National Institute for Health and Care Excellence

Health Technology Evaluation

Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (Review of TA598) [ID6191]

Response to stakeholder organisation 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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	AstraZeneca	None	No action required.
	The Royal College of Pathologists	None	No action required.
	Target Ovarian Cancer	None	No action required.
	Ovacome Ovarian Cancer charity	None	No action required.

Section	Stakeholder	Comments [sic]	Action
Wording	AstraZeneca	To align the remit with the MHRA (Medicines and Healthcare Products Regulatory Agency) marketing authorisation of olaparib for this indication, please consider the addition of 'adult patients', 'advanced' and 'high-grade' as follows: *To appraise the clinical and cost effectiveness of olaparib within its marketing authorisation for the maintenance treatment of adult patients with advanced BRCA (breast cancer gene) mutated high-grade ovarian, fallopian tube and peritoneal cancer who are in response to first-line platinum-based chemotherapy*[Error! Reference source not found.].	Comment noted. The wording of the remit has been updated to closer align with the MHRA marketing authorisation of olaparib for this indication.
	The Royal College of Pathologists	Yes	Comment noted. No action required.
	Target Ovarian Cancer	None	No action required.
	Ovacome Ovarian Cancer charity	None	No action required.
Timing issues	AstraZeneca	We accept the timelines proposed by NICE (National Institute for Health and Care Excellence) for this appraisal.	Comment noted. No action required.
	The Royal College of Pathologists	Priority	Comment noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the

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			marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.
	Ovacome Ovarian Cancer charity	Olaparib offers maintenance treatment first line, with an evidence base which demonstrates it effectively extends progression free and overall survival. Those with ovarian cancer face a potentially life-limiting disease. Therefore, it is urgent that this technology is appraised.	Comment noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.
	Target Ovarian Cancer	None	No action required.
Additional comments on the draft remit	AstraZeneca	No additional comments.	No action required.
	The Royal College of Pathologists	None	No action required.
	Target Ovarian Cancer	None	No action required.

Section	Stakeholder	Comments [sic]	Action
	Ovacome Ovarian Cancer charity	None	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	Although the background information in the draft scope accurately lists NICE recommended first-line treatments for aOC (advanced ovarian cancer), it does not distinguish between induction and maintenance treatments, and does not outline the relative positioning of these therapies in the current UK treatment pathway. It is important to highlight that in aOC, the first prescribing decision made by clinicians relates to the choice of induction regimen, i.e., whether to deliver this in the neoadjuvant or adjuvant setting, and whether to include bevacizumab or not. This choice is informed by many factors, including clinicopathological features of a patient's disease, as well as surgical outcome. The second prescribing decision made by clinicians relates to the choice of maintenance regimen. The key influencers for this decision are a patients biomarker status (i.e., if they harbour a BRCA mutation and / or if they are HRD (homologous recombination deficiency) positive), as well as the prior induction regimen that a patient received[Error! Reference source not found.]. This interplay between induction and maintenance regimens is an important	Comment noted. The background section has been updated to describe the positioning of different therapies in the UK treatment pathway.

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		nuance that informs our response to the draft scope 'comparators' section below on Pages 4&5.	
	The Royal College of Pathologists	Reasonably informative	Comment noted. No action required.
	Target Ovarian Cancer	None	No action required.
	Ovacome Ovarian Cancer charity	None	No action required.
The technology/ intervention	AstraZeneca	The draft scope currently refers to the use of olaparib in combination with bevacizumab in the first-line setting (the 'PAOLA-1' regimen***Error! Reference source not found.***) as a 'related marketing authorisation'. We recommend removing the word 'related', as there are distinct differences in the eligible patient population for these two indications. Key differences include the use of bevacizumab in the induction setting, as well as biomarker status i.e., PAOLA-1 is intended for patients that are HRD positive, whereas SOLO-1 is only accessible to a smaller subset of patients that harbour a germline or somatic BRCA1/2 mutation. We therefore suggest amending this to: *'Olaparib <u>also</u> has a ~~related~~ marketing authorisation in the UK in combination with bevacizumab for the maintenance treatment of adults with advanced (FIGO (International Federation of Gynaecology and Obstetrics) stages III and*	Comment noted. The use of the word 'related' is standard wording for NICE scopes. No action required.

