National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Rucaparib for treating relapsed ovarian, fallopian tube or peritoneal cancer that has a BRCA mutation [ID1184]

Response to consultee and commentator comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Clovis Oncology	To align with our MAA submission, we suggest the following rewording: "To appraise the clinical and cost effectiveness of rucaparib within its marketing authorisation for monotherapy treatment of advanced ovarian cancer in adult patients with deleterious BRCA mutated tumours, inclusive of both germline BRCA and somatic BRCA mutations, and who have been treated with two or more prior lines of chemotherapy."	Comment noted. The remit is intended to be a broad outline of the appraisal - no changes considered necessary.
	Janssen	The wording of the remit is appropriate and reflects the issues of clinical and cost effectiveness of rucaparib for treating relapsed ovarian, fallopian tube or peritoneal cancer that has a BRCA mutation.	Comment noted. No action required.
	National Cancer Research Institute	The remit states 'appraisal of rucaparib within its marketing authorisation'. Rucuparib does not yet have a marketing authorisation in the UK. An application was submitted to the EMA in November for use as monotherapy in the treatment of advanced ovarian cancer in patients with deleterious BRCA-mutated tumours inclusive of both germline and somatic BRCA mutations. However, Rucaparib is also being investigated as maintenance treatment for advanced ovarian cancer in the ARIEL 3 study. The results of	Comment noted. The current appraisal will not include maintenance treatment.

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		ARIEL 3 study are due very soon and if positive then our experts believe a supplemental NDA for second-line maintenance treatment will be submitted. If this will also be considered in the appraisal indications should be considered separately and will require different comparators. Our experts recommend clarifying that it is epithelial ovarian, fallopian tube and peritoneal cancers.	
	Ovacome	Yes	Comment noted. No action required.
Timing Issues	British Gynaecological Cancer Society	There is an urgent clinical need to address as the outcome for patients with advanced ovarian cancer are very poor and survival inferior to other European countries; drugs such as rucaparib represent targeted approach that is usually more effective.	Comment noted. No action required.
	National Cancer Research Institute	Recurrent ovarian cancer is an area of unmet need. PARP inhibitors represent a significant advance in the treatment of recurrent ovarian cancer, giving another therapeutic option with the potential to avoid or delay the need for cytotoxic chemotherapy. There is, therefore, an urgency to assess these agents.	Comment noted. No action required.
	Ovacome	Currently no PARP inhibitors are available to platinum–resistant patients and for platinum sensitive patients only as maintenance therapy. Rucaparib has the potential to offer a new patient group the option of a PARP inhibitor, and an increased choice of treatment for BRCA patients with progressive disease. Therefore, it is urgent that this technology is appraised.	Comment noted. No action required.
	Ovarian Cancer Action	Ovarian cancer is the biggest gynaecological cancer killer in the UK, killing more women than the other four gynaecological cancers combined (womb, cervical, vagina and vulva), and the 5-year survival is only 49%. As such	Comment noted. No action required.

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		Ovarian Cancer Action believes this appraisal should go ahead in a timely manner so as to give women facing a diagnosis the best chance at survival.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Gynaecological Cancer Society	The background about ovarian cancer and rucaparib does not take (or at least it is not clear in the wording) into account the population of patients with somatic BRCA mutation ; this distinction is important to make as somatic mutation testing is now available and there was a clear benefit for patients with BRCA somatic mutation not only germline.	Comment noted. The scope has been amended to include more detail on BRCA 1 and 2 mutations.
	Clovis Oncology	Following additions/modifications will reflect a more complete and up-to-date background information: Paragraph 1: BRCA 1 and 2 can be germline and somatic so the paragraph needs to be amended to include the non-inherited BRCA 1 and 2. Paragraph 2: The office for national statistics had their latest release on May 24th so please update the new data as “In 2015, 5,771people were diagnosed with ovarian cancer in England and there were 3,325 deaths from ovarian cancer in 2015” The updated ONS data can be found here. Paragraph 4: In accordance with its marketing authorisation and NICE guidelines, olaparib is indicated as maintenance treatment. Since rucaparib has a treatment indication, which is different than maintenance indication, it is important to specifically mention in the background that olaparib is indicated for maintenance only.	Comment noted. The scope has been amended to include more detail on BRCA 1 and 2 mutations. Paragraph 2 has been updated with the latest information from the Office for National Statistics. Paragraph 4 has been amended to make clear that olaparib is indicated for maintenance treatment.

