NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Olaparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer [ID1296]

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. AstraZeneca
   b. British Gynaecological Cancer Society
   c. Ovarian Cancer Action
   d. Ovacome
   e. Target Ovarian Cancer

   There were no comments received from patient or clinical experts.

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Evidence Review Group Critique of company response to ACD** prepared by BMJ-TAG

5. **Evidence Review Group response to company letter July 2019** prepared by BMJ-TAG

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

Olaparib 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.

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1		Ovarian Cancer Action	One of the main concerns we have is that if tablet form of Olaparib is not approved in this consultation and the company press ahead with their intention of phasing out capsules it will leave 100s of women in the future unable to access Olaparib under the current guidelines. We appreciate that the company have said that they will continue to produce capsules until the very last person CURRENTLY on them stops taking them BUT does this mean after this point the guideline TA381 will simply cease to exist and future women who would be eligible now would not have access in the future? If the end result of this technology appraisal is that in the future women with ovarian cancer have fewer options for treatment than they do right now this would represent a crushing blow to the progress we have seen over the last three years. Ovarian cancer treatment has seen so few breakthroughs and developments over the past twenty years, and lags way behind other cancers so it is essential that we do not lose access to treatments that have only been approved relatively recently.	Thank you for your comment. The committee has now recommended olaparib tablets in the same population as the population who previously had access to olaparib capsules. This means that when the company phases out the capsules, people who would have had access to this formulation of olaparib previously, will now be able to access the tablet formulation instead. The new guidance updates and replaces NICE technology appraisal guidance 381
2		Ovarian Cancer Action	Ovarian cancer patient quote: given that capsules are already in use, and given that they are felt to have equal efficacy then surely the capsules should be considered for this change in the drugs role, to make the treatment affordable under NICEs costings guidelines. All medication needs to be prescribed responsibly in its most affordable effective form within a cost limited service such as the NHS, to help make more new treatments available for everyone.	Thank you for your comment. The committee concluded that it is reasonable to assume that the tablet and capsule formulations of olaparib have similar efficacy, but the price of the different formulations varies (the tablets are more expensive) and they are also licensed in a broader population than the capsules; olaparib capsules are only licensed for people with a BRCA mutation whereas the marketing authorisation for the tablet formulation covers adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy irrespective of BRCA mutation status. For this reason, the tablets were appraised separately and conclusions the committee reached relating to the tablet do not necessarily apply to the capsule formulation.

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				However, the committee has now recommended olaparib tablets in the same population as the population who previously had access to olaparib capsules so these people will continue to have access to olaparib, albeit in a different formulation.
3		Ovarian Cancer Action	We are still concerned that the impact on women who take the drug is being underestimated. Please see quotes from a patient who has been using this drug for the last two years: Huge extensions of life...the last chemo (4th time) didn't get rid of all the disease....so without Olaparib I very much doubt I would be here. It is most probably my last chance for any real extension of life. This obviously has massive implications for my friends and family. So far I've been on Olaparib 20 months. The most amazing 20 months. It brings incredible HOPE. Data shows that 20% of women are on the drug for 5 years plus. That is my target. So what difference on a daily basis....apart from the first three months which was tough..(side effects such as really bad nausea/fatigue etc etc)...I live a wonderful, manageable life. I can do the things to lead a great life. I still have to manage the fatigue, and stress of living with cancer, but can plan short term things like holidays and trips with my family. I play tennis, I paint. I am able to celebrate important life events of my children...ie my son going to Uni. Plan adventures with them. Share another Christmas. Build more memories with my children. Try and become a better person. Use my experiences of cancer and help others. Be more empathetic and compassionate....it goes on and on....what do we all want out of life?	Thank you for your comment. The committee considered this feedback and remains of the view that olaparib treatment results in meaningful clinical benefit to patients in terms of delaying disease progression and extending life
1		Target Ovarian Cancer	**The importance of olaparib in improving progression free survival** Target Ovarian Cancer believes that women with ovarian cancer and their clinicians need all relevant treatment options available in the armoury for managing ovarian cancer. This is particularly important as the disease progresses and women are treated for multiple recurrences. In particular, apart from the obvious immediate benefit to women with ovarian cancer in terms of quality of life, extending progression free survival is likely to prolong the usefulness of platinum-based chemotherapy.	Thank you for your comment. The committee considered this feedback and remains of the view that olaparib treatment results in meaningful clinical benefit to patients in terms of delaying disease progression and extending life
2		Target Ovarian Cancer	**The future of TA381** We are disappointed that NICE has not recommended olaparib within its marketing authorisation for recurrent disease. We are concerned that if this guidance will leave a subgroup of women without an option to be treated with a PARP inhibitor. TA528 recommends that women with a BRCA mutation can only access niraparib as part of second line treatment on the basis that olaparib is available for this group for third line treatment. There will be a group of women that have undergone second line treatment prior to approval of niraparib, who are yet to relapse and require third line treatment, who will be unable to access olaparib under this guidance. It is currently unclear on the status of TA381 and the future of olaparib in capsule form for women yet to start treatment if the tablet form is unsuccessful in securing NICE approval.	Thank you for your comment. The committee considered this feedback and remains of the view that olaparib treatment offers meaningful clinical benefits to patients in terms of delaying disease progression and extending life. The committee has now recommended olaparib tablets in the same population as the population who previously had access to olaparib capsules. This means that when the company phases out the capsules, people

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				who would have had access to this formulation of olaparib previously will now be able to access the tablet formulation instead. The new guidance updates and replaces NICE technology appraisal guidance 381
3		Target Ovarian Cancer	**Cost effectiveness** Target Ovarian Cancer notes that the tablet formulation of olaparib does not comply with cost effectiveness models. However we observe the following: *3.3 the tablet formulation is likely to have a positive impact on quality of life.* *3.4 the tablet and capsule formulation have similar efficacy.* *3.6 olaparib improves PFS irrespective of BRCA mutation, but people with BRCA-mutation positive disease may experience greater benefit.* *3.8 olaparib has a manageable adverse-effects profile.* We urge the manufacturer and NICE to work together to resolve the issue of cost effectiveness.	Thank you for your comment. The committee considered this feedback and remains of the view that olaparib treatment offers meaningful clinical benefits to patients in terms of delaying disease progression and extending life, regardless of whether the person has a BRCA mutation. The company has now offered to discount to the price of olaparib for people with a BRCA mutation, but no discount has been offered for people without a BRCA mutation. This means that the committee's previous conclusion that olaparib is not cost effective in people without a BRCA mutation remains unchanged. However, the committee has now been able to recommend olaparib for people with a BRCA mutation. It is recommended in this group as a routine treatment option for people that have had 3 or more courses of platinum-based chemotherapy and via the CDF for people that have had 2 courses of platinum-based chemotherapy
4		Target Ovarian Cancer	**Quality of life** Women and their families feel very strongly that olaparib is a game changer in terms of ovarian cancer treatment. The quotes below, submitted in response to an online survey conducted by Target Ovarian Cancer, show the difference olaparib has made to women with ovarian cancer and their families. *"It has given us hope. After several cycles of chemotherapy olaparib is less invasive and improves quality of life. This is a major breakthrough and should be freely offered to cancer patients that have met the criteria. It is life changing."* *"I have now been on olaparib for over eight months and can honestly say it allows you to start to live and feel 'normal' again. None of the terrible side effects of chemo and best of all, most importantly, it has kept my ovarian cancer away."* *"My dearest friend has been taking olaparib for over two years. She is now able to live a near normal life, something which chemotherapy took from her. This drug is her lifeline."*	Thank you for your comment. The committee considered this feedback and remains of the view that olaparib treatment offers meaningful clinical benefits to patients in terms of delaying disease progression and extending life.

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			"I still have my wife after being told she probably wouldn't live beyond eight to nine months. This was over two years ago. We were out of options until olaparib. She is well and enjoying life."	
1		BRITISH GYNAECOLOGICAL CANCER SOCIETY	The ACD has not taken sufficient account of two important secondary endpoints, Time to First Subsequent Treatment (TFST) and PFS2, a surrogate for overall survival. Thus, the ACD has not taken all of the relevant evidence into account, and as such the clinical and cost effectiveness. This compromises the interpretation of the evidence and the provisional recommendations for guidance to the NHS. PFS has been accepted by scientific community, peer review journals and licensing authorities as a relevant primary endpoint, so it is difficult to understand why the ERG (pg 24) states that PFS is a poor predictor of progression. Patients were not unblinded on progression and TFST is a clinically meaningful end point for patients, representing the time that patients can remain free from further intravenous cytotoxic chemotherapy. This exploratory endpoint in Study 19 was prospectively built into the analysis of SOLO2. The difference in median TFST was 20.8 months in SOLO2 [TFST HR 0·28 (95% CI 0·21–0·38), p<0·0001] compared to a difference in the median PFS of 13.8 months [PFS HR 0·33, (95% CI 0·24–0·44); p<0·0001]. This clinically relevant endpoint should be taken into consideration. The EMA have accepted PFS2 as a supporting endpoint for patients with an improved PFS in situations where OS data are not mature, recognising that in many trials a significant number of patients cross over to the trial drug, or other PARP inhibitor, and that long post progression survival makes it more challenging for trials to show significant OS benefit. The PFS2 data in SOLO2 in the population with a BRCA mutation show a significant continuing benefit for patients on olaparib at the time of second progression. In fact, the median time to second progression in the olaparib arm has not yet been reached; Of the 119 events, 70 [36%] occurred in the olaparib group compared with 49 [50%] in the placebo group. The median PFS2 in the placebo group is 18·4 months (15·4–22·8), suggesting that the results of further chemotherapy for many patients was relatively short-lived. This is the case in spite of cross over to PARP inhibitor in the placebo arm for some patients (This number crossing over (pg 69/185) has been redacted). The ACD should take account of the PFS2 findings, the fact that the median PFS2 for olaparib has not been reached, and the relatively short median PFS2 in the control arm compared to the median PFS. These two endpoints have clinical relevance and do not appear to have been taken into account in evaluating the clinical benefit of olaparib maintenance therapy in these patients	Thank you for your comment. The committee heard from the company, ERG and clinical experts that radiological progression does not reflect clinical progression. The committee heard from clinical exerts at the meeting that in UK clinical practice people stop taking olaparib following disease progression, defined by symptoms and increased levels of CA125 protein and that therefore people did continue taking olaparib after radiological progression. Using time to first subsequent treatment for modelling progression meant that the health benefits of being progression-free would be accrued within the model, without associated treatment costs, favouring olaparib.
2		BRITISH GYNAECOLOGICAL CANCER SOCIETY	3.10 (page 9/14). Most patients discontinued treatment on radiological progression. The time to treatment discontinuation has been used as a model for symptomatic progression. It is unclear what the justification for this assumption was. This comment	Thank you for your comment. The committee heard from the company, ERG and clinical experts that radiological progression does not

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			relates to the long period before treatment was restarted after progression (see comment 1 above). Treatment would not be withheld if a patient had symptoms, so the time to treatment discontinuation is an inferior indicator of symptomatic progression that time to first subsequent treatment. The ERG should justify why time to treatment discontinuation is 'more reflective of real life clinical practiced', and why it was used.	reflect clinical progression. The committee heard from clinical exerts at the meeting that in UK clinical practice people stop taking olaparib following disease progression, defined by symptoms and increased levels of CA125 protein and that therefore people did continue taking olaparib after radiological progression. Using time to first subsequent treatment for modelling progression meant that the health benefits of being progression-free would be accrued within the model, without associated treatment costs, favouring olaparib.
1		Ovacome Ovarian Cancer Charity	We are concerned that the physical and psychological impact of olaparib availability to this group has not been taken fully into account. The development of biological therapies which extend progression free survival is offering hope of improved quality of life between chemotherapies when there had been no new chemotherapy options for many years.	Thank you for your comment. The committee considered this feedback and remains of the view that olaparib treatment offers meaningful clinical benefits to patients in terms of delaying disease progression and extending life.
2		Ovacome Ovarian Cancer Charity	The results of the SOLO-1 and SOLO-2 trials have shown significant progression free survival with tolerable side effects. This technology could make a huge difference to ovarian cancer relapse times which would extend times between platinum therapies potentially prolonging platinum chemotherapy use; it would also allow for improved quality of life during longer progression-free periods for women with life-limiting illness.	Thank you for your comment. The committee considered this feedback and remains of the view that olaparib treatment offers meaningful clinical benefits to patients in terms of delaying disease progression and extending life.
3		Ovacome Ovarian Cancer Charity	As an oral medication olaparib can be managed at home, limiting the inconvenience to daily life for women with life-limiting illness, which is not an option with further chemotherapy treatment at more frequent intervals.	Thank you for your comment. The committee considered this feedback and remains of the view that olaparib treatment offers meaningful clinical benefits to patients in terms of delaying disease progression and extending life.
4		Ovacome Ovarian Cancer Charity	Having a choice of maintenance therapy which extends progression free survival and continued input from oncology teams offers significant psychological as well as health benefits, as women often feel abandoned and left to wait for the next recurrence after chemotherapy ends.	Thank you for your comment. The committee considered this feedback and remains of the view that olaparib treatment offers meaningful clinical benefits to patients in terms of delaying disease progression and extending life.

