National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Olaparib for maintenance treatment of BRCA 1 or 2 mutated, relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer in people whose relapsed disease has responded to platinum-based chemotherapy

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	AstraZeneca UK	AstraZeneca (AZ) believes it would be appropriate to refer this topic to NICE for appraisal	Comment noted.
	Target Ovarian Cancer	We believe it is appropriate that NICE considers Olaparib as a treatment for platinum sensitive women with ovarian cancer whose cancer has returned	Comment noted.
Wording	AstraZeneca UK	Yes	Comment noted. It was agreed at the scoping workshop that the wording of the draft remit should be amended to reflect the anticipated marketing authorisation and should be defined as 'To appraise the clinical and cost effectiveness of olaparib within its licensed indication for

Section	Consultee/ Commentator	Comments	Action
			maintenance treatment of BRCA 1 or 2 mutated relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer in people whose relapsed disease has responded to platinum-based chemotherapy'.
	Target Ovarian Cancer	The current wording says that women should have relapsed and be platinum sensitive, following response to platinum based treatment. This is in effect the same thing, so do not require both. Relapsed, platinum sensitive ovarian cancer should suffice. Whilst it is appropriate to consider this for women with a confirmed mutation in their BRCA1 or 2 gene, it would be appropriate for the group to consider whether the remit be widened to those women whose tumours behave in a similar fashion, commonly referred to as BRCAness. However difficulties in establishing which patients would fall into this category, may prevent this consideration.	Comment noted. It was agreed at the scoping workshop that the wording of the draft remit should be amended to reflect the anticipated marketing authorisation and should be defined as 'To appraise the clinical and cost effectiveness of olaparib within its licensed indication for maintenance treatment of BRCA 1 or 2 mutated relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer in

Section	Consultee/ Commentator	Comments	Action
			people whose relapsed disease has responded to platinum-based chemotherapy'.
Timing Issues	AstraZeneca UK	Olaparib is expected to gain a UK Marketing Authorisation in [redacted] There are currently no other treatments that are licensed in the NHS for the maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer in people who have tested positive for BRCA 1 or 2 mutations, following response to prior platinum-based chemotherapy. Therefore, AZ believes a timely appraisal as close as possible to the expected date of marketing authorisation would be appropriate	Comment noted. Once referral is received from the Department of Health, the appraisal of olaparib will be scheduled into the Technology Appraisals work programme. NICE intends to ensure the most appropriate timing of the appraisal in relation to marketing authorisation depending on availability of space on its programme.
	Target Ovarian Cancer	Given the lack of approved new treatments for women with ovarian cancer, it is important that this appraisal goes ahead in a timely manner.	Comment noted. Once referral is received from the Department of Health, the appraisal of olaparib will be scheduled into the Technology Appraisals work programme. NICE intends to ensure the most appropriate timing

Section	Consultee/ Commentator	Comments	Action
			of the appraisal in relation to marketing authorisation depending on availability of space on its programme.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	AstraZeneca UK	No comments	Comment noted.
	Target Ovarian Cancer	Approximately 15% of women diagnosed with high grade serous or endometrioid epithelial ovarian cancer carry a mutation in one or other of their BRCA genes. This is irrespective of whether they have multiple cases of the disease in their family. Zhang, S., Royer R. et al (2011) Gynecologic Oncology 121 (2): 353-357 It is imperative that if the remit is to be in women with a confirmed BRCA mutation, then there is ease of accessibility to genetic testing and counselling for all women diagnosed with these types of ovarian cancer. NICE is inconsistent in its use of wording re platinum sensitivity. The definition refers to platinum sensitive as being more than six months since last treatment, however later in the document it refers to partially platinum sensitive, which is normally used to describe women who relapse between six and twelve months after last platinum treatment.	Comment noted. Considerations of the diagnostic test to establish the presence or absence of BRCA 1 or 2 mutated gene will be taken into account in line with section 5.9 of the Guide to the Methods of Technology Appraisals (please see Other considerations section in the scope). It was clarified at the scoping workshop that for the purpose of this