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	National Cancer Research Institute	NICE technology appraisal guidance 389 only makes recommendations on first recurrence. This should be made clear since the initial marketing authorisation for rucaparib will be after at least 2 lines. It should be clarified that the marketing authorisation for olaparib is after at least 2 lines of platinum therapy. It is the NICE appraisal that limits it to after 3 lines of platinum treatment.	Comment noted. The exact wording from the recommendations in technology appraisal 389 has been used. For olaparib, the recommendation from the NICE appraisal has been used because this is indicative of its use in clinical practice.
	Ovacome	The NICE pathway defines advanced ovarian cancer and stages II-IV. This appraisal defines advanced ovarian cancer as stages III-IV. This needs consistency.	Comment noted. The scope has been amended.
	Ovarian Cancer Action	Please include information on the prevalence of BRCA mutations and the increased risks they confer so as to give a greater understanding of the impact of this treatment. The prevalence of BRCA1/2 mutations in serous ovarian cancer patients has been found to be as high as 17-20% and up to 25% in those with high-grade serous cancer (Alsop K, et al. J Clin Oncol 2012;30:2654-63; Schrader KA, et al. Obstet Gynecol 2012;120:235–40). Of these, as many as half have no family history to have prompted genetic testing and therefore had no opportunity to take risk-reducing action. In addition, even with knowledge of a BRCA mutation, these patients have no reliable screening methods to detect cancer at an early stage, their only option for significant risk reduction is surgical removal of their ovaries and fallopian tubes	Comment noted. The scope has been amended to include more detail on the prevalence of BRCA 1 and 2 mutations.

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		In order for this treatment to reach the relevant patients, it is vital that all women are offered genetic testing and genetic counselling at the time of their diagnosis with ovarian cancer. Although this should be the case, we know it is inconsistent across the country and continue to campaign for consistency in this regard.	
The technology/ intervention	British Gynaecological Cancer Society	Yes	Comment noted. No action needed.
	Clovis Oncology	Please rephrase the technology as below: "Rucaparib (Rubraca, Clovis Oncology) is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3, which play a role in DNA repair. rucaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis, and cell death. Increased rucaparib-induced cytotoxicity was observed in tumour cell lines with deficiencies in BRCA1/2 and other DNA repair genes. Rucaparib has been shown to decrease tumour growth in mouse xenograft models of human cancer with or without deficiencies in BRCA. Rucaparib is administered orally at home setting.	Comment noted. The scope has been updated with some of the suggested changes, taking into account the level of detail appropriate for inclusion in scopes.
	National Cancer Research Institute	Rucaparib is also being studied as a maintenance treatment after response to platinum based chemotherapy in relapsed disease.	Comment noted. No action needed for the present scope.
	Ovacome	Yes	Comment noted. No action needed.

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	Ovarian Cancer Action	Please include some brief detail regarding the efficacy of PARP inhibitors in BRCA+ patients in particular in order to explain why use is currently restricted to this population. Please include dosage information and how the drug is administered (i.e. frequency), as this should factor into health-related quality of life assessment.	Comment noted. We do not include frequency of administration or information on the efficacy of a technology in our scopes.
Population	British Gynaecological Cancer Society	Population groups should clearly specify BRCA germline and BRCA somatic mutations as both groups benefited; the 2 phase II studies (ARIEL 2 and study 10) have also analysed the response in patients with platinum-resistant and platinum-sensitive cancer and although the benefit was clearly higher in patients with platinum-sensitive disease the PFS in patients with platinum-resistant disease was also extended (7.4 months) as compared to chemotherapy with platinum (<6 months by definition); there are 2 phase III confirmatory studies ongoing –in the treatment setting and in the maintenance setting; the studies will provide more data.	Comment noted. We have updated the population to make clear that germline and somatic mutations are included. The following has been added to the 'Other considerations' section of the scope: 'Where the evidence allows, consideration will be given to subgroups with platinum-sensitive and platinum-resistant disease'.
	Clovis Oncology	The population has been defined appropriately.	Comment noted. The population has been updated to make clear that it includes germline and somatic BRCA mutations.