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5		Ovacome Ovarian Cancer Charity	Our members have made the following comments regarding olaparib: "I had olaparib after 3rd line chemo. It gave me 12 months of good quality of life, precious time spent with family enjoying time together and feeling well. I am so grateful to have been able to access this drug which was effective for me for that period of time- no amount of money can buy precious time" "I have been on a trial for Olaparib for 4 years 11 months. Although it's a double blind trial my onc[ologist] is in no doubt I am on it due to various side effects. It's given me a life, a chance to work full time, see grandchildren born and grow, a chance to travel, feel well. Basically a life, is there a price that can be put on that? Me being on this has impacted not just me but those who love me." "[My wife] found chemo hard to tolerate and this got worse with each successive round. The side effects of olaparib have always been much much less than chemo and have reduced with time, such that [she] now feels very well […] [My wife's] (and my own) quality of life has been so much better since she has started olaparib. She is back to walking regularly again and we have been on several holidays and short breaks in the past year. Making up for lost time!"	Thank you for your comment. The committee considered this feedback and remains of the view that olaparib treatment offers meaningful clinical benefits to patients in terms of delaying disease progression and extending life.
6		Ovacome Ovarian Cancer Charity	Ovarian cancer is frequently managed as a chronic condition rather than curative and therefore expanding available maintenance therapies which extend progression-free survival for this group of patients is vital.	Thank you for your comment. The committee considered this feedback and remains of the view that olaparib treatment offers meaningful clinical benefits to patients in terms of delaying disease progression and extending life.
1		Astra Zeneca	Thank you for the opportunity to comment on the Appraisal Consultation Document for olaparib as a maintenance treatment option for women with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer (PSR OC). AstraZeneca are currently working with NICE, NHS England and the Cancer Drugs Fund to agree a commercial access arrangement for this indication. As discussed in the Appraisal Consultation Document, olaparib significantly improves progression-free survival (PFS) in patients with PSR OC, compared to the current standard of care (i.e. routine surveillance/placebo). Clinical experts have explained that some patients are considered to be 'super-responders' to olaparib, with a substantial proportion receiving durable benefit and remaining on treatment without progression for several years (1). The long-term response achieved with olaparib is clearly beneficial to patients with PSR OC, but does introduce some financial uncertainty about long-term costs associated with olaparib maintenance treatment. For this reason, AstraZeneca have proposed a commercial access arrangement [redacted]The mechanisms for implementation of this type of arrangement are under discussion with NICE, NHS England and Cancer Drugs Fund stakeholders	Thank you for your comment. The company's new commercial arrangement has informed the committee's decision to recommend olaparib in the population with a BRCA mutation. Because the commercial arrangement does not apply to people without a BRCA mutation, the committee has been unable to make recommendations for this group, but recognises that there is evidence that olaparib works in this population and around 40% of 'super-responders' in the study 19 trial do not have a BRCA mutation

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2		Astra Zeneca	**We are concerned that Section 3.2 of the Appraisal Consultation Document does not clearly define routine surveillance as the comparator for this appraisal. This is inconsistent with the Final Scope.** At present, there are no active maintenance treatments available for routine use (i.e. baseline commissioning) in women with PSR OC, after response to platinum-based chemotherapy. The current standard of care is **routine surveillance** to monitor for clinical signs or symptoms of progression. This typically consists of regular clinical examinations and monitoring of blood counts and serum CA-125 levels, with radiologic imaging only performed if a patient develops symptoms or clinical signs that indicate recurrent disease. The statement that *"Niraparib is the only available targeted treatment option for people with relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer"* in Section 3.2 of the Appraisal Consultation Document is misleading for the following reasons: 1) Niraparib is not defined as a comparator in the scope for the current appraisal (1). 2) NICE have concluded that niraparib is not recommended for routine use within the NHS in England and Wales (2). Under the current NICE recommendation for use of niraparib through the Cancer Drugs Fund (TA528), access to niraparib is restricted to a subgroup of patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy in adults if: • they have a germline BRCA mutation and have had 2 courses of platinum-based chemotherapy OR • they do not have a germline BRCA mutation and have had 2 or more courses of platinum-based chemotherapy AND • the conditions in the managed access agreement for niraparib are followed. 3) Olaparib capsules are currently available as a maintenance treatment option for a subgroup of patients within the licensed indication, who have BRCAm PSR OC and have received three or more lines of platinum-based chemotherapy (TA381) (3). Despite the fact that niraparib is not a comparator for this appraisal, the Company Submission included supplementary data from a recently published Bayesian network meta-analysis of olaparib, niraparib and rucaparib in patients with BRCAm PSR OC, based on the results of the Phase III SOLO2, NOVA and ARIEL-3 trials (4). These analyses show that:	Thank you for your comment. This section of the guidance has now been removed to avoid any misinterpretation of the relevant comparator for the appraisal

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			• **Olaparib tablets, niraparib and rucaparib have similar efficacy in BRCAm PSR OC**, with no significant differences in the hazard ratios (HR) reported for either Investigator-assessed PFS or Blinded Independent Central Review (BICR)-assessed PFS, compared to placebo (Table 2 and Figure 1). • **Olaparib tablets have a superior tolerability profile compared with niraparib and rucaparib in BRCAm PSR OC**, with significantly reduced odds of patients experiencing Grade ≥ 3 AEs and treatment interruption (Table 3 and Figure 2).	
3		Astra Zeneca	**Section 3.4 of the Appraisal Consultation Document fails to recognise that differences in the pharmacokinetic profiles of olaparib capsules and tablets indicate that favourable efficacy outcomes may be observed with the tablet formulation.** As described in the Company Submission, the tablet formulation of olaparib was developed to improve patient convenience and reduce the high pill burden associated with the capsule formulation. It uses different technology to improve the solubility of olaparib, meaning that the therapeutic dose can be delivered in fewer dose units compared to the capsule formulation. A lower pill burden should improve patient experience on olaparib and may increase medication adherence. The Appraisal Consultation Docuovarian cment states that it is reasonable to assume that the tablet and capsule formulations of olaparib have similar efficacy and acknowledges that the capsule and tablet formulations of olaparib cannot be considered bioequivalent on a milligram for milligram basis. We wish to clarify that: 1) **Olaparib tablets are more bioavailable than the capsule formulation.** Higher exposures are observed with olaparib tablets versus olaparib capsules, with differences in steady state maximum plasma concentration (Cmax), steady state minimum plasma concentration (Cmin), and the area under the plasma concentration-time curve (AUC) (5). **2) Despite a similar relative effect (as measured by hazard ratios) a difference in the magnitude of difference in the median estimates was observed for PFS and TFST benefit in SOLO2, compared with Study 19 (**Error! Reference source not found.**)**: • Olaparib tablets were investigated in SOLO2, a large, double-blind, randomised controlled trial conducted in women with BRCAm PSR OC, who were in response to platinum-based chemotherapy (N = 295). In this trial, olaparib tablets significantly improved median	Thank you for your comment. The committee remains of the view that it is reasonable to assume that the tablet and capsule formulations of olaparib have similar efficacy but accept that SOLO 2 provides the most relevant evidence for people with a BRCA mutation

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			progression-free survival (PFS) by **13.6 months** (HR, 0.30; 95% CI, 0.22 to 0.41; P < 0.0001), and extended median time to subsequent therapy or death (TFST) by **20.8 months** (HR, 0.28; 95% CI, 0.21 to 0.38; P < 0.0001), versus the current standard of care (i.e. routine surveillance/placebo (6). • In contrast, olaparib capsules were investigated in Study 19, a large, double-blind randomised controlled trial conducted in women with PSR OC, unselected by BRCAm status (N = 265). In the intention-to-treat population, olaparib capsules significantly improved median PFS by 3.6 months (HR, 0.35; 95% CI 0.25 to 0.49; P<0.00001), and extended median TFST by 6.7 months (HR, 0.39; 95% CI, 0.30 to 0.52; P<0.00001) (7), compared to placebo. In the non-randomised subgroup of patients with BRCAm PSR OC, olaparib capsules extended median PFS by **6.9 months** (HR, 0.18; 95% CI, 0.10 to 0.31; P<0.00001) and median TFST by **9.4 months** (HR, 0.33; 95% CI, 0.22 to 0.49; P<0.00001) (7), compared to placebo.	
4		Astra Zeneca	**The Appraisal Consultation Document does not acknowledge the UK chart review presented in the Company Submission within the discussion regarding end-of-life criteria (Section 3.13). This study provides the best available data on normal life expectancy in the proposed population as it reports real-world survival data collected directly from 13 NHS Trusts in England, Wales and Scotland. Median OS in women with BRCAm PSR OC in routine clinical practice within the NHS was demonstrated to be 19.3 months – clearly qualifying for end-of-life consideration.** The UK chart review study is a high-quality observational study that was specifically designed to investigate real-world survival outcomes in women with BRCAm PSR OC in current UK clinical practice, after response to second-line platinum-based chemotherapy. We reiterate that: • The UK chart review study was conducted using the NHS-defined service evaluation methodology. The methods used for data collection and analysis were robust, with low risk of bias in patient selection and comprehensive data validation. Eligible patients were identified through a systematic chronological review of patient records, not individual case selection. • The UK chart review study included a large sample of patients with PSR OC (N = 233) from 13 general district hospitals and academic clinical practices distributed across England, Wales and Scotland (Clatterbridge Cancer Centre, St. George's Hospital, Airedale General Hospital, Barts Cancer Institute, City Hospital, Queen Alexandra Hospital, Weston Park Hospital, Southampton General Hospital, York Hospital, Mount Vernon Hospital, Beatson, Velindre Cancer Centre, and Singleton Hospital).	Thank you for your comment. The committee considered the evidence from the chart review alongside other evidence on the life expectance of patients receiving the standard of care at both the first and second committee meetings. The committee's conclusions regarding the applicability of the end of life criteria are captured in section 3.13 of the Final appraisal document

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			• The inclusion of patients from a mixture of large and small hospitals was critical for ensuring that the study accurately reflected outcomes in real-world clinical practice, as previous studies have demonstrated that survival outcomes for patients who are managed at UK centres with high clinical trial activity may be up to 45% better than the national average across the UK (8). • Median OS from the time of response to second-line platinum-based chemotherapy for UK patients with PSR OC after was **19.3 months,** ranging from 18.2 months to 19.8 months in pre-defined sensitivity analyses. Median OS from the time of response to third-line platinum-based chemotherapy was substantially shorter at **8.3 months**. • The robustness of the results of the UK chart review is supported by high consistency with OS data previously considered in TA381 from a large UK-based Phase III trial (ICON6, median OS **19.9 months** from the start of second-line platinum-based chemotherapy (9)) and a similarly-designed observational study conducted in Australia (median OS **21.9 months** from after completion of second-line platinum-based chemotherapy in patients with BRCAm PSR OC) (10). Full details of the methods and results of the UK chart review study were provided with the Company Submission within the Observational Study Report.	
5		Astra Zeneca	**The Committee have concluded that *"Olaparib improves progression-free survival compared with placebo but the benefit appears to be greater in the BRCA mutation-positive subgroup"* (Section 3.6). SOLO2 provides the best available data source for the evaluation of olaparib in BRCAm PSR OC, as it was a high-quality Phase III trial designed and powered to compare the proposed formulation (olaparib tablets) versus routine surveillance (placebo), in this specific patient group.** As described in the Company Submission, SOLO2 was a large, high-quality randomised, double-blind, placebo-controlled Phase III trial (N = 295) which conclusively demonstrates that maintenance treatment with olaparib tablets significantly improves PFS in patients with BRCAm PSR OC (HR, 0.30; P < 0.0001) (6). There was a **13.6-month** improvement in median PFS with olaparib tablets versus placebo (19.1 months for olaparib versus 5.5 months for placebo) and a **20.8-month** improvement in median TFST (27.9 months for olaparib versus 7.1 for placebo; HR, 0.28; P < 0.0001). The benefits of olaparib were maintained beyond disease progression, with significant extension in time from randomisation to second progression or death (PFS2; HR 0.50; P = 0.0002) and time to second subsequent therapy or death (TSST; HR, 0.37; P < 0.0001), versus placebo (6). data are currently immature (24.4% maturity) and suggest a trend towards improvement in OS with olaparib (HR, 0.80; 95% CI, 0.50 to 1.31) (6). Final analyses will be event-driven and are planned to be conducted at approximately	Thank you for your comment. The committee remains of the view that olaparib treatment offers meaningful clinical benefits to patients in terms of delaying disease progression and extending life, regardless of whether the person has a BRCA mutation. However, they also accept the view that SOLO 2 provides the most relevant evidence for people with a BRCA mutation and this has informed the decision to make olaparib tablets available in the CDF for people with a BRCA mutation who have received 2 previous courses of chemotherapy

