribed dose to model niraparib costs in the model (as described in the ERG report).

In the ACD the committee considered that, "*niraparib dose in the economic model should reflect prescribed dose* " and "*dose used in the model should reflect the dose of niraparib in the summary of product characteristic (SmPC) and NOVA*".

However, the ERG notes that the company has stated that for the modelling of prescribed or actual dose, the 300 mg dose is captured in the weighted average. However, as per the company's original model, the dose in the first cycle was 8,400 mg (300 mg per day for 28 days). Whereas the company's actual dose consumed approach models the first cycle dose as [redacted]. The company state that their base case approach aligns dose consumed with survival benefits achieved, but the ERG consider that the company's argument eliminates the generalisability of dosing in routine clinical practice. Outside of a trial setting, the NHS would incur the cost of the prescribed initial dose as per SmPC guidelines, irrespective of dose consumed by a patient as a result of adjustment. Due to variability around reuse

of prescribed doses by patients in the NHS and in order to be realistic about the upper bound of drug costs to the NHS, it is preferable to model costs conservatively, as stated by the NHSE Cancer Drugs Fund clinical lead at the committee meeting.

2.10 BRCA terminology (comment 10)

The ERG considers the company's comments on BRCA terminology used in the ACD are to be addressed by NICE.

2.11 End of life (comment 11)

The company has reiterated the data from SACT[4] and Lord *et al.*[3] as evidence supporting the use of niraparib as an end-of-life therapy for the non-gBRCAmut 2L+ population.

The company's mean estimate of OS for routine surveillance when using SACT data for niraparib is [redacted] years. However, the ERG reiterates that although the SACT scenario provide an illustrative estimate of the potential benefit of niraparib on survival compared with routine surveillance in clinical practice, this analysis is built on several assumptions and should not be considered to provide a robust estimate of survival for routine surveillance (see response to comment 3 in Section 2.3). The company's estimates of OS for routine surveillance is based on a calculation using extrapolated OS data from SACT for niraparib and a 1:1 PFS:OS ratio.

As discussed in response to comment 3 and 8 (Sections 2.3 and 2.8), the company's scenario analysis comparing Lord *et al.* with the SACT ITT population does not inform the efficacy of niraparib in the population relevant to this ACD, the non-gBRCAmut 2L+ population. Although the median life expectancy of the population in Lord *et al.* is less than 24 months, mean OS for routine surveillance is [redacted] years, and this scenario does not provide an estimate of the extension to life in the relevant population.

In the company's updated base case the undiscounted mean OS estimate for routine surveillance for the non-gBRCAmut 2L+ subgroup is [redacted] years based on the routine surveillance arm of Study 19, and the undiscounted mean extension of life with niraparib treatment is [redacted] years. The OS results from NOVA adjusted for missing data and subsequent PARPi treatment on the placebo arm show no statistically significant survival benefit.

The ERG notes that in the original appraisal of olaparib (TA381), the committee accepted that the end-of-life criteria applied for a subgroup of people with a BRCA mutation who had responded to 3

or more courses of platinum-based chemotherapy (PBC). As non-gBRCAmut 2L+ patients have a worse prognosis and shorter life expectancy than patients with a BRCA mutation, life expectancy for the subgroup of non-gBRCAmut patients who have had 3 or more courses of PBC (non-gBRCAmut 3L+) is highly likely to have a life expectancy shorter than 24 months. However, the ERG appreciates that any further comment on this potential position for niraparib would be purely speculative without the company providing a formal subgroup analysis to support it.

2.12 Unmet need for non-gBRCAmut 2L+ patients (comment 12)

The ERG considers the company's comments on unmet need for non-gBRCAmut 2L+ patients are to be addressed by NICE.

3 ERG additional analysis

As a reminder, the key assumptions feeding into the ERG base case that deviate from the company's updated base case are as follows:

The assumptions included in the ERG base case are as follows:

- Hazards k=1 spline for PFS;
- Gompertz distribution for TTD;
- Utilities based on progression status and removal of disutility associated with adverse events (AEs);
- Prescribed dose data from TA528.

Based on the company's comments on the ACD, the ERG has not seen any compelling evidence to change its preferred base case assumptions. The ERG's base case results are presented in Table 6.

Table 6. ERG's base case cost effectiveness 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.							

However, scenarios around the ERG base case exploring the following assumptions are presented in Table 7 for committee reference:

1. MAIC adjusted OS for niraparib;
2. No overall survival benefit for niraparib;
3. Treatment specific utilities.

Table 7. ERG deterministic scenario analyses

	Results per patient	Niraparib	Routine surveillance	Incremental value
0a	**Company updated base case**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	**37,273**
0b	**ERG base case**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	**51,684**
1	**MAIC adjusted OS for niraparib**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	**48,250**
2	**No OS benefit for niraparib**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]

	ICER (£/QALY)	-	-	**499,857**
3	**Treatment specific utilities**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	**-**	**-**	**45,663**

Abbreviations: ERG, Evidence Review Group, ICER, incremental cost-effectiveness ratio; MAIC, matched adjusted indirect comparison; OS, overall survival; QALY, quality adjusted life year.

4 References

1. Matulonis U, editor Long term safety and secondary efficacy endpoints in the ENGOT OV16/NOVA phase 3 trial of niraparib in recurrent ovarian cancer. Presented at the Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer; 2021.
2. DSU N. TSD 18: Methods for population-adjusted indirect comparisons in submissions to NICE. 2016.
3. Lord R, Rauniyar J, Morris T, Condon O, Jones R, Miller R, 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. *International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society* 2020; **30**: 1026-33.
4. Public Health E. Niraparib for treating ovarian cancer (TA528). Niraparib overall survival (OS) refresh (patient trace 3rd February 2021). 2021.

Scenario	Interventions	Total		Incremental		ICER (£/QALY)
		Costs (£)	QALYs	Costs (£)	QALYs	
Updated base case (MAIC adjusted OS)	Routine surveillance	[redacted]	[redacted]	-	-	-
	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	37,273
Prescribed dose scenario	Routine surveillance	[redacted]	[redacted]	-	-	-
	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	40,087

Abbreviations: gBRCA, germline breast cancer susceptibility gene mutation; ICER, incremental cost-effectiveness ratio; MAIC, matched adjusted indirect comparison; PFS, progression-free survival; OS, overall survival; QALY, quality-adjusted life year.