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	Janssen	Yes, the population is defined appropriately.	Comment noted. The population has been updated to make clear that it includes germline and somatic BRCA mutations.
	National Cancer Research Institute	The trials of rucaparib have included both women with both platinum resistant and sensitive disease but studies of the comparators will often have limited inclusion to either platinum sensitive or platinum resistant disease so it may be easier to consider these populations separately. Our experts recommend clarifying that germline and somatic BRCA mutated tumours are included. If maintenance treatment is to be included then the population should also include women without BRCA mutations as per the inclusion criteria for ARIEL 3.	Comment noted. The population has been updated to make clear that it includes germline and somatic BRCA mutations. The following has been added to the 'Other considerations' section of the scope: 'Where the evidence allows, consideration will be given to subgroups with platinum-sensitive and platinum-resistant disease'.
	Ovarian Cancer Action	We agree the population is defined appropriately. However, we suggest assessing platinum sensitive patients separately.	Comment noted. The following has been added to the 'Other considerations' section of the scope: 'Where the evidence allows,

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			consideration will be given to subgroups with platinum-sensitive and platinum-resistant disease'.
Comparators	AstraZeneca	Olaparib should only be considered as a comparator for rucaparib in the 3rd line maintenance setting, where it is recommended by NICE (i.e. for patients who have responded to third line platinum based chemotherapy).	Comment noted. The comparator section has been amended to make clear that for people with platinum sensitive disease, platinum based chemotherapy followed by maintenance treatment with olaparib in those who respond to chemotherapy, is a comparator.
	British Gynaecological Cancer Society	Currently the only available maintenance treatment of patients with platinum sensitive relapsed ovarian cancer is olaparib which is restricted to patients with known BRCAm who have received 3 or more lines of platinum chemotherapy. This constitutes a very limited population of patients and the vast majority of patients with relapsed disease are unable to access maintenance therapy. Chemotherapy comparators are correctly identified but give limited PFS.	Comment noted. No action needed.

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	Clovis Oncology	Please note that in line with its marketing authorisation olaparib is indicated for maintenance only while current rucaparib MAA is for treatment setting.	Comment noted. The comparator section has been amended.
	Janssen	All appropriate comparators have been included. We note that pegylated liposomal doxorubicin hydrochloride in combination with platinum has been included as a comparator, despite it not having a license as a combination therapy. We acknowledge that this is in line with NICE 'Managing advanced (stage II-IV) ovarian cancer' pathway, but in any published technology guidance we ask NICE to make it clear that this is an off license use of pegylated liposomal doxorubicin hydrochloride, as has been done in the NICE 'Managing advanced (stage II-IV) ovarian cancer'.	Comments noted. A footnote has been added to the scope.
	National Cancer Research Institute	The first line treatment for platinum sensitive recurrent disease is platinum in combination with PLD or with paclitaxel or platinum alone. At later platinum sensitive recurrence (ie after 2 lines) then platinum alone, platinum with PLD or paclitaxel or gemcitabine may be used depending on comorbidities, performance status, previous toxicity and patient preference. Women with BRCA mutations are eligible to receive olaparib as maintenance treatment after further response to 3rd line platinum in England and at least 2 lines in Scotland. The SOLO 2 trial included patients after at least 2 lines of prior platinum. In platinum resistant disease weekly paclitaxel is the most commonly used first line regimen. PLD is also used as a single agent. When comparing studies it is important that the number of prior lines allowed is considered. Niraparib has FDA approval as maintenance treatment for women with relapsed epithelial ovarian cancer in response to platinum based chemotherapy and so it is likely that it will also receive marketing	Comments noted. The comparators have been amended following consultation. Niraparib cannot be added as a comparator because it has not been launched in Europe. Tesaro has been added as a comparator company.

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		authorisation in Europe in the near future. If so, it should be included in the comparators. Tesaro should be added as a comparator company.	
	Ovacome	Yes. These are IV treatments and as such it should also be noted that Rucaparib as an oral medication offers patients greater choice regarding means of administration and possibly also greater flexibility regarding location of treatment.	Comment noted. The method of administration (oral) is included in the technology section.
Outcomes	British Gynaecological Cancer Society	The outcomes are appropriate.	Comment noted. No action needed.
	Clovis Oncology	Please note that the treatment comparisons will be carried out for overall survival and progression-free survival. However, response rates, adverse events and health-related quality of life will be reported in the clinical section based on the clinical study report; no comparisons will be made in the cost-effectiveness model.	Comment noted. No action needed.
	Janssen	The outcomes are appropriate to capture health related benefits of the technology.	Comment noted. No action needed.
	National Cancer Research Institute	Yes. In addition, PARP inhibitors can result in very long progression free intervals in a proportion of patients. As a result the median PFS may not give an accurate picture of the potential benefit for some women. The proportion progression free at specific time intervals may also be of importance.	Comment noted. No action needed.