Section	Consultee/ Commentator	Comments	Action
		There is a licensed maintenance treatment for relapsed platinum sensitive ovarian cancer – Bevacizumab, but it is not NICE approved.	appraisal, the definition of relapsed, platinum-sensitive ovarian cancer will cover platinum-sensitive ovarian cancer and partially platinum-sensitive ovarian cancer. It was agreed that bevacizumab is not an appropriate comparator for olaparib.
The technology/ intervention	AstraZeneca UK	Agreed	Comment noted.
	Target Ovarian Cancer	We are uncertain whether 'high grade endometrial cancer' in this context relates to endometrial cancer, or endometroid ovarian cancer. Perhaps it is worth checking this.	Comment noted. Reference to high grade endometroid ovarian cancer has been removed from the technology section in the scope as it is not expected that the anticipated marketing authorisation for olaparib will cover this subgroup.
Population	AstraZeneca UK	Agreed	Comment noted. It was agreed at the scoping workshop that the

Section	Consultee/ Commentator	Comments	Action
			population should be amended to be in line with the anticipated marketing authorisation and the draft remit. The population has been defined in the scope as 'People with BRCA 1 or 2 mutated, relapsed, platinum-sensitive ovarian, fallopian tube or peritoneal cancer whose relapsed disease has responded to platinum-based chemotherapy'.
	Target Ovarian Cancer	See comments in the remit re use of platinum sensitive and responded to platinum therapy. Also there should be clarity around whether the population includes partially platinum sensitive. We feel it is positive that the drug could be available to women who have had a number of recurrences, as long as they remain platinum sensitive, and have not had Olaparib before.	Comments noted. It was agreed at the scoping workshop that the population should be amended to be in line with the anticipated marketing authorisation and the draft remit. The population has been defined in the scope as 'People with BRCA 1 or 2 mutated, relapsed, platinum-sensitive

Section	Consultee/ Commentator	Comments	Action
			ovarian, fallopian tube or peritoneal cancer whose relapsed disease has responded to platinum-based chemotherapy'. It was clarified at the scoping workshop that for the purpose of this appraisal, the definition of relapsed, platinum-sensitive ovarian cancer will cover platinum-sensitive ovarian cancer and partially platinum-sensitive ovarian cancer. Olaparib will be appraised within its licensed indication.
Comparators	AstraZeneca UK	Agreed – more details under "Questions for consultation"	Comment noted. It was agreed at the scoping workshop that the appropriate comparator for olaparib is routine surveillance.
	Target Ovarian Cancer	How will relapse be determined? It has become more commonplace to determine relapse by onset of symptoms rather than a rising CA125. It is not clear at this point, how this will be determined in this case. If on symptoms	Comment noted. It was agreed at the scoping

Section	Consultee/ Commentator	Comments	Action
		then the term routine surveillance is not required. If on rising CA125, then it would include surveillance until symptoms.	workshop that the appropriate comparator for olaparib is routine surveillance. .
Outcomes	AstraZeneca UK	Agreed	Comment noted. It was agreed at the scoping workshop that response rate should be removed and progression-free survival 2 and time to next line of therapy should be added to the outcomes list in the scope.
	Target Ovarian Cancer	Secondary progression free survival should also be considered. This is important because increases in PFS and SPFS result in better quality of life for women, in that they are well for longer.	Comment noted. It was agreed at the scoping workshop that response rate should be removed and progression-free survival 2 and time to next line of therapy should be added to the outcomes list in the scope.
Economic analysis	AstraZeneca UK	The economic analysis will adopt a lifetime horizon	Comment noted.

