National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab
Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Ovacome Ovarian Cancer Charity	Yes.	Thank you. No action needed.
	Target Ovarian Cancer	The draft remit/appraisal objective accurately sets out the group and technology under consideration.	Thank you for your comment. No action needed.
	AstraZeneca UK Ltd	We suggest revising the wording of the draft remit, as follows: *"To appraise the clinical and cost effectiveness of olaparib in combination with bevacizumab within its marketing authorisation as maintenance treatment* ***for adults with newly diagnosed*** *advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer* ***who are in complete or partial response after first-line platinum-taxane chemotherapy with bevacizumab****"*	Thank you for your comment. The remit was updated to clarify that bevacizumab is used in the first-line chemotherapy.

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Timing Issues	Ovacome Ovarian Cancer Charity	Currently there is no first line maintenance treatment routinely available. This treatment has the potential to offer a patient group with a high level of relapsed disease significant progression free survival at first line. Therefore, it is urgent that this technology is appraised.	Thank you for your comment. No action needed.
	Target Ovarian Cancer	Until recently there had been no change in treatment options for ovarian cancer in decades. Some women can now access bevacizumab through the Cancer Drugs Fund and PARP inhibitors niraparib and rucaparib are available for maintenance treatment for both women who have a BRCA mutation and those that do not. Olaparib is already available for women who have a BRCA mutation from first and second line of treatment on the Cancer Drugs Fund and in routine commissioning from third line onwards. This expansion of treatment options is welcome but has led to a more complex treatment pathway. By reviewing olaparib now it presents an opportunity to assess its use as part of the wider treatment pathway.	Thank you for your comments. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
	AstraZeneca UK Ltd	Latest statistics from Cancer Research UK show that there are ~7,500 new cases of ovarian cancer each year, the equivalent of 20 new cases every day[1]. Ovarian cancer is mostly asymptomatic in its early stages, meaning that most women (six in 10) have advanced disease at the time of diagnosis[1]. Over 4,000 women die from ovarian cancer each year in the UK – **that's approximately 11 deaths each day**[1]. As stated in the Background section of the draft scope, although many women who are well enough to undergo surgery and/or chemotherapy initially respond well to treatment, the majority experience relapse within two years, in the absence of further anti-cancer maintenance therapy.	Thank you for your comments. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into

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		The only treatment that has been available for some time in the UK in the maintenance setting is the anti- vascular endothelial growth factor (VEGF) therapy, bevacizumab. In August this year, NICE recommended olaparib for use within the Cancer Drugs Fund as an option for the maintenance treatment of **BRCA mutation-positive**, advanced ovarian, fallopian tube or peritoneal cancer that has responded to first-line platinum-based chemotherapy. PAOLA-1/ENGOT-ov25 (hereafter, PAOLA-1), the pivotal clinical trial relevant to this appraisal, evaluated the efficacy and safety of **olaparib maintenance therapy in combination with bevacizumab** in women with newly diagnosed advanced ovarian, fallopian tube, or peritoneal cancer, who were in complete or partial response after platinum-taxane chemotherapy with bevacizumab. Patients were eligible for the PAOLA-1 study **regardless of surgical outcome* or *BRCA1/2* mutation status** and are therefore, representative of a broad real-world patient group. PAOLA-1 data were presented at the Presidential Symposium of the European Society of Medical Oncology (ESMO) Annual Conference this year[2]. **We request that this appraisal be prioritised considering the aforementioned information, to allow women to access olaparib plus bevacizumab maintenance therapy aligned to its anticipated European Commission Marketing Authorisation date in [redacted].** *Where patients had upfront or interval surgery	its work programme. No action needed.

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		1. Cancer Research UK – Ovarian Cancer Statistics. Available at https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer#heading-Zero. Last accessed 4th December 2019. **2. Ray-Coquard I *et al*. Presentation LBA2_PR presented at ESMO Annual Conference 2019, 27 September - 1 October, Barcelona, Spain**	
Additional comments on the draft remit	AstraZeneca UK Ltd	Any additional comments on the draft remit We suggest the appraisal title be revised as follows, for clarity and consistency: "Olaparib in combination with bevacizumab for maintenance treatment of adults with newly diagnosed advanced ovarian, fallopian tube and peritoneal cancer who are in partial or complete response after first-line platinum-taxane chemotherapy with bevacizumab." We have included below a slide from the ESMO Presidential Symposium where PAOLA-1 data were presented in September this year, in case helpful. Kindly note that this slide is subject to copyright and not intended for publication on the NICE website. It is provided to NICE for reference only. [The slide is not reproduced here] Ray-Coquard I *et al*. Presentation LBA2_PR presented at ESMO Annual Conference 2019, 27 September - 1 October, Barcelona, Spain	Thank you for your comment. The title was updated to clarify that bevacizumab is used in the first-line chemotherapy.

Comment 2: the draft scope

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Background information	Ovacome Ovarian Cancer Charity	The NICE pathway defines advanced ovarian cancer and stages II-IV. This appraisal defines advanced ovarian cancer as stages III-IV. This needs consistency.	Thank you for your comment. This has been corrected in the scope.
	Target Ovarian Cancer	Yes.	Thank you. No action needed.
	Royal College of Pathologists	Suggest the following changes to improve precision of information. The most common type of ovarian cancer, high-grade serous carcinoma (HGSC) is thought to arise