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		It is unlikely that the overall survival data will be mature enough to be evaluated at this time.	
	Ovacome	Yes, as long as health-related quality of life takes into account the psychological benefit of having PARP inhibitor availability where none existed before (platinum resistant disease) and a further treatment line (BRCA patients).	Comment noted. No action needed.
	Ovarian Cancer Action	Whilst we are extremely committed to increasing overall survival and progression-free survival, Ovarian Cancer Action has received numerous anecdotal comments and concerns regarding side effects of treatments. We assert that adverse effects of treatment and health-related quality of life should certainly be considered as significant in any outcome assessments.	Comment noted. These are included as outcomes.
Economic analysis	National Cancer Research Institute	Testing for germline mutations in BRCA 1 and 2 is standard of care. Somatic mutation testing is being developed. When comparing PARPi monotherapy and chemotherapy + PARP I maintenance the costs of the whole treatment from start of chemotherapy need to be taken into account.	Comment noted.
	Ovarian Cancer Action	Ovarian Cancer Action see BRCA as an opportunity for cancer prevention. In any economic analysis, it is worthwhile pointing out that the genetic testing offered as part of ovarian cancer treatment pathways to assess eligibility for PARP inhibitors provides information to the patient's family that will, in future years, reduce the incidences of ovarian cancer. This will reduce overall spending in the NHS for generations. Based on the current statistics of 7400 diagnoses per year in the UK, approximately 1200 of those may be caused by a BRCA mutation, and these cases could be prevented through risk-reducing surgery provided the individuals know about this in time.	Comment noted.

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Innovation	AstraZeneca	We do not consider this technology to innovative: Rucaparib has a similar mechanism of action to olaparib, which is recommended by NICE and has been available on the NHS since January 2016. In addition another PARP inhibitor (niraparib) is currently being assessed by NICE.	Comments noted.
	British Gynaecological Cancer Society	Rucaparib is an example of targeted individualised approach to cancer treatment for patients with BRCA somatic or germline mutation. This approach is not only innovative but cost effective and is likely to extend survival for patients. Although the overall survival data is not available there are two definitive phase II studies ongoing that will support this data.	Comments noted.
	Clovis Oncology	Yes. Rucaparib is a PARP inhibitor and belongs to new class of chemotherapeutic agents. By blocking the activity of PARPs in cancer cells, rucaparib is expected to stop the cancer cells from being able to repair damaged DNA and this eventually leads to the death of the cancer cells, thereby slowing down the growth of the cancer.	Comments noted.
	National Cancer Research Institute	Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Yes Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? YES – treatment that delays progression and the need for further chemotherapy without a detrimental effect on quality of life can allow people to maintain their performance status and global health for longer. As a result they can continue to work or care for families etc.	Comments noted.

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		Time to subsequent therapy and time to second subsequent therapy offer alternative surrogates of overall survival.	
	Ovacome	Yes. Rucaparib offers platinum-resistant patients the opportunity of a PARP inhibitor where none is currently available. It also offers a PARP inhibitor as a treatment line for BRCA patients where at the moment a PARP inhibitor is used as a maintenance therapy.	Comments noted.
	Ovarian Cancer Action	Currently the access to Olaparib is limited to BRCA+ patients with platinum sensitive ovarian cancer who have had 3 lines of chemotherapy. It is not available for patients with a BRCA mutation who have not responded to platinum as their last therapy (platinum resistant disease). The population description in this consultation for Rucaparib offers the possibility of its use in patients with BRCA mutations who have platinum resistant disease as well as those with platinum sensitive disease provided they have received 2 or more prior lines of therapy. Furthermore it is for use after two or more prior lines of therapy whereas Olaparib is approved for after three or more lines. As such this would give patients with BRCA mutations access to PARP inhibitors in two situations in which we do not currently have access to Olaparib: 1. Platinum resistant disease 2. After first relapse (2nd line of therapy) It will not, however, give access to PARP inhibitors for patients without BRCA mutations or those with homologous recombination deficiency (HRD). We are hopeful that this gap will be filled by Niraparib in the near future.	Comments noted.