Section	Consultee/ Commentator	Comments	Action
Equality and Diversity	AstraZeneca UK	No comments	Comment noted. No action required.
Innovation	AstraZeneca UK	AZ considers Olaparib to be innovative in the proposed indication as it is the first PARP inhibitor to be submitted for regulatory approval. It presents a new Mode of Action (MOA). Furthermore, it is the first stratified medicine to be approved for use in ovarian cancer (patients to test positive for BRCA 1/2 mutation). Therefore, it presents a novel mechanism of action in a stratified population which will benefit most from use of the product. It is also the first oral maintenance treatment in relapsed, platinum-sensitive ovarian cancer. AZ does not foresee any significant and substantial health-related benefits within the patient population that are unlikely to be included in the QALY calculation. However, we see the potential for increased testing of BRCA mutation status as a result of a treatment being available may have a wider benefit and further family testing may have the potential to lead to improved health outcomes due to knowledge of BRCAm status and options to screen or undertake preventative surgery.	Comment noted. The potential for olaparib to be considered an innovative technology will be considered by the Appraisal Committee at the appraisal stage. Scoping workshop attendees noted the potential additional benefits of olaparib as its availability would increase testing of BRCA gene mutation. It was noted that if any additional benefits associated with the diagnostic test were to be taken into account in the appraisal as a result of olaparib becoming available in the NHS, then the associated cost of the diagnostic test should also be incorporated into the

Section	Consultee/ Commentator	Comments	Action
			assessment of clinical and cost effectiveness (in line with section 5.9 of the Guide to the Methods of Technology Appraisals).
	Target Ovarian Cancer	The use of PARP inhibitors may represent a step change, not only for BRCA related cancers, but also for tumours displaying BRCA qualities. There have been no new life extending treatments for ovarian cancer approved in over twenty years. See comment above about secondary progression free survival.	Comment noted. The potential for olaparib to be considered an innovative technology will be considered by the Appraisal Committee at the appraisal stage. Scoping workshop attendees noted the potential additional benefits of olaparib as its availability would increase testing of BRCA gene mutation. It was noted that if any additional benefits associated with the diagnostic test were to be taken into account in the appraisal as a result of olaparib becoming available in the NHS, then the associated

Section	Consultee/ Commentator	Comments	Action
			cost of the diagnostic test should also be incorporated into the assessment of clinical and cost effectiveness (in line with section 5.9 of the Guide to the Methods of Technology Appraisals).
NICE Pathways	AstraZeneca UK	It is proposed that olaparib will be used as maintenance treatment for advanced ovarian, fallopian tube or primary peritoneal cancer.after the second or subsequent platinum-based chemotherapy in women who are in partial or complete response. Within the existing NICE pathway, it is therefore proposed that olaparib would be placed as maintenance therapy after second-line and subsequent chemotherapy. The NICE Familiar Breast Cancer Guideline (CG164 – 1.5.13) recommends offering genetic testing in specialist genetic clinics to a person with breast or ovarian cancer if their combined BRCA1 and BRCA2 mutation carrier probability is 10% or more. Between 15 and 20% of patients with ovarian cancer have the BRCA1/2 gene mutation as reported in the Ovarian Cancer Action report “BRCA1/2 gene testing for ovarian cancer patients and their families - a policy report”. Therefore, as olaparib is licensed for women who have tested positive for BRCA 1 or 2 mutations, AZ believes the genetic test to inform the treatment decision should be included in the existing pathway.	Comment noted. Considerations about the diagnostic test to establish the presence or absence of BRCA 1 or 2 mutated gene will be taken into account in line with section 5.9 of the Guide to the Methods of Technology Appraisals (please see Other considerations section in the scope).
Questions for	AstraZeneca UK	**Have all relevant comparators for olaparib been included in the scope?**	**Comments noted.** Olaparib will be

Section	Consultee/ Commentator	Comments	Action
consultation		Yes **Which treatments are considered to be established clinical practice in the NHS for the maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer in people who have tested positive for BRCA 1 or 2 mutations, following response to prior platinum-based chemotherapy?** There are currently no other treatments that are licensed in the NHS for the maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer in people who have tested positive for BRCA 1 or 2 mutations, following response to prior platinum-based chemotherapy. **Is bevacizuamb an appropriate comparator for olaparib?** Bevacizumab is licensed in the consolidation setting after second-line chemotherapy for platinum-sensitive ovarian cancer. This is based on the OCEANS study (Aghajanian et al., 2012), which assessed bevacizumab in combination with carboplatin and gemcitabine for 6-10 cycles followed by bevacizumab monotherapy until disease progression. No study evaluating bevacizumab purely in the maintenance setting for women with PSROC who have tested positive for BRCA 1 or 2 mutations has been identified, thus limiting any comparison between bevacizumab and olaparib in this setting. In studies of consolidation therapy such as OCEANS, the primary outcome of PFS is measured from the start of chemotherapy (usually over 4 to 6 months). However, in the pivotal study of Olaparib as a maintenance therapy (Study 19), PFS is measured from the end of chemotherapy and the start of	appraised within its licensed indication.