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		IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab, and whose cancer is associated with HRD positive status defined by either a BRCA1/2 mutation and/or genomic instability.'	
	The Royal College of Pathologists	Yes	Comment noted. No action required.
	Target Ovarian Cancer	None	No action required.
	Ovacome Ovarian Cancer charity	None	No action required.
Population	AstraZeneca	To align the scope population with the MHRA marketing authorisation of olaparib in this indication, please consider the addition of 'adult patients' and 'high-grade' as follows: *Adult patients with advanced, BRCA-mutated, high-grade ovarian, fallopian tube or peritoneal cancer who are in response (completely or partially) following completion of first-line platinum-based chemotherapy.*[1]	Comment noted. The wording of the population has been updated to closer align with the MHRA marketing authorisation olaparib in this indication.
	The Royal College of Pathologists	Yes	Comment noted. No action required.

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	Target Ovarian Cancer	None	No action required.
	Ovacome Ovarian Cancer charity	None	No action required.
Subgroups	AstraZeneca	None	No action required.
	The Royal College of Pathologists	None	No action required.
	Target Ovarian Cancer	None	No action required.
	Ovacome Ovarian Cancer charity	None	No action required.
Comparators	AstraZeneca	The draft scope currently includes both 'routine surveillance' and 'olaparib plus bevacizumab subject to NICE evaluation '(PAOLA-1 indication[Error! Reference source not found.]) as relevant comparators for the olaparib monotherapy (SOLO-1 indication[1]) CDF exit submission. However, AstraZeneca does not consider the PAOLA-1 indication to be an appropriate comparator for the following reasons:	Comment noted. Olaparib plus bevacizumab (subject to NICE evaluation) has been removed as a comparator. The

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		Firstly, the SOLO-1 regimen and the PAOLA-1 regimen are used in different patient populations, so the SOLO-1 regimen is not expected to displace the use of the PAOLA-1 regimen in UK clinical practice. Therefore, the PAOLA-1 regimen does not reflect the true opportunity costs of the SOLO-1 regimen and it is not an appropriate comparator. UK clinical experts[Error! Reference source not found.] have confirmed that the eligible population for each regimen can be viewed as distinct for several reasons outlined below, and as depicted in **Error! Reference source not found.**: • In aOC, the first prescribing decision made by clinicians relates to the choice of induction regimen. This choice is informed by many factors, including clinicopathological features of the patient's disease, as well as surgical outcome. Clinicians state that they tend to offer induction bevacizumab in a distinct group of patients, particularly those who have stage IV disease, or sub-optimal debulking during primary cytoreductive surgery, aligned to the patient group who demonstrated an OS (overall survival) benefit in the ICON7 trial[Error! Reference source not found.]. • The second prescribing decision made by clinicians relates to the choice of maintenance therapy. This decision is also informed by several factors, but the key influencers are a patients biomarker status (i.e., if they harbour a BRCA mutation and / or if they are HRD (homologous recombination deficiency) positive), as well as the prior induction regimen that a patient received[Error! Reference source not found.]. Patients who responded to bevacizumab in the induction setting would generally continue receiving bevacizumab in the maintenance setting, either as monotherapy or in combination with olaparib as part of the PAOLA-1 regimen. There is a common clinical sentiment that continuation of bevacizumab in the maintenance setting is key to maximising its efficacy, and best aligns with the administration schedule used in clinical trials (e.g., ICON 7[Error! Reference source not found.] and GOG-218[Error! Reference source not found.]). Therefore, patients	description of population has also been updated to 'adults that have responded (completely or partially) to first-line platinum-based chemotherapy without bevacizumab'.

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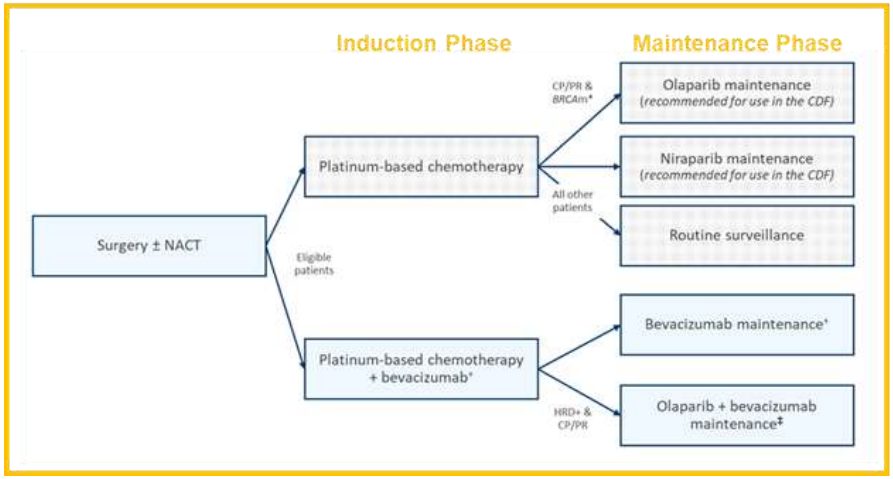
		who are potentially eligible for the PAOLA-1 regimen (having been offered and experienced a response to bevacizumab in the induction setting), are a distinct cohort that would not generally be offered PARP (poly (ADP-ribose) polymerase) inhibitor monotherapy, such as the SOLO-1 regimen. • Also, the distinct nature of these patient populations is reflected in the eligibility criteria for the SOLO-1 trial itself; patients who had received bevacizumab in the induction setting were excluded from the study. Secondly, the PAOLA-1 indication is currently reimbursed through the Cancer Drugs Fund (CDF). As per the NICE Process and Methods Manual [PMG36] Section 2.2.15: '*Technologies that NICE has recommended with managed access are not considered established practice in the NHS (national health service) and are not considered suitable comparators*[Error! Reference source not found.].' **Figure 1: First-line treatment pathway for advanced ovarian cancer patients in the UK**  	