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Other considerations	British Gynaecological Cancer Society	The BRCA germline and somatic testing is crucial for patients. Germline BRCA testing is widely available however testing for somatic mutations is not. This has to be taken into consideration.	Comment noted.
Questions for consultation	AstraZeneca	Scoping question: Where do you consider rucaparib will fit into the existing NICE pathway, ovarian cancer? It appears that rucaparib may fit into the existing NICE pathway for ovarian cancer EITHER as a third-line treatment option OR as a second-line maintenance therapy. Olaparib should only be considered as a comparator for rucaparib in the 3rd line maintenance setting, where it is funded by the NHS. Scoping question: Is there any substantial new evidence for the comparator technology/ies that has not been considered? Since the Final Appraisal Determination for olaparib in December 2015, the new clinical evidence demonstrating the efficacy of olaparib has become available from the Study 19 final overall survival analysis, and the Phase 3 SOLO2 randomised controlled trial.	Comments noted.
	National Cancer Research Institute	Does the population defined in the table reflect the likely place in therapy of rucaparib? Rucaparib may be used as both monotherapy after at least 2 prior lines of chemotherapy in women with BRCA mutated tumours or as maintenance treatment after response to at least second line platinum therapy in both BRCA mutated and wild type tumours. Have all relevant comparators for rucaparib been included in the scope? Carboplatin and gemcitabine should also be included as this may be used in later lines of therapy.	Comments noted. Gemcitabine and carboplatin has been added to the comparators.

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		Niraparib should be included if it gains marketing authorisation in the UK. Are there any other subgroups of people in whom rucaparib is expected to be more clinically effective and cost effective or other groups that should be examined separately? The ARIEL 3 study is investigating the potential of the Foundation medicine HRD signature to predict benefit from rucaparib in BRCA wild type tumours. Depending on the results of the study a population with HRD positive tumours may have a greater benefit than those with HRD negative tumours. Where do you consider rucaparib will fit into the existing NICE pathway, ovarian cancer? Managing stage II to IV, second and subsequent lines of therapy NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. The multiple technology appraisal (MTA) process may be more appropriate given that rucaparib may have more than one indication and there is overlap with the indications for olaparib and niraparib. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. I do not anticipate any barriers.	
	Ovarian Cancer Action	As detailed above, Ovarian Cancer Action believes this proposal will make a substantial impact on the treatment of ovarian cancer due to giving access to PARP inhibitors in two situations where there is not currently access: 1. Platinum resistant disease	Comment noted.

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		2. After first relapse (2nd line of therapy)	
	Ovacome	Where to fit in NICE pathway for ovarian cancer: Management of advanced (stage II-IV) ovarian cancer.	Comment noted.
Additional comments on the draft scope	Ovarian Cancer Action	Ovarian Cancer Action are in support of the proposed use of Rucaparib, as there is an urgent need to improve the availability of treatments for ovarian cancer patients who have relapsed disease. In order to improve survival rates we must ensure that patients have access to the best available treatment, and at the earliest opportunity. These new options are life-changing for the patients we see every day, offering hope for the future. We are also supportive of the ongoing research into these options, including larger Phase 3 trials of Rucaparib, which will provide further information on its usage in ovarian cancer and potentially other populations of patients that may benefit in the future. It is worthy of note that, in the ARIEL-2 study, Rucaparib showed efficacy in those without a BRCA mutation deemed LOH high (a marker of homologous recombination deficiency). However, as this testing is not funded or available in the UK, it is more difficult to accurately assess which patients without a germline BRCA mutation would also benefit from Rucaparib. We assert that further research should be supported to clarify and confirm which further populations would benefit from Rucaparib. This would hopefully expand the use of such treatments in the future, and offer increased survival chances to as many ovarian cancer patients as possible.	Comment noted.
	Ovarian Cancer Action	Comments on the provisional matrix of consultees and commentators Due to the higher prevalence of BRCA mutations in the Jewish population, it would be appropriate to add JNetics (formerly known as Jewish Genetic Disorders UK) to the list of consultees:	Comment noted.

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		www.Jnetics.org	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Pfizer
RCOG