Section	Consultee/ Commentator	Comments	Action
		maintenance therapy. Therefore, key outcomes such as PFS and OS would not be comparable across these different study designs Furthermore, bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer is currently not recommended by NICE (TA285) and as such is not routinely used in clinical practice in England & Wales. AZ understands that in patients who have previously responded to platinum based chemotherapy in ovarian cancer, Avastin (bevacizumab) is being used as a treatment option at 1st relapse (2nd line), currently funded through the Cancer Drugs Fund (CDF). However, it is important to note that compared to the positioning & expected license for olaparib the data and use of Avastin is in an unselected population. All patients that relapse are eligible for Avastin in combination with a gemcitabine/carboplatin chemotherapy regimen and will continue to receive Avastin treatment until it is determined that they are not responding. Olaparib will only be suitable to patients at first or subsequent relapse after they have responded to their platinum based chemotherapy. Consequently not all patients who relapse will be eligible for olaparib Also, olaparib will only be licensed to patients that are BRCA mutation positive following response to any platinum-based chemotherapy. **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, for example subgroups based on response to platinum-based chemotherapy (complete or partial response)?** Beyond the subgroup of women who have tested positive for BRCA 1 or 2 mutations, there are no other subgroups of people in whom olaparib is expected to be more clinically effective and cost effective.	

Section	Consultee/ Commentator	Comments	Action
		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. We agree that the STA process is appropriate for appraising this technology	
	Target Ovarian Cancer	The supporting documentation asks whether Bevacizumab should be a comparator. It is not routinely funded by the NHS, but some women are gaining access via the Cancer Drugs Fund. If it is to be used as a comparator then care should be taken to ensure only Bevacizumab data from BRCA positive patients is considered, so it is a like for like comparison. This would actually be a small population (the CDF has given access to Bevacizumab approximately 1,000 women with ovarian cancer, but for newly diagnosed women with remaining tumours, or in the first recurrence setting). Additionally it is important to note that at present Avastin is only available via the CDF for a first recurrence, in addition to new diagnoses. We hope it may become available to women with multiple recurrences, but this is likely only in the platinum resistant setting. Hence it is unlikely to be a suitable comparator.	Comments noted. It was agreed at the scoping workshop that the appropriate comparator for olaparib is routine surveillance. .
Additional comments on the draft scope	AstraZeneca UK	Any additional comments on the draft scope AZ suggests to add under section **Related NICE recommendations and NICE Pathways** the NICE Familial Breast Cancer Guideline (CG-164) as it highlights specific recommendations regarding genetic testing in people with breast or ovarian cancer AZ suggests to add under section Related National Policy the recently **published parliamentary report** by Ovarian Cancer Action labelled *"BRCA1/2 gene testing for ovarian cancer patients and their families - a policy*	Comment noted. NICE Clinical Guideline 164 'Familial breast cancer' has been added to the Related NICE recommendations and NICE Pathways section in the scope. Any other documents considered relevant for

Section	Consultee/ Commentator	Comments	Action
		report"	this appraisal can be included in the evidence submission to NICE.

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

Department of Health
Healthcare Improvement Scotland
Royal College of Nursing

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Olaparib for maintenance treatment of BRCA 1 or 2 mutated, relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer in people whose relapsed disease has responded to platinum-based chemotherapy [ID735]
Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Health Research Authority	Health Research Authority		removed	This organisation has asked to be removed from all TA matrices. Health Research Authority has been removed from the matrix under 'relevant research groups'.

2.	Research Institute for the Care of Older people	NICE Secretariat		removed	This organisation does not have an interest related to the topic. Research Institute for the Care of Older people have been removed from the matrix under 'relevant research groups