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		Patients are eligible for olaparib maintenance treatment if they are in response (complete or partial) following first-line chemotherapy and are diagnosed with BRCA1/2-mutated OC* *Abbreviations: aOC, advanced ovarian cancer; BRCA, breast cancer gene; CDF, Cancer Drugs Fund; CP, complete response; HRD, homologous recombination deficiency; NACT, neo-adjuvant chemotherapy; PR, partial response.* **For these reasons, 'olaparib plus bevacizumab (subject to NICE evaluation)', i.e., the PAOLA-1 regimen, is not an appropriate comparator for this appraisal. The only relevant comparator in this setting is routine surveillance.	
	The Royal College of Pathologists	Yes	Comment noted. No action required.
	Target Ovarian Cancer	Olaparib and bevacizumab is currently available in the Cancer Drugs Fund. If CDF indications are being considered as comparators, then niraparib from the first line of treatment should also be considered.	Comment noted. Technologies reimbursed through the Cancer Drugs Fund are not considered suitable comparators. Olaparib and bevacizumab was considered as a potential comparator because it is currently undergoing review. However, olaparib and bevacizumab has now been removed as a

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			comparator in this scope.
	Ovacome Ovarian Cancer charity	None	No action required.
Outcomes	AstraZeneca	In line with the SOLO-1 study design, we suggest amending outcome measure 'Time from randomisation to second progression (PFS2)' to 'progression-free survival 2 (i.e., progression-free survival on next line of therapy)'.	Comment noted. Outcomes should not include terms specific to clinical trials i.e. time from randomisation. No action required.
	The Royal College of Pathologists	Yes	Comment noted. No action required.
	Target Ovarian Cancer	We would like to see a wider definition of quality of life. Patients often report that being able to take treatments at home with less of need to visit hospitals as improving their quality of life as it allows them more time with friends and family and means they do not to live their lives around appointments.	Comment noted. The appraisal committee will consider all relevant quality of life outcomes when making recommendations.
	Ovacome Ovarian Cancer charity	Yes, as long as health-related quality of life takes into account the psychological benefit of having maintenance therapy rather than routine surveillance. The time after treatment under routine surveillance can be psychologically very hard to cope with. Having a choice of maintenance	Comment noted. The appraisal committee will consider all relevant

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		treatment and continued input from oncology teams offers a significant psychological benefit as well as physical health benefits.	quality of life outcomes when making recommendations.
Economic analysis	AstraZeneca	The draft scope states that 'the economic modelling should include the cost associated with diagnostic testing in people with platinum-sensitive ovarian, fallopian tube and peritoneal cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.' However, as per the national genomic test directory for cancer[Error! Reference source not found.], HRD panel testing (code M2.5) is already routinely available for patients with ovarian cancer if the '*patient is eligible for first-line treatment and has a diagnosis of high-grade ovarian cancer'*. The results of a HRD test routinely includes BRCA 1/2 mutation status and would therefore identify patients who would be eligible for the SOLO-1 regimen. Given that the diagnostic test to identify the target population for the SOLO-1 regimen is already routinely used in UK clinical practice, there is not expected to be any related incremental costs to the NHS. For this reason, it is not appropriate to include the cost of diagnostic testing in the base case economic analysis.	Comment noted. The scope specifies that the economic modelling should only include costs associated with diagnostic testing in those who would not otherwise have been tested – which will be determined during topic appraisal. No action required.
	The Royal College of Pathologists	Reasonable approach	Comment noted. No action required.