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
			60% OS data maturity ([redacted]). Whilst further follow-up is required to address clinical uncertainty regarding the extent to which the PFS benefit observed with olaparib tablets in SOLO2 will translate to a long-term OS benefit, AstraZeneca is confident that with the commercial access arrangement being discussed with NICE, NHS England and the Cancer Drugs Fund, olaparib will be considered to be cost-effective compared with routine surveillance in the subgroup of women with BRCAm PSR OC. Based on this, we propose that the Committee consider olaparib as a candidate for the Cancer Drugs Fund.	
6		Astra Zeneca	**The modelling approach used to evaluate cost-effectiveness of olaparib tablets in the subgroup of patients with BRCAm PSR OC should be considered suitable for decision making, as it is near identical in design to the approach previously accepted in the NICE appraisal of niraparib (TA528).** In considering the evaluation of olaparib tablets in patients with BRCAm PSR OC using available SOLO2 data, it is important to note that: 1) Mature PFS data are available from SOLO2, meaning that time spent in the progression-free health state can be modelled directly, without relying on analyses of TFST or TDT. 2) SOLO2 OS data are currently immature for reliable long-term extrapolation (24.4% maturity), meaning that there is a degree of uncertainty regarding the extent to which the PFS benefit observed with olaparib tablets in SOLO2 will translate to a long-term OS benefit (as observed with olaparib capsules). 3) There was a similar level of OS data immaturity (<20% maturity) reported for the pivotal Phase III trial (NOVA) considered in the recent NICE appraisal of niraparib (TA528). The Bayesian network meta-analysis presented in Table 2 and Figure 1) shows that there is no evidence to suggest a difference in efficacy between olaparib tablets and niraparib may differ in patients with BRCAm PSR OC, so it is appropriate for similar economic modelling methods to be used to evaluate both PARP inhibitors, to ensure **consistency across appraisals**. In TA528, the cost-effectiveness of niraparib versus placebo in patients with PSR OC was evaluated using a decision analytic model based on mean value parameters. The model estimated the mean OS benefit of niraparib versus placebo based on a ratio of the mean PFS gain to mean OS gain observed with olaparib capsules in patients with BRCAm PSR OC in Study 19. The Company Submission estimated that there was a **1:2** ratio of mean PFS gain to mean OS gain observed with olaparib capsules in patients with BRCAm PSR OC Study 19 based on **digitised** Kaplan-Meier data. The Committee for this appraisal deemed the means-based decision analytic modelling approach to be	Thank you for your comment. The similarities between the company's alternative model and the model used in TA528 have been recognised by the committee throughout the appraisal. It is noted in the FAD for TA528 that the committee did not accept the overall survival estimates for niraparib derived from that model to be robust. Specifically, it states that 'use of a ratio between overall and progression-free survival meant that the estimate of overall survival benefit was entirely dependent on the size of the modelled progression-free survival benefit, which was subject to considerable uncertainty.' (TA528 FAD, section 3.13). The committee for the current appraisal remains of the view that this conclusion is equally relevant to the company's alternative model. However, at the second committee meeting the committee accepted the view that SOLO 2 provides the most relevant evidence for people with a BRCA mutation and that if further data from the trial support the assumption underlying the projected OS benefit in the company's alternative model then olaparib is likely to be cost effective. This has informed the committee's decision to make olaparib tablets available in the CDF for people with a BRCA mutation who have received 2 previous courses of chemotherapy

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			acceptable for decision making and considered that **the choice of model structure (partition survival vs means-based approach) was not critical, as long as the same assumptions for survival were used** (11). AstraZeneca's approach to modelling the cost-effectiveness of olaparib tablets in patients with BRCAm PSR OC is **near identical** to the means-based decision analytic modelling approach previously accepted by the Committee in TA518. Instead of using data from an analysis of digitised Kaplan-Meier curves, we have calculated that the actual ratio of mean PFS gain to mean OS gain observed in Study 19 in patients with BRCAm PSR OC ranged from [redacted], based on **individual patient-level data** (see Table 4). The analyses conducted to derive these ratios are described on page 9 of the Addendum to the Company's response to ERG Clarification Questions. **Consistent with the fact that olaparib tablets are anticipated to have similar efficacy compared to niraparib, the SOLO2 model predicts very similar mean OS gains to the TA528 model, when the same survival assumptions are applied**. If a 1:2 ratio of mean PFS gain to mean OS gain is assumed, the SOLO2 model predicts an overall mean OS gain of [redacted] years with olaparib tablets versus routine surveillance in patients with BRCAm PSR OC, while the TA528 model predicts an overall mean OS gain of 5.94 years with niraparib versus routine surveillance (Table 5). AstraZeneca is confident that this analysis, in combination with the commercial access arrangement being discussed with NICE NHSE England and the Cancer Drugs Fund demonstrates the cost-effectiveness of olaparib tablets in patients with BRCAm PSR OC.	
7		Astra Zeneca	**We disagree with the Committee's consideration that *"For modelling progression-free survival, time to treatment discontinuation is a better indicator of symptomatic progression than time to first subsequent therapy"* (Section 3.10).** These comments are not relevant to the economic evaluation of olaparib tablets in patients with BRCAm PSR OC, as mature PFS data are available for this patient subgroup from the Phase III SOLO2 trial. However, we believe that in cases where mature PFS data are not available, time to first subsequent therapy or death (TFST) provides a more clinically relevant endpoint to use as a proxy for symptomatic progression for economic modelling purposes than time to treatment discontinuation or death (TDT). As explained in the Company's response to the ERG report for this evaluation: 1) **Disease progression is not the only trigger for discontinuation of olaparib maintenance therapy.** In SOLO2, 37 of 112 patients (33.0%) who discontinued olaparib before the data cut-off for the primary analysis, did so	Thank you for your comment. The text has been amended to clarify the committees key concern that using time to first subsequent therapy is not a reliable method for modelling because it means that health benefits of being progression-free would be accrued within the model, without associated treatment costs, favouring olaparib. The sentence which stated that time to first subsequent therapy and time to treatment discontinuation were exploratory outcomes has been removed.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>based on the patient's decision (n=5), due to an adverse event (n=22), or for other reasons (e.g. loss to follow up or protocol non-compliance, n=10). In Study 19, 28 of 122 patients (23%) who discontinued treatment with olaparib, did so based on the patient's decision (n=14), due to an adverse event (n=8), or due to other reasons (n=6).

2) Patients with ovarian cancer typically receive subsequent treatment for relapsed disease at the time of symptomatic progression. It is well-established that there is no survival benefit associated with early treatment of relapsed ovarian, fallopian tube or peritoneal cancer in the absence of symptomatic progression. Because of this, re-treatment for relapsed disease is usually only initiated when symptoms develop or are about to develop (e.g. due to early renal obstruction or significant gastrointestinal serosal involvement) in current clinical practice in the UK.

3) There is no evidence to suggest that a patient's health-related quality of life deteriorates because of olaparib treatment discontinuation. SOLO2 and Study 19 have consistently shown that olaparib is generally well-tolerated and not associated with a detriment in health-related quality of life versus placebo in the proposed patient population. In contrast, the chemotherapy agents that are currently used for treatment of recurrent ovarian cancer are associated with significant and cumulative toxicities which may negatively impact quality of life and activities of daily living (e.g. severe nausea, vomiting, fatigue, alopecia and neuropathy). Because of this, TFST is considered to have a more meaningful impact on health-related quality of life and healthcare resource use than TDT.

We note that it is also incorrect to state that TFST and TDT "are exploratory outcomes, defined post hoc after unblinding of data" (Section 3.10) – these endpoints were included as pre-specified secondary analyses in SOLO2.</td><td></td></tr>
<tr><td>NA</td><td></td><td>Astra Zeneca</td><td>Table 1: Summary of clinical efficacy observed with olaparib capsules in Study 19 and olaparib tablets in SOLO2

<table>
<tr><th rowspan="3">Endpoint</th><th colspan="4">Study 19</th><th colspan="2">SOLO2</th></tr>
<tr><th colspan="2">PSR OC</th><th colspan="2">BRCAm PSR OC</th><th colspan="2">BRCAm PSR OC</th></tr>
<tr><th>Olaparib capsules
(N = 136)</th><th>Placebo
(N = 129)</th><th>Olaparib capsules
(N = 74)</th><th>Placebo
(N = 62)</th><th>Olaparib tablets
(N = 196)</th><th>Placebo
(N = 99)</th></tr>
<tr><td colspan="7">PFS (Investigator Assessment)</td></tr>
</table></td><td></td></tr>
</table>

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

Events, n/N (%)	60/136 (44)	93/129 (72)	26/74 (35)	46/62 (74)	107/196 (54.6)	80/99 (80.8)
Median PFS, months	8.4	4.8	11.2	4.3	19.1	5.5
Difference in median PFS, months	3.6		6.9		13.6	
HR (95% CI)	0.35 (0.25 to 0.49)		0.18 (0.10 to 0.31)		0.30 (0.22 to 0.41)	
P-value	P < 0.00001		P < 0.00001		P < 0.0001	
PFS (BICR)						
Events, n/N (%)	54/133 (40.6)	81/127 (63.8)	22/74 (29.7)	36/60 (60.0)	81/196 (41.3)	70/99 (70.7)
Median PFS, months	8.5	5.1	NC	4.8	30.2	5.5
Difference in median PFS, months	3.4		NC		24.7	
HR (95% CI)	0.39 (0.28 to 0.56)		0.22 (0.12 to 0.40)		0.25 (0.18 to 0.35)	
Nominal P-value	P < 0.00001		P <		P < 0.0001	
TFST						
Events, n/N (%)	106/136 (78)	124/128 (97)	55/74 (74)	59/62 (95)	92/196 (46.9)	79/99 (79.8)
Median TFST, months	13.3	6.7	15.6	6.2	27.9	7.1
Difference in median TFST, months	6.7		9.4		20.8	
HR (95% CI)	0.39 (0.30 to 0.52)		0.33 (0.22 to 0.49)		0.28 (0.21 to 0.38)	
Nominal P-value	P < 0.00001		P < 0.00001		P < 0.0001	

Table 2: Summary of data on the efficacy of olaparib, niraparib and rucaparib versus placebo in BRCAm PSR OC (Sackeyfio et al 2018) (4)

PARP	Study	PARP inhibitor vs placebo

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

inhibitor		Investigator-assessed PFS HR (95% CI)	BICR PFS HR (95% CI)
Olaparib	SOLO2	0.30 (0.22 to 0.41)	0.25 (0.18 to 0.35)
Niraparib	NOVA	0.27 (0.18 to 0.40)	0.27 (0.17 to 0.41)
Rucaparib	ARIEL3	0.23 (0.16 to 0.34)	0.2 (0.13 to 0.32)

Figure 1: Bayesian network meta-analysis of the efficacy of olaparib, niraparib and rucaparib in BRCAm PSR OC (Sackeyfio et al 2018) (4)

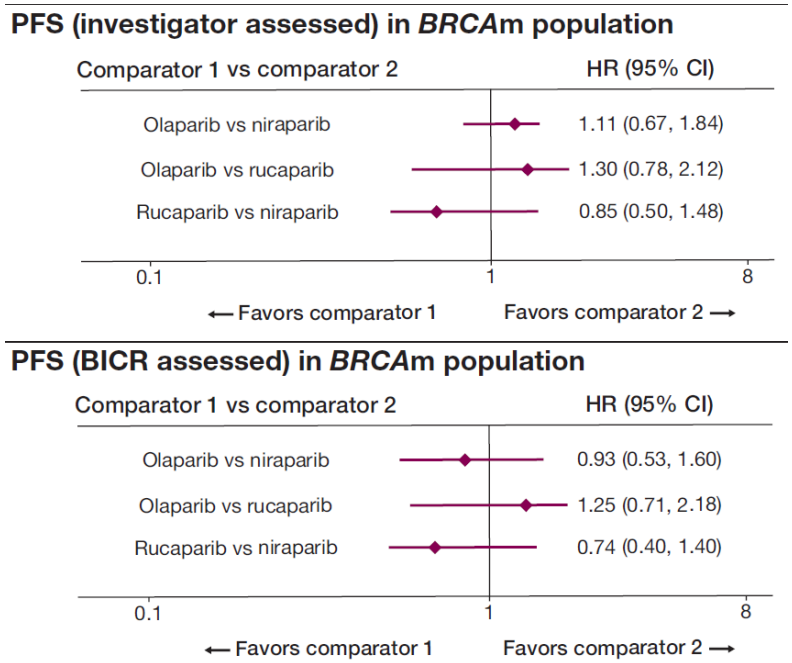

Table 3: Summary of data on the tolerability of olaparib, niraparib and rucaparib versus placebo in BRCAm PSR OC (Sackeyfio et al 2018) (4)

PARP	Study	PARP inhibitor vs placebo

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><th>inhibitor</th><th></th><th>Grade ≥ 3 AEs (%)</th><th>Dose interruption (%)</th><th>Dose reduction (%)</th></tr>
<tr><td>Olaparib</td><td>SOLO2</td><td>36.9 vs 18.2</td><td>45.1 vs 18.2</td><td>25.1 vs 3.0</td></tr>
<tr><td>Niraparib</td><td>NOVA</td><td>74.1 vs 22.9</td><td>66.5 vs 14.5</td><td>68.9 vs 5.0</td></tr>
<tr><td>Rucaparib</td><td>ARIEL3</td><td>54.6 vs 13.8</td><td>63.7 vs 10.1</td><td>54.6 vs 4.2</td></tr>
</table>
Figure 2: Bayesian network meta-analysis of the tolerability of olaparib, niraparib and rucaparib in BRCAm PSR OC (Sackeyfio et al 2018) (4)
</td><td></td></tr>
</table>

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

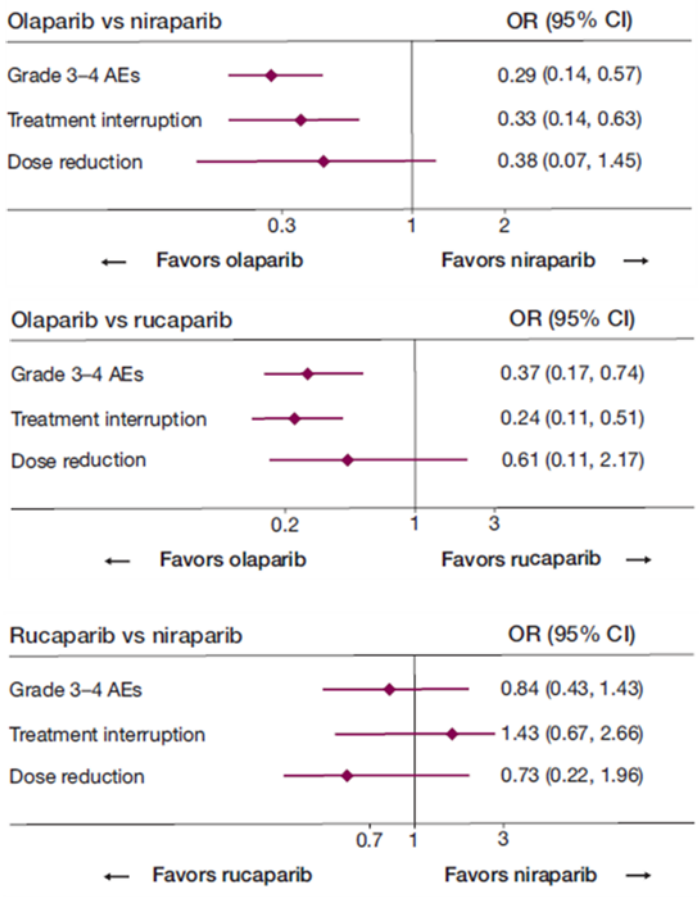

Table 4: Ratio of PFS:OS gain observed with olaparib versus placebo in Study 19

	Population			
	2nd or later line PSR OC (ITT population, unselected for BRCAm	**2nd or later line BRCAm subgroup** (N=136)	**2nd line BRCAm subgroup** (N=78)	**3rd or later line BRCAm subgroup** (N=58)

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

	status) (N=265)			
Ratio of mean PFS:OS gain, calculated from patient-level data	[redacted]	[redacted]	[redacted]	[redacted]

Table 5: Comparison of model outcomes (mean [years]; discounted)

Outcome	**Study 19** (capsules)			**SOLO2** (tablets)*			**NOVA****		
	Olaparib	**RS**	Δ	**Olaparib**	**RS**	Δ	**Niraparib**	**RS**	Δ
OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.40	3.48	5.94

*PFS (BICR) from SOLO2 2L BRCAm used to allow for consistency with TA528.
**Estimates extracted from Table 1 (page 28) of Appendix 1 of the committee papers that accompanied the FAD in TA528.

References

1. National Institute for Health and Care Excellence. Appraisal consultation document - Olaparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer 2018 [Available from: https://www.nice.org.uk/guidance/gid-ta10303/documents/129.
2. National Institute for Health and Care Excellence. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer. Technology appraisal guidance [TA528] 2018 [Available from: https://www.nice.org.uk/guidance/ta528.
3. National Institute for Health and Care Excellence. Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy [TA381] 2016 [Available from: https://www.nice.org.uk/guidance/ta381.
4. Sackeyfio A, Nussey F, Friedlander M, Pujade-Lauraine E. Comparative efficacy and tolerability of the PARP inhibitors olaparib 300 mg tablets BID, niraparib 300 mg capsules QD and rucaparib 600 mg tablets BID as maintenance treatment in BRCA-mutated (BRCAm) platinum-sensitive relapsed ovarian cancer (PSROC). SGO Annual Meeting on Women's Cancer. New Orleans: US; 2018.
5. Mateo J, Moreno V, Gupta A, Kaye SB, Dean E, Middleton MR, et al. An Adaptive Study to Determine the Optimal Dose of the Tablet Formulation of the PARP

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			Inhibitor Olaparib. Targeted oncology. 2016;11(3):401-15. 6. AstraZeneca. A Phase III Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed BRCA Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy. Clinical Study Report DCO1 2017. 7. AstraZeneca. A Phase II, randomised, double blind, multicentre study to assess the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens. Clinical Study Report DCO4 2016. 8. Khoja L, Nolan K, Mekki R, Milani A, Mescallado N, Ashcroft L, et al. Improved Survival from Ovarian Cancer in Patients Treated in Phase III Trial Active Cancer Centres in the UK. Clin Oncol (R Coll Radiol). 2016;28(12):760-5. 9. Ledermann JA, Embleton AC, Perren T, Jayson GC, Rustin GJS, Kaye SB, et al. Overall survival results of ICON6: A trial of chemotherapy and cediranib in relapsed ovarian cancer. Journal of Clinical Oncology. 2017;35(15_suppl):5506. 10. Hirst C, Parry D, Alsop K, deFazio A, Fereday S, Mitchell G, et al. Survival in patients with BRCA mutation-positive platinum-sensitive recurrent ovarian cancer. Journal of Clinical Oncology. 2014;32(15_suppl):e16519-e. 11. National Institute for Health and Care Excellence. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer [Final appraisal determination] 2018 [Available from: https://www.nice.org.uk/guidance/ta528/documents/final-appraisal-determination-document.	

Comments received from members of the public through the NICE Website

Role	Section	Comment [sic]	Response
Relative		Dear Sir/Madam I've heard the horrifying news about Ovarian Cancer tablets Olaparib Lynpraza. My Mum was on lynpraza for 18 months, wow they were amazing, they gave her, her life back, she actually felt well for the first time since her diagnosis in 2013, stage 3/4 , her cancer can't be cured only controlled with treatment Olaparib makes Huge difference, chemo strips everything, even good cells it makes you feel ill, whereas tablets don't, they give you your life back, it only takes away bad cells, you can live again, see family, see places, eat what you desire, don't lose your hair, they are a medical miracle When on chemo you can't see anyone each time for 10 days because of the risk and fear of infection, tablets are not like this. You don't have to have constant picc line in as that in its self is another fear as can cause problems. Dont give up on these tablets because then you will be giving up on the ladies that already suffer too much, this is much needed alternative for bodies that need break from chemo as it can keep you stable especially if your situation is only controlled not cured. We as family wish desperately the Mum could go back onto lynpraza but unfortunately you can only go it once, we will forever be thankful for these amazing tablets, my Mum fostered for 30 years and always cared for family, puts everyone before herself, these tablets made her feel in control of her own life again, as her daughter it was wonderful to see my Mum back again as she was, it was like she hadn't been diagnosed with the c word Please please don't just get rid of the tablets that hold so much importance to new medical hope, they give hope, they give life, they are a miracle in the darkest times.	Thank you for your comment. The committee has now recommended olaparib for patients with a BRCA mutation. The NICE recommendations specify that olaparib is made available via routine commissioning for people who have had 3 or more courses of platinum-based chemotherapy, and within the Cancer Drugs Fund for people who have had 2 courses of platinum-based chemotherapy.

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – ID296

Organisation name	AstraZeneca UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA
Comment number	**Comments**
1	Thank you for the opportunity to comment on the Appraisal Consultation Document for olaparib as a maintenance treatment option for women with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer (PSR OC). AstraZeneca are currently working with NICE, NHS England and the Cancer Drugs Fund to agree a commercial access arrangement for this indication. As discussed in the Appraisal Consultation Document, olaparib significantly improves progression-free survival (PFS) in patients with PSR OC, compared to the current standard of care (i.e. routine surveillance/placebo). Clinical experts have explained that some patients are considered to be 'super-responders' to olaparib, with a substantial proportion receiving durable benefit and remaining on treatment without progression for several years (1). The long-term response achieved with olaparib is clearly beneficial to patients with PSR OC, but does introduce some financial uncertainty about long-term costs associated with olaparib maintenance treatment. For this reason, AstraZeneca have proposed a commercial access arrangement [redacted] The mechanisms for implementation of this type of arrangement are under discussion with NICE, NHS England and Cancer Drugs Fund stakeholders
2	**We are concerned that Section 3.2 of the Appraisal Consultation Document does not clearly define routine surveillance as the comparator for this appraisal. This is inconsistent with the Final Scope.** At present, there are no active maintenance treatments available for routine use (i.e. baseline commissioning) in women with PSR OC, after response to platinum-based chemotherapy. The current standard of care is **routine surveillance** to monitor for clinical signs or symptoms of progression. This typically consists of regular clinical examinations and monitoring of blood counts and serum CA-125 levels, with radiologic imaging only performed if a patient develops symptoms or clinical signs that indicate recurrent disease. The statement that *"Niraparib is the only available targeted treatment option for people with relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer"* in Section 3.2 of the Appraisal Consultation Document is misleading for the following reasons: 1) Niraparib is not defined as a comparator in the scope for the current appraisal (1). 2) NICE have concluded that niraparib is not recommended for routine use within the NHS in England and Wales (2). Under the current NICE recommendation for use of niraparib through the Cancer Drugs Fund (TA528), access to niraparib is restricted to a subgroup of patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy in adults if: • they have a germline BRCA mutation and have had 2 courses of platinum-

Consultation on the appraisal consultation document – ID296

	based chemotherapy OR • they do not have a germline BRCA mutation and have had 2 or more courses of platinum-based chemotherapy AND • the conditions in the managed access agreement for niraparib are followed. 3) Olaparib capsules are currently available as a maintenance treatment option for a subgroup of patients within the licensed indication, who have BRCAm PSR OC and have received three or more lines of platinum-based chemotherapy (TA381) (3). Despite the fact that niraparib is not a comparator for this appraisal, the Company Submission included supplementary data from a recently published Bayesian network meta-analysis of olaparib, niraparib and rucaparib in patients with BRCAm PSR OC, based on the results of the Phase III SOLO2, NOVA and ARIEL-3 trials (4). These analyses show that: • **Olaparib tablets, niraparib and rucaparib have similar efficacy in BRCAm PSR OC**, with no significant differences in the hazard ratios (HR) reported for either Investigator-assessed PFS or Blinded Independent Central Review (BICR)-assessed PFS, compared to placebo (Table 2 and Figure 1). • **Olaparib tablets have a superior tolerability profile compared with niraparib and rucaparib in BRCAm PSR OC**, with significantly reduced odds of patients experiencing Grade ≥ 3 AEs and treatment interruption (Table 3 and Figure 2).
3	**Section 3.4 of the Appraisal Consultation Document fails to recognise that differences in the pharmacokinetic profiles of olaparib capsules and tablets indicate that favourable efficacy outcomes may be observed with the tablet formulation.** As described in the Company Submission, the tablet formulation of olaparib was developed to improve patient convenience and reduce the high pill burden associated with the capsule formulation. It uses different technology to improve the solubility of olaparib, meaning that the therapeutic dose can be delivered in fewer dose units compared to the capsule formulation. A lower pill burden should improve patient experience on olaparib and may increase medication adherence. The Appraisal Consultation Document states that it is reasonable to assume that the tablet and capsule formulations of olaparib have similar efficacy and acknowledges that the capsule and tablet formulations of olaparib cannot be considered bioequivalent on a milligram for milligram basis. We wish to clarify that: 1) **Olaparib tablets are more bioavailable than the capsule formulation.** Higher exposures are observed with olaparib tablets versus olaparib capsules, with differences in steady state maximum plasma concentration (Cmax), steady state minimum plasma concentration (Cmin), and the area under the plasma concentration-time curve (AUC) (5). **2) Despite a similar relative effect (as measured by hazard ratios) a difference in the magnitude of difference in the median estimates was observed for PFS and TFST benefit in SOLO2, compared with Study 19 (** **3) Table** 1**)**: • Olaparib tablets were investigated in SOLO2, a large, double-blind, randomised controlled trial conducted in women with BRCAm PSR OC, who were in response to platinum-based chemotherapy (N = 295). In this trial, olaparib tablets significantly improved median progression-free survival (PFS) by **13.6 months** (HR, 0.30; 95% CI, 0.22 to 0.41; P <

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	0.0001), and extended median time to subsequent therapy or death (TFST) by **20.8 months** (HR, 0.28; 95% CI, 0.21 to 0.38; P < 0.0001), versus the current standard of care (i.e. routine surveillance/placebo (6). • In contrast, olaparib capsules were investigated in Study 19, a large, double-blind randomised controlled trial conducted in women with PSR OC, unselected by BRCAm status (N = 265). In the intention-to-treat population, olaparib capsules significantly improved median PFS by 3.6 months (HR, 0.35; 95% CI 0.25 to 0.49; P<0.00001), and extended median TFST by 6.7 months (HR, 0.39; 95% CI, 0.30 to 0.52; P<0.00001) (7), compared to placebo. In the non-randomised subgroup of patients with BRCAm PSR OC, olaparib capsules extended median PFS by **6.9 months** (HR, 0.18; 95% CI, 0.10 to 0.31; P<0.00001) and median TFST by **9.4 months** (HR, 0.33; 95% CI, 0.22 to 0.49; P<0.00001) (7), compared to placebo.
4	**The Appraisal Consultation Document does not acknowledge the UK chart review presented in the Company Submission within the discussion regarding end-of-life criteria (Section 3.13). This study provides the best available data on normal life expectancy in the proposed population as it reports real-world survival data collected directly from 13 NHS Trusts in England, Wales and Scotland. Median OS in women with BRCAm PSR OC in routine clinical practice within the NHS was demonstrated to be 19.3 months – clearly qualifying for end-of-life consideration.** The UK chart review study is a high-quality observational study that was specifically designed to investigate real-world survival outcomes in women with BRCAm PSR OC in current UK clinical practice, after response to second-line platinum-based chemotherapy. We reiterate that: • The UK chart review study was conducted using the NHS-defined service evaluation methodology. The methods used for data collection and analysis were robust, with low risk of bias in patient selection and comprehensive data validation. Eligible patients were identified through a systematic chronological review of patient records, not individual case selection. • The UK chart review study included a large sample of patients with PSR OC (N = 233) from 13 general district hospitals and academic clinical practices distributed across England, Wales and Scotland (Clatterbridge Cancer Centre, St. George's Hospital, Airedale General Hospital, Barts Cancer Institute, City Hospital, Queen Alexandra Hospital, Weston Park Hospital, Southampton General Hospital, York Hospital, Mount Vernon Hospital, Beatson, Velindre Cancer Centre, and Singleton Hospital). • The inclusion of patients from a mixture of large and small hospitals was critical for ensuring that the study accurately reflected outcomes in real-world clinical practice, as previous studies have demonstrated that survival outcomes for patients who are managed at UK centres with high clinical trial activity may be up to 45% better than the national average across the UK (8). • Median OS from the time of response to second-line platinum-based chemotherapy for UK patients with PSR OC after was **19.3 months,** ranging from 18.2 months to 19.8 months in pre-defined sensitivity analyses. Median OS from the time of response to third-line platinum-based chemotherapy was substantially shorter at **8.3 months**. • The robustness of the results of the UK chart review is supported by high consistency with OS data previously considered in TA381 from a large UK-based Phase III trial (ICON6, median OS **19.9 months** from the start of second-line platinum-based chemotherapy (9)) and a similarly-designed observational study

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	conducted in Australia (median OS **21.9 months** from after completion of second-line platinum-based chemotherapy in patients with BRCAm PSR OC) (10). Full details of the methods and results of the UK chart review study were provided with the Company Submission within the Observational Study Report.
5	**The Committee have concluded that *"Olaparib improves progression-free survival compared with placebo but the benefit appears to be greater in the BRCA mutation-positive subgroup"* (Section 3.6). SOLO2 provides the best available data source for the evaluation of olaparib in BRCAm PSR OC, as it was a high-quality Phase III trial designed and powered to compare the proposed formulation (olaparib tablets) versus routine surveillance (placebo), in this specific patient group.** As described in the Company Submission, SOLO2 was a large, high-quality randomised, double-blind, placebo-controlled Phase III trial (N = 295) which conclusively demonstrates that maintenance treatment with olaparib tablets significantly improves PFS in patients with BRCAm PSR OC (HR, 0.30; P < 0.0001) (6). There was a **13.6-month** improvement in median PFS with olaparib tablets versus placebo (19.1 months for olaparib versus 5.5 months for placebo) and a **20.8-month** improvement in median TFST (27.9 months for olaparib versus 7.1 for placebo; HR, 0.28; P < 0.0001). The benefits of olaparib were maintained beyond disease progression, with significant extension in time from randomisation to second progression or death (PFS2; HR 0.50; P = 0.0002) and time to second subsequent therapy or death (TSST; HR, 0.37; P < 0.0001), versus placebo (6). data are currently immature (24.4% maturity) and suggest a trend towards improvement in OS with olaparib (HR, 0.80; 95% CI, 0.50 to 1.31) (6). Final analyses will be event-driven and are planned to be conducted at approximately 60% OS data maturity ([redacted]). Whilst further follow-up is required to address clinical uncertainty regarding the extent to which the PFS benefit observed with olaparib tablets in SOLO2 will translate to a long-term OS benefit, AstraZeneca is confident that with the commercial access arrangement being discussed with NICE, NHS England and the Cancer Drugs Fund, olaparib will be considered to be cost-effective compared with routine surveillance in the subgroup of women with BRCAm PSR OC. Based on this, we propose that the Committee consider olaparib as a candidate for the Cancer Drugs Fund.
6	**The modelling approach used to evaluate cost-effectiveness of olaparib tablets in the subgroup of patients with BRCAm PSR OC should be considered suitable for decision making, as it is near identical in design to the approach previously accepted in the NICE appraisal of niraparib (TA528).** In considering the evaluation of olaparib tablets in patients with BRCAm PSR OC using available SOLO2 data, it is important to note that: 1) Mature PFS data are available from SOLO2, meaning that time spent in the progression-free health state can be modelled directly, without relying on analyses of TFST or TDT. 2) SOLO2 OS data are currently immature for reliable long-term extrapolation (24.4% maturity), meaning that there is a degree of uncertainty regarding the extent to which the PFS benefit observed with olaparib tablets in SOLO2 will translate to a long-term OS benefit (as observed with olaparib capsules). 3) There was a similar level of OS data immaturity (<20% maturity) reported for the pivotal Phase III trial (NOVA) considered in the recent NICE appraisal of niraparib (TA528). The Bayesian network meta-analysis presented in Table 2 and Figure 1) shows that there is no evidence to suggest a difference in efficacy between olaparib

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	tablets and niraparib may differ in patients with BRCAm PSR OC, so it is appropriate for similar economic modelling methods to be used to evaluate both PARP inhibitors, to ensure **consistency across appraisals**. In TA528, the cost-effectiveness of niraparib versus placebo in patients with PSR OC was evaluated using a decision analytic model based on mean value parameters. The model estimated the mean OS benefit of niraparib versus placebo based on a ratio of the mean PFS gain to mean OS gain observed with olaparib capsules in patients with BRCAm PSR OC in Study 19. The Company Submission estimated that there was a **1:2** ratio of mean PFS gain to mean OS gain observed with olaparib capsules in patients with BRCAm PSR OC Study 19 based on **digitised** Kaplan-Meier data. The Committee for this appraisal deemed the means-based decision analytic modelling approach to be **acceptable for decision making** and considered that **the choice of model structure (partition survival vs means-based approach) was not critical, as long as the same assumptions for survival were used** (11). AstraZeneca's approach to modelling the cost-effectiveness of olaparib tablets in patients with BRCAm PSR OC is **near identical** to the means-based decision analytic modelling approach previously accepted by the Committee in TA518. Instead of using data from an analysis of digitised Kaplan-Meier curves, we have calculated that the actual ratio of mean PFS gain to mean OS gain observed in Study 19 in patients with BRCAm PSR OC ranged from [redacted], based on **individual patient-level data** (see Table 4). The analyses conducted to derive these ratios are described on page 9 of the Addendum to the Company's response to ERG Clarification Questions. **Consistent with the fact that olaparib tablets are anticipated to have similar efficacy compared to niraparib, the SOLO2 model predicts very similar mean OS gains to the TA528 model, when the same survival assumptions are applied**. If a 1:2 ratio of mean PFS gain to mean OS gain is assumed, the SOLO2 model predicts an overall mean OS gain of [redacted] years with olaparib tablets versus routine surveillance in patients with BRCAm PSR OC, while the TA528 model predicts an overall mean OS gain of 5.94 years with niraparib versus routine surveillance (Table 5). AstraZeneca is confident that this analysis, in combination with the commercial access arrangement being discussed with NICE NHSE England and the Cancer Drugs Fund demonstrates the cost-effectiveness of olaparib tablets in patients with BRCAm PSR OC.
7	**We disagree with the Committee's consideration that *"For modelling progression-free survival, time to treatment discontinuation is a better indicator of symptomatic progression than time to first subsequent therapy"* (Section 3.10).** These comments are not relevant to the economic evaluation of olaparib tablets in patients with BRCAm PSR OC, as mature PFS data are available for this patient subgroup from the Phase III SOLO2 trial. However, we believe that in cases where mature PFS data are not available, time to first subsequent therapy or death (TFST) provides a more clinically relevant endpoint to use as a proxy for symptomatic progression for economic modelling purposes than time to treatment discontinuation or death (TDT). As explained in the Company's response to the ERG report for this evaluation: 1) **Disease progression is not the only trigger for discontinuation of olaparib maintenance therapy.** In SOLO2, 37 of 112 patients (33.0%) who discontinued olaparib before the data cut-off for the primary analysis, did so based on the patient's decision (n=5), due to an adverse event (n=22), or for other reasons (e.g. loss to follow up or protocol non-compliance, n=10). In Study 19, 28 of 122 patients (23%) who discontinued treatment with olaparib, did so based on the patient's

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	decision (n=14), due to an adverse event (n=8), or due to other reasons (n=6). 2) **Patients with ovarian cancer typically receive subsequent treatment for relapsed disease at the time of symptomatic progression.** It is well-established that there is no survival benefit associated with early treatment of relapsed ovarian, fallopian tube or peritoneal cancer in the absence of symptomatic progression. Because of this, re-treatment for relapsed disease is usually only initiated when symptoms develop or are about to develop (e.g. due to early renal obstruction or significant gastrointestinal serosal involvement) in current clinical practice in the UK. 3) **There is no evidence to suggest that a patient's health-related quality of life deteriorates because of olaparib treatment discontinuation.** SOLO2 and Study 19 have consistently shown that olaparib is generally well-tolerated and not associated with a detriment in health-related quality of life versus placebo in the proposed patient population. In contrast, the chemotherapy agents that are currently used for treatment of recurrent ovarian cancer are associated with significant and cumulative toxicities which may negatively impact quality of life and activities of daily living (e.g. severe nausea, vomiting, fatigue, alopecia and neuropathy). Because of this, TFST is considered to have a more meaningful impact on health-related quality of life and healthcare resource use than TDT. We note that it is also incorrect to state that TFST and TDT *"are exploratory outcomes, defined post hoc after unblinding of data"* (Section 3.10) – these endpoints were included as pre-specified secondary analyses in SOLO2.

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Table 1: Summary of clinical efficacy observed with olaparib capsules in Study 19 and olaparib tablets in SOLO2

Endpoint	Study 19				SOLO2	
	PSR OC		BRCAm PSR OC		BRCAm PSR OC	
	Olaparib capsules (N = 136)	Placebo (N = 129)	Olaparib capsules (N = 74)	Placebo (N = 62)	Olaparib tablets (N = 196)	Placebo (N = 99)
PFS (Investigator Assessment)						
Events, n/N (%)	60/136 (44)	93/129 (72)	26/74 (35)	46/62 (74)	107/196 (54.6)	80/99 (80.8)
Median PFS, months	8.4	4.8	11.2	4.3	19.1	5.5
Difference in median PFS, months	3.6		6.9		13.6	
HR (95% CI)	0.35 (0.25 to 0.49)		0.18 (0.10 to 0.31)		0.30 (0.22 to 0.41)	
P-value	P < 0.00001		P < 0.00001		P < 0.0001	
PFS (BICR)						
Events, n/N (%)	54/133 (40.6)	81/127 (63.8)	22/74 (29.7)	36/60 (60.0)	81/196 (41.3)	70/99 (70.7)
Median PFS, months	8.5	5.1	NC	4.8	30.2	5.5
Difference in median PFS, months	3.4		NC		24.7	
HR (95% CI)	0.39 (0.28 to 0.56)		0.22 (0.12 to 0.40)		0.25 (0.18 to 0.35)	
Nominal P-value	P < 0.00001		P <		P < 0.0001	
TFST						
Events, n/N (%)	106/136 (78)	124/128 (97)	55/74 (74)	59/62 (95)	92/196 (46.9)	79/99 (79.8)
Median TFST, months	13.3	6.7	15.6	6.2	27.9	7.1
Difference in median TFST, months	6.7		9.4		20.8	
HR (95% CI)	0.39 (0.30 to 0.52)		0.33 (0.22 to 0.49)		0.28 (0.21 to 0.38)	
Nominal P-value	P < 0.00001		P < 0.00001		P < 0.0001	

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Table 2: Summary of data on the efficacy of olaparib, niraparib and rucaparib versus placebo in BRCAm PSR OC (Sackeyfio et al 2018) (4)

PARP inhibitor	Study	PARP inhibitor vs placebo	
		Investigator-assessed PFS HR (95% CI)	BICR PFS HR (95% CI)
Olaparib	SOLO2	0.30 (0.22 to 0.41)	0.25 (0.18 to 0.35)
Niraparib	NOVA	0.27 (0.18 to 0.40)	0.27 (0.17 to 0.41)
Rucaparib	ARIEL3	0.23 (0.16 to 0.34)	0.2 (0.13 to 0.32)

Figure 1: Bayesian network meta-analysis of the efficacy of olaparib, niraparib and rucaparib in BRCAm PSR OC (Sackeyfio et al 2018) (4)

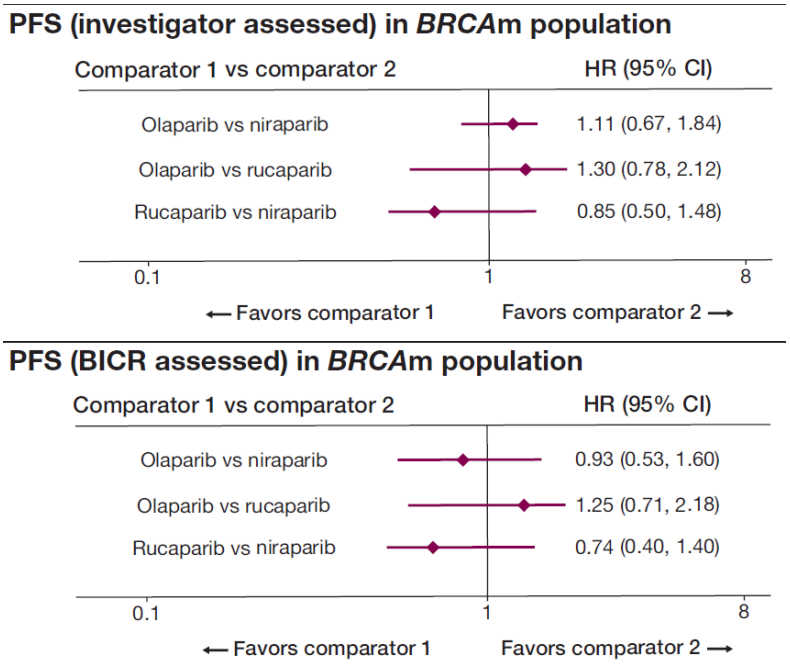

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Table 3: Summary of data on the tolerability of olaparib, niraparib and rucaparib versus placebo in BRCAm PSR OC (Sackeyfio et al 2018) (4)

PARP inhibitor	Study	PARP inhibitor vs placebo		
		Grade ≥ 3 AEs (%)	Dose interruption (%)	Dose reduction (%)
Olaparib	SOLO2	36.9 vs 18.2	45.1 vs 18.2	25.1 vs 3.0
Niraparib	NOVA	74.1 vs 22.9	66.5 vs 14.5	68.9 vs 5.0
Rucaparib	ARIEL3	54.6 vs 13.8	63.7 vs 10.1	54.6 vs 4.2

Figure 2: Bayesian network meta-analysis of the tolerability of olaparib, niraparib and rucaparib in BRCAm PSR OC (Sackeyfio et al 2018) (4)

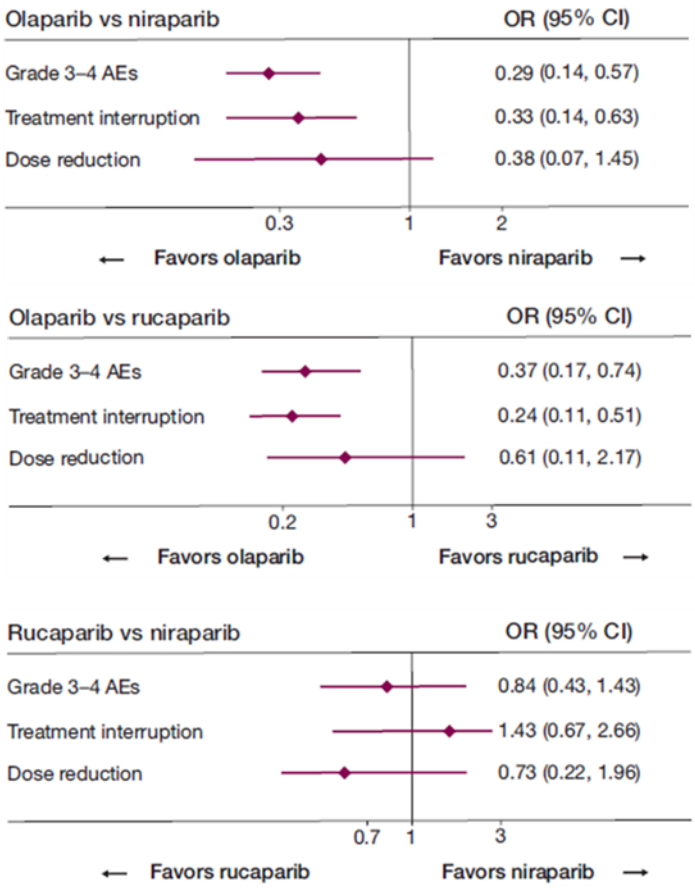

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Table 4: Ratio of PFS:OS gain observed with olaparib versus placebo in Study 19

	Population			
	2nd or later line PSR OC (ITT population, unselected for BRCAm status) (N=265)	**2nd or later line BRCAm subgroup** (N=136)	**2nd line BRCAm subgroup** (N=78)	**3rd or later line BRCAm subgroup** (N=58)
Ratio of mean PFS:OS gain, calculated from patient-level data	[redacted]	[redacted]	[redacted]	[redacted]

Table 5: Comparison of model outcomes (mean [years]; discounted)

Outcome	**Study 19** (capsules)			**SOLO2** (tablets)*			**NOVA****		
	Olaparib	**RS**	Δ	**Olaparib**	**RS**	Δ	**Niraparib**	**RS**	Δ
OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.40	3.48	5.94

*PFS (BICR) from SOLO2 2L BRCAm used to allow for consistency with TA528.
**Estimates extracted from Table 1 (page 28) of Appendix 1 of the committee papers that accompanied the FAD in TA528.

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2 July 2019

Dear [redacted],

Re: NICE appraisal of olaparib tablets in platinum-sensitive recurrent ovarian, fallopian tube and peritoneal cancer (PSR OC), that has responded to platinum-based chemotherapy [ID1296]

The NICE appraisal of olaparib tablets in women with PSR OC that has responded to platinum-based chemotherapy [ID1296] is scheduled for second committee meeting on 16 July 2019. We are committed to providing this innovative treatment to patients and are writing to confirm the following points:

1. **AstraZeneca request consideration of an optimised recommendation for olaparib tablets in the subgroup of women with BRCA-mutated (BRCAm) PSR OC**.

   Whilst olaparib significantly improves progression-free survival (PFS) in patients with PSR OC irrespective of BRCAm status (supported by Study 19), the committee has concluded that patients with BRCAm disease appear to receive a greater clinical benefit from olaparib maintenance treatment than those with non-BRCAm disease (see Appraisal Consultation Document [ACD], Section 3.6).

2. **The SOLO2 trial provides the most robust evidence available for olaparib tablets in BRCAm PSR OC.**

   SOLO2 provides the best available evidence on the efficacy and safety of olaparib tablets in BRCAm PSR OC, as it was a large (N = 295) Phase 3 trial which directly compared the proposed intervention and comparator in the sub-population of interest. In this trial, olaparib tablets reduced the risk of progression or death by 70% versus placebo (hazard ratio [HR], 0.30; p<0.0001),

reduced the risk of second progression or death by 50% (HR, 0.50; p=0.0002). and significantly improved time to first subsequent therapy (HR, 0.28; p<0.0001) and time to second subsequent therapy (HR, 0.37; 0.0001). Overall survival (OS) data are currently immature (24.4% maturity) and suggest a trend towards improvement in OS with olaparib (HR, 0.80; 95% CI, 0.50 to 1.31).

In contrast, Study 19 was a Phase 2 trial of olaparib capsules in women with PSR OC and the BRCAm subgroup was identified through a small retrospective subgroup analysis (N = 136).

3. **The SOLO2 cost-effectiveness model is suitable for use by NICE in decision making and was accepted by NICE in the appraisal of niraparib in PSR OC (TA528).**

   The decision-analytic model used to estimate the cost-effectiveness of olaparib based on data from the SOLO2 trial is near identical in structure to that used by NICE in its decision making for niraparib (TA528). Using this model enables NICE to ensure that consistent methods and assumptions are applied across appraisals of PARP inhibitors in PSR OC.

   The 1:2 ratio of incremental PFS:OS gain with olaparib tablets versus routine surveillance used in the model is conservative compared to the actual ratio of PFS:OS gain observed in BRCAm PSR OC patients in Study 19 (ratio of [redacted], see AZ response to ACD, Section 6 and Table 4).

   In recognition of the committee's uncertainty regarding the PFS:OS ratio that will be observed with further follow up of patients in the SOLO2 trial, an additional scenario is presented below which:

   i) Uses a 1:1.5 PFS:OS ratio instead of 1:2 ratio
   ii) Models time spent in the progression free health state based on PFS assessed by blinded independent central review (BICR) for consistency with TA528, and
   iii) Applies a confidential discount for olaparib tablets in this indication

4. **AstraZeneca and NHS England have agreed in principle [redacted] for use of olaparib tablets in the proposed population of patients with BRCAm PSR OC who have responded to platinum-based chemotherapy**.

   [redacted]

The cost-effectiveness results presented below show that use of olaparib is highly cost-effective in patients with BRCAm PSR OC [redacted], with base case incremental cost-effectiveness ratios ranging from [redacted] **and** [redacted].

Table 1: Updated cost-effectiveness results for olaparib tablets in BRCAm PSR OC, with use of PFS-BICR results (for consistency with TA528) [redacted]

Scenario	**Endpoint**	**ICER for olaparib tablets vs routine surveillance** [redacted]
AZ base case: 1:2 PFS:OS ratio	2L BRCAm	[redacted]
	3L+ BRCAm	[redacted]
Exploratory analysis: 1:1.5 PFS:OS ratio	2L BRCAm	[redacted]
	3L+ BRCAm	[redacted]

We trust that this information is helpful and are happy to provide further detail if required for the committee meeting on 16 July 2019.

For ease of reference, please note that:

- Full details regarding the clinical efficacy of olaparib tablets in BRCAm PSR OC are available in Section B.2.6 of Document B of the submission dossier
- Full details of the SOLO2 model are available in the August 2018 Addendum to AstraZeneca's response to clarification questions
- Clinical data supporting use of the 1:2 ratio of incremental PFS:OS gain are presented in Section 6 and Table 4 of AstraZeneca's response to the ACD

ACD - Consultees & Commentators: Ovarian, fallopian tube, peritoneal cancer - olaparib (maintenance, after platinum therapy) [ID1296]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 30/11/2018 **email:** [TACommA@nice.org.uk/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):	BRITISH GYNAECOLOGICAL CANCER SOCIETY
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**none**

Please return to: **[insert email address]** / NICE DOCS

ACD - Consultees & Commentators: Ovarian, fallopian tube, peritoneal cancer - olaparib (maintenance, after platinum therapy) [ID1296]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 30/11/2018 **email:** [TACommA@nice.org.uk/NICE DOCS

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.
1	The ACD has not taken sufficient account of two important secondary endpoints, Time to First Subsequent Treatment (TFST) and PFS2, a surrogate for overall survival. Thus, the ACD has not taken all of the relevant evidence into account, and as such the clinical and cost effectiveness. This compromises the interpretation of the evidence and the provisional recommendations for guidance to the NHS. PFS has been accepted by scientific community, peer review journals and licensing authorities as a relevant primary endpoint, so it is difficult to understand why the ERG (pg 24) states that PFS is a poor predictor of progression. Patients were not unblinded on progression and TFST is a clinically meaningful end point for patients, representing the time that patients can remain free from further intravenous cytotoxic chemotherapy. This exploratory endpoint in Study 19 was prospectively built into the analysis of SOLO2. The difference in median TFST was 20.8 months in SOLO2 [TFST HR 0·28 (95% CI 0·21–0·38), p<0·0001] compared to a difference in the median PFS of 13.8 months [PFS HR 0·33, (95% CI 0·24–0·44); p<0·0001]. This clinically relevant endpoint should be taken into consideration. The EMA have accepted PFS2 as a supporting endpoint for patients with an improved PFS in situations where OS data are not mature, recognising that in many trials a significant number of patients cross over to the trial drug, or other PARP inhibitor, and that long post progression survival makes it more challenging for trials to show significant OS benefit. The PFS2 data in SOLO2 in the population with a BRCA mutation show a significant continuing benefit for patients on olaparib at the time of second progression. In fact, the median time to second progression in the olaparib arm has not yet been reached; Of the 119 events, 70 [36%] occurred in the olaparib group compared with 49 [50%] in the placebo group. The median PFS2 in the placebo group is 18·4 months (15·4–22·8), suggesting that the results of further chemotherapy for many patients was relatively short-lived. This is the case in spite of cross over to PARP inhibitor in the placebo arm for some patients (This number crossing over (pg 69/185) has been redacted). The ACD should take account of the PFS2 findings, the fact that the median PFS2 for olaparib has not been reached, and the relatively short median PFS2 in the control arm compared to the median PFS. These two endpoints have clinical relevance and do not appear to have been taken into account in evaluating the clinical benefit of olaparib maintenance therapy in these patients
2	3.10 (page 9/14). Most patients discontinued treatment on radiological progression. The time to treatment discontinuation has been used as a model for symptomatic progression.

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NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 30/11/2018 **email:** [TACommA@nice.org.uk/NICE DOCS

	It is unclear what the justification for this assumption was. This comment relates to the long period before treatment was restarted after progression (see comment 1 above). Treatment would not be withheld if a patient had symptoms, so the time to treatment discontinuation is an inferior indicator of symptomatic progression that time to first subsequent treatment. The ERG should justify why time to treatment discontinuation is 'more reflective of real life clinical practiced', and why it was used.
3	
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Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- 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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[insert guidance topic title]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments [insert time] on [insert DD/MM/YY] **email:** [insert TAComm email address]/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):	Ovarian Cancer Action
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:	[redacted]

Comment number	Comments Insert each comment in a new row.

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[insert guidance topic title]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments [insert time] on [insert DD/MM/YY] **email:** [insert TAComm email address]/NICE DOCS

	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	One of the main concerns we have is that if tablet form of Olaparib is not approved in this consultation and the company press ahead with their intention of phasing out capsules it will leave 100s of women in the future unable to access Olaparib under the current guidelines. We appreciate that the company have said that they will continue to produce capsules until the very last person CURRENTLY on them stops taking them BUT does this mean after this point the guideline TA381 will simply cease to exist and future women who would be eligible now would not have access in the future? If the end result of this technology appraisal is that in the future women with ovarian cancer have fewer options for treatment than they do right now this would represent a crushing blow to the progress we have seen over the last three years. Ovarian cancer treatment has seen so few breakthroughs and developments over the past twenty years, and lags way behind other cancers so it is essential that we do not lose access to treatments that have only been approved relatively recently.
2	Ovarian cancer patient quote: given that capsules are already in use, and given that they are felt to have equal efficacy then surely the capsules should be considered for this change in the drugs role, to make the treatment affordable under NICEs costings guidelines. All medication needs to be prescribed responsibly in its most affordable effective form within a cost limited service such as the NHS, to help make more new treatments available for everyone.
3	We are still concerned that the impact on women who take the drug is being underestimated. Please see quotes from a patient who has been using this drug for the last two years: Huge extensions of life...the last chemo (4th time) didn't get rid of all the disease....so without Olaparib I very much doubt I would be here. It is most probably my last chance for any real extension of life. This obviously has massive implications for my friends and family. So far I've been on Olaparib 20 months. The most amazing 20 months. It brings incredible HOPE. Data shows that 20% of women are on the drug for 5 years plus. That is my target. So what difference on a daily basis....apart from the first three months which was tough..(side effects such as really bad nausea/fatigue etc etc)...I live a wonderful, manageable life. I can do the things to lead a great life. I still have to manage the fatigue, and stress of living with cancer, but can plan short term things like holidays and trips with my family. I play tennis, I paint. I am able to celebrate important life events of my children...ie my son going to Uni. Plan adventures with them. Share another Christmas. Build more memories with my children. Try and become a better person. Use my experiences of cancer and help others. Be more empathetic and compassionate....it goes on and on....what do we all want out of life?
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Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more

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than 1 set of comments from each organisation.

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- 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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[ID1296]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on [insert 30/11/18 **email:** [insert TAComm email address]/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):	Ovacome Ovarian Cancer Charity
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 number	Comments Insert each comment in a new row.

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[ID1296]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on [insert 30/11/18 **email:** [insert TAComm email address]/NICE DOCS

	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	We are concerned that the physical and psychological impact of olaparib availability to this group has not been taken fully into account. The development of biological therapies which extend progression free survival is offering hope of improved quality of life between chemotherapies when there had been no new chemotherapy options for many years.
2	The results of the SOLO-1 and SOLO-2 trials have shown significant progression free survival with tolerable side effects. This technology could make a huge difference to ovarian cancer relapse times which would extend times between platinum therapies potentially prolonging platinum chemotherapy use; it would also allow for improved quality of life during longer progression-free periods for women with life-limiting illness.
3	As an oral medication olaparib can be managed at home, limiting the inconvenience to daily life for women with life-limiting illness, which is not an option with further chemotherapy treatment at more frequent intervals.
4	Having a choice of maintenance therapy which extends progression free survival and continued input from oncology teams offers significant psychological as well as health benefits, as women often feel abandoned and left to wait for the next recurrence after chemotherapy ends.
5	Our members have made the following comments regarding olaparib: “I had olaparib after 3rd line chemo. It gave me 12 months of good quality of life, precious time spent with family enjoying time together and feeling well. I am so grateful to have been able to access this drug which was effective for me for that period of time- no amount of money can buy precious time” “I have been on a trial for Olaparib for 4 years 11 months. Although it’s a double blind trial my onc[ologist] is in no doubt I am on it due to various side effects. It’s given me a life, a chance to work full time, see grandchildren born and grow, a chance to travel, feel well. Basically a life, is there a price that can be put on that? Me being on this has impacted not just me but those who love me.” “[My wife] found chemo hard to tolerate and this got worse with each successive round. The side effects of olaparib have always been much much less than chemo and have reduced with time, such that [she] now feels very well […] [My wife’s] (and my own) quality of life has been so much better since she has started olaparib. She is back to walking regularly again and we have been on several holidays and short breaks in the past year. Making up for lost time!”
6	Ovarian cancer is frequently managed as a chronic condition rather than curative and therefore expanding available maintenance therapies which extend progression-free survival for this group of patients is vital.

Insert extra rows as needed

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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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Olaparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer [ID1296]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments [insert time] on [insert DD/MM/YY] **email:** [insert TAComm email address]/NICE DOCS

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.	N/A
Name of commentator person completing form:	[redacted]

Comment number	Comments
1	**The importance of olaparib in improving progression free survival** Target Ovarian Cancer believes that women with ovarian cancer and their clinicians need all relevant treatment options available in the armoury for managing ovarian cancer. This is particularly important as the disease progresses and women are treated for multiple recurrences. In particular, apart from the obvious immediate benefit to women with ovarian cancer in terms of quality of life, extending progression free survival is likely to prolong the usefulness of platinum-based chemotherapy.
2	**The future of TA381** We are disappointed that NICE has not recommended olaparib within its marketing authorisation for recurrent disease. We are concerned that if this guidance will leave a subgroup of women without an option to be treated with a PARP inhibitor. TA528 recommends that women with a BRCA mutation can only access niraparib as part of second line treatment on the basis that olaparib is available for this group for third line treatment. There will be a group of women that have undergone second line treatment prior to approval of niraparib, who are yet to relapse and require third line treatment, who will be unable to access olaparib under this guidance. It is currently unclear on the status of TA381 and the future of olaparib in capsule form for women yet to start treatment if the tablet

	form is unsuccessful in securing NICE approval.
3	**Cost effectiveness** Target Ovarian Cancer notes that the tablet formulation of olaparib does not comply with cost effectiveness models. However we observe the following: *3.3 the tablet formulation is likely to have a positive impact on quality of life.* *3.4 the tablet and capsule formulation have similar efficacy.* *3.6 olaparib improves PFS irrespective of BRCA mutation, but people with BRCA-mutation positive disease may experience greater benefit.* *3.8 olaparib has a manageable adverse-effects profile.* We urge the manufacturer and NICE to work together to resolve the issue of cost effectiveness.
4	**Quality of life** Women and their families feel very strongly that olaparib is a game changer in terms of ovarian cancer treatment. The quotes below, submitted in response to an online survey conducted by Target Ovarian Cancer, show the difference olaparib has made to women with ovarian cancer and their families. *"It has given us hope. After several cycles of chemotherapy olaparib is less invasive and improves quality of life. This is a major breakthrough and should be freely offered to cancer patients that have met the criteria. It is life changing."* *"I have now been on olaparib for over eight months and can honestly say it allows you to start to live and feel 'normal' again. None of the terrible side effects of chemo and best of all, most importantly, it has kept my ovarian cancer away."* *"My dearest friend has been taking olaparib for over two years. She is now able to live a near normal life, something which chemotherapy took from her. This drug is her lifeline."* *"I still have my wife after being told she probably wouldn't live beyond eight to nine months. This was over two years ago. We were out of options until olaparib. She is well and enjoying life."*

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Dear Sir/Madam

I've heard the horrifying news about Ovarian Cancer tablets Olaprid Lynpraza.
My Mum was on lynpraza for 18 months, wow they were amazing, they gave her, her life back, she actually felt well for the first time since her diagnosis in 2013, stage 3/4 , her cancer can't be cured only controlled with treatment

olaparid makes Huge difference, chemo strips everything, even good cells it makes you feel ill, whereas tablets don't, they give you your life back, it only takes away bad cells, you can live again, see family, see places, eat what you desire, don't lose your hair, they are a medical miracle

When on chemo you can't see anyone each time for 10 days because of the risk and fear of infection, tablets are not like this.

You don't have to have constant picc line in as that in its self is another fear as can cause problems.

Dont give up on these tablets because then you will be giving up on the ladies that already suffer too much, this is much needed alternative for bodies that need break from chemo as it can keep you stable especially if your situation is only controlled not cured.

We as family wish desperately the Mum could go back onto lynpraza but unfortunately you can only go it once, we will forever be thankful for these amazing tablets, my Mum fostered for 30 years and always cared for family , puts everyone before herself, these tablets made her feel in controll of her own life again, as her daughter it was wonderful to see my Mum back again as she was, it was like she hadn't been diagnosed with the c word

Please please don't just get rid of the tablets that hold so much importance to new medical hope, they give hope, they give life, they are a miracle in the darkest times.

Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (including a review of technology appraisal no. 381)

ERG response to company's consultation comments

This report was commissioned by the NIHR HTA Programme as project number 18/54/05

BMJ Technology Assessment Group

The company for the appraisal of olaparib submitted comments on the appraisal consultation document (ACD) and this document provides the Evidence Review Group (ERG) response to comment 5 and 6, which concerns the use of SOLO2 as the best data source for the BRCA population and the alternative SOLO2 model. At the time of the submission of the ERG report, overall survival (OS) data from SOLO2 was immature and as such the company submitted a new model (referred to hereafter as the SOLO2 model). The SOLO2 model was based on the same assumptions used for the appraisal of niraparib (TA528), and the company asked that olaparib be considered for the cancer drugs fund (CDF) for the BRCA population.

In TA528, the committee recommended that niraparib be made available through the CDF for the 2nd line BRCA and 2nd line+ non-BRCA populations. Niraparib was not recommended for the 3rd line BRCA population. The ICER range (as published in the final appraisal determination) for the 2nd line BRCA group was £20,694 (company) to £54,632 (ERG).

The ERG considers that it is useful to provide a brief comparative overview of the key modelling assumptions made in TA528 and the assumptions made in the SOLO2 model provided by the company for the appraisal of olaparib for the BRCA population. Table 1 presents the company's ICERs from the SOLO2 model. The ERG scenario analyses provided in Table 2 are solely for illustrative purposes to help the committee understand the impact on the ICER when the assumptions made in TA528 and SOLO2 model are aligned.

The SOLO2 model and its input parameters have not undergone a thorough investigation and assessment as the ERG considers the assumptions made in the model, particularly around the use of a means-based approach and a 1:2 PFS to OS ratio, are not appropriate for decision making and it was sent by the company after the ERG report was submitted.

Key assumptions made by the company in its base case model for TA528

- A 1:2 PFS to OS ratio – the ERG preferred to assume that the risk of death upon progression is equal in both treatment groups (i.e. 1:1 PFS to OS ratio) as there is no evidence in the wider ovarian cancer literature to support the 1:2 ratio;

- Progression-free survival (PFS) data used to model PFS health state;

- Tim to treatment discontinuation (TTD) used to model costs – the ERG base case analyses assumed that TTD was equal to PFS as there was a disconnect between the two sources of data which meant that benefits were accrued without the appropriate associated treatment costs to obtain them.

Company base case assumptions made by the company in the SOLO2 model

- A 1:2 PFS to OS ratio;
- Time to first subsequent treatment (TFST) data used to model the PFS health state;
- TTD data used to estimate costs (the difference between mean TFST and mean TTD is approximately [redacted]).

ERG changes made to the SOLO2 model to align with ERG preferences for TA528

- Risk of death upon progression is equal to 1 (i.e. 1:1 PFS to OS ratio);
- PFS data used to model the PFS health state;
- TTD data used to estimate costs as difference between mean PFS and mean TTD is approximately [redacted] – the ERG considered that difference between the two estimates is important, but as mentioned previously, the model and inputs have not been through rigorous review and so the ERG made this simplifying assumption for the purposes of providing an illustrative range of ICERs.

Table 1. Summary of company scenario analyses for the BRCAm subgroup using SOLO2 data – List price

Population	Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
2nd line+ BRCAm	Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	-
	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2nd line BRCAm	Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	-
	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd line+ BRCAm	Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	-
	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation, ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year.

Table 2 Summary of ERG scenario analyses for the BRCAm subgroup using SOLO2 data – List price

Population	Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
2nd line+ BRCAm	Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	-
	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2nd line BRCAm	Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	-
	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd line+ BRCAm	Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	-
	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation, ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year.

Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (including a review of technology appraisal no. 381)

ERG response to letter from Astra Zeneca

July 2019

This report was commissioned by the NIHR HTA Programme as project number 18/54/05

BMJ Technology Assessment Group

The company for the appraisal of olaparib submitted a letter to the National Institute of Health and Care Excellence (NICE) in advance of the second appraisal committee meeting (ACM) due to take place on the 16th of July 2019. In the letter, the company raise four points for committee consideration:

1. The company requested consideration of an optimised recommendation for olaparib tablets in the breast cancer susceptibility gene mutation (BRCAm) subgroup;

2. The SOLO2 trial provides robust evidence for olaparib tablets in the BRCAm subgroup;

3. The alternative SOLO2 means-based cost-effectiveness model is suitable for decision making, with the justification that the structure was accepted by NICE for TA528 (niraparib); and

4. The company have proposed [redacted] agreement for a [redacted] discount on olaparib tablets for the BRCAm subgroup with NHS England.

The company presented new cost-effectiveness results for BRCAm patients who have had 2 or 3 lines of platinum-based chemotherapy (hereafter, 2L BRCAm and 3L+ BRCAm), which includes the proposed [redacted] and use of progression-free survival (PFS) estimates based on blinded independent central review (BICR) instead of time to first subsequent therapy (TFST) as per the original analysis from SOLO2. This change in the company's approach is in response to the ACD, Section 3.10, where the committee indicated that TFST was not a good indicator of symptomatic progression. No other changes to the modelling or additional evidence have been provided by the company.

In summary, the ERG concludes that:

- While SOLO2 compares olaparib tablets and routine surveillance in the BRCAm subgroup, overall survival (OS) data from the trial are currently immature. In the appraisal consultation document (ACD), Section 3.4, the committee concluded that it is reasonable to assume that the tablet and capsule formulations of olaparib have similar efficacy. Based on the committee view, the ERG considers that Study 19 is the best available source of mature data for both PFS and OS outcomes, as it maintains the integrity and relationship between the two outcomes, which is appropriate for modelling cost-effectiveness.

- In the ACD, Section 3.11, the committee stated that the SOLO2 means-based model was not suitable for decision making. The company has not presented any new evidence to challenge the committee's conclusion. Thus, the ERG considers that company's original partitioned survival model using Study 19 data is the most appropriate approach to estimate cost-effectiveness for the BRCAm subgroup.

Review of company's updated Base case analysis

In the company's letter to NICE, revised base case results using the company's alternative SOLO2 means-based model were provided, which included a proposed [redacted] agreement for a [redacted] discount on olaparib tablets for the BRCAm subgroup with NHS England. In addition to the discount, the company revised its assumption for modelling the PFS health state. In the original analysis, provided as an addendum to the company's clarification response, TFST from SOLO2 was used to model the progression-free health state. In the revised analysis, the company has selected to use PFS assessed by the BICR for the PFS health state.

In the ACD, Section 3.11, the committee concluded that, "***the company's alternative model for the BRCA mutation-positive subgroup is not suitable for decision***". The company state that the SOLO2 means-based model is fit for decision making and it asserts that the model structure was accepted by the committee for TA528 (niraparib). Table 1 presents the company's updated base case results for the BRCAm subgroup using the SOLO2 means-based model.

Table 1. Summary of company cost-effectiveness analyses for the BRCAm subgroup using SOLO2 data including [redacted]

Population	Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
2nd line BRCAm	Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	-
	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd line+ BRCAm	Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	-
	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation, ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year.

As discussed in the ERG's addendum response and illustrative SOLO2 analyses document, the ERG does not consider the company's SOLO2 means-based model to be fit for decision making as the calculation of OS is entirely dependent on the size of the PFS benefit, due to the use of a PFS to OS ratio (which the company has set as 1:2). The ERG considers that a PFS to OS relationship is unreliable and requires further validation. Both of these points were also supported in the final appraisal determination (FAD) for TA528 (niraparib). As no new evidence has been supplied by the company, the ERG's stance on the use of the SOLO2 means-based model is similarly unchanged.

Furthermore, as discussed in the ERG report, Section 4.3.2.1, there was a substantial difference in PFS estimates assessed by the BICR compared with the investigator assessed PFS. Median PFS for olaparib as assessed by the investigator was 19.1 months and for the BICR analysis median PFS was estimated to be 30.2 months. The ERG considers that one of the main drivers of the difference between the two estimates is due to the use of informative censoring.

The company's use of PFS assessed by BICR is as a more favourable assumption for olaparib compared with using PFS assessed by the investigator. If investigator-assessed PFS is used for the company base case, the ICERs for 2L BRCAm and 3L+ BRCAm are [redacted] and [redacted], respectively. Thus, using BICR PFS combined with the PFS to OS ratio of 1:2, only serves to inflate the assumed overall survival benefit, thus enforcing the ERG's view that a means-based model produces unreliable estimates of cost- effectiveness.

The ERG maintains that the most appropriate model available for decision making is the company's original partitioned survival model using Study 19 data and it should be used to assess the cost-effectiveness of the BRCAm population. The ERG acknowledges that SOLO 2 is a methodologically more robust study for the BRCAm population than Study 19 as it is a prospectively randomised controlled trial, whereas the BRCAm population from Study 19 was identified retrospectively. However, OS is currently immature from SOLO 2 and as the committee has concluded that, "***it is reasonable to assume that the tablet and capsule formulations of olaparib have similar efficacy***", Study 19 is appropriate to use for the economic model due to the maturity of data for both PFS and OS outcomes. As such, Study 19 is the most reliable source of PFS and OS as it maintains the integrity and inter-relationship of the outcomes to estimate the cost effectiveness of olaparib tablets.

Using the ERG's preferred assumptions as discussed in the ERG report, Section 6.3 (outlined below) and applying the company's proposed [redacted] agreement, Table 2 presents the ERG's base case ICERs for the 2LBRCAm and 3L+ BRCAm subgroups.

The ERG's preferred assumptions are as follows:

- 50-year time horizon;
- TTD (1-knot spline) for modelling the progression-free health state;
- Inclusion of drug wastage;
- Distribution of subsequent therapy over 30.44 days;
- Use of SOLO2 health state utility values by line of therapy

Table 2. Summary of ERG base case analysis for the BRCAm subgroup using Study 19 data including [redacted]

Population	Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
2nd line BRCAm	Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	-
	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3rd line+ BRCAm	Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	-
	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation, ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year.