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	Target Ovarian Cancer	None	No action required.
	Ovacome Ovarian Cancer charity	None	No action required.
Equality	AstraZeneca	No equality considerations have been identified at this stage.	Comment noted. No action required.
	The Royal College of Pathologists	No issue with equality	Comment noted. No action required.
	Target Ovarian Cancer	None	No action required.
	Ovacome Ovarian Cancer charity	None	No action required.
Other considerations	AstraZeneca	N/A	No action required.
	The Royal College of Pathologists	None	No action required.

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	Target Ovarian Cancer	None	No action required.
	Ovacome Ovarian Cancer charity	None	No action required.
Innovation	AstraZeneca	First-line treatment of advanced ovarian cancer is of critical importance as this is the only setting in which there is curative potential through achieving long-term remission[Error! Reference source not found.,Error! Reference source not found.]. Once patients' relapse, the disease becomes incurable and the clinical goal becomes to further delay progression, and to preserve quality of life.[Error! Reference source not found.,Error! Reference source not found.,Error! Reference source not found.] The pivotal phase III SOLO-1 study has the longest follow up[14] (DCO3 (data cut off 3), 7th March 2022) seen from a PARP inhibitor in this setting, as presented at ESMO (European Society for Medical Oncology) 2022. Olaparib provided a clinically meaningful improvement in OS, with 67.0% of patients treated remaining alive at 7 years vs 46.5% of placebo patients (OS HR (hazard ratio) = 0.55 (95% CI (confidence interval) 0.40–0.76). This OS benefit was still shown despite 44.3% of patients in the placebo group receiving subsequent PARP inhibitor therapy. At the time of the original submission (2019), SOLO-1 OS data were considered as immature by the NICE committee. As part of the CDF exit submission, the company will present more mature 7-year OS data to address the previous uncertainties and to support the positioning of olaparib as the standard of care for adult patients with BRCA-mutated advanced, high-	Comment noted. No action required.

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		grade ovarian, fallopian tube or peritoneal cancer that has responded (completely or partially) to first-line platinum-based chemotherapy.	
	The Royal College of Pathologists	There are two other PARP inhibitors licenced in this indication – Niraparib and Rucaparib. These two drugs are also licenced in patients without BRCA1/2 mutations. Olaparib would be added to the list but be limited to those with BRCA1/2 mutation (either germline or somatic).	Comment noted. No action required.
	Ovacome Ovarian Cancer charity	Ovarian cancer is most commonly diagnosed at stage III and therefore from the outset those diagnosed know that they have a high chance of recurrence. Thus once treatment finishes they are in an extremely difficult position where they can feel they are left waiting for their disease to recur. Having available maintenance therapies offers a further treatment option to extend progression free and overall survival. It also provides the psychological support of continued treatment and contact with oncology teams. It has the potential to significantly and substantially benefit quality of life for those with ovarian cancer both physically and psychologically. Clinical trial data alongside qualitative data of patient experience will account for health benefits.	Comment noted. No action required.
	Target Ovarian Cancer	None	No action required.
	Ovacome Ovarian Cancer charity	None	No action required.
Questions for consultation	AstraZeneca	**Have all relevant comparators for olaparib been included in the scope?** Please refer to the response in the 'comparator' section.	Comment noted. No action required.

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		Are any routinely commissioned maintenance treatments currently used for BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to initial platinum-based chemotherapy? No; there are other therapies available in the CDF, however there are no treatments reimbursed via routine commissioning. **Is olaparib plus bevacizumab (subject to NICE evaluation) a relevant comparator?** No, please refer to the response in the 'comparator' section. **Is there a clearly defined population who would be offered first-line platinum-based chemotherapy in combination with bevacizumab compared with first-line platinum-based chemotherapy alone?** Yes, please refer to the response in the 'comparator' section. **Are the outcomes listed appropriate?** Please refer to the response in the 'outcomes' section. **Are there any subgroups of people in whom olaparib is expected to be more clinically effective and cost effective or other groups that should be examined separately?** No. **Do you consider that the use of olaparib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** No. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.**	

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		• Primary PFS DCO (17th May 2018) • Updated PFS DCO (5th March 2020) • 7-year descriptive OS DCO (7th March 2022)	
	The Royal College of Pathologists	None	No action required.
	Target Ovarian Cancer	None	No action required.
	Ovacome Ovarian Cancer charity	None	No action required.
Additional comments on the draft scope	AstraZeneca	N/A	No action required.
	The Royal College of Pathologists	None	No action required.
	Target Ovarian Cancer	None	No action required.
	Ovacome Ovarian Cancer charity	None	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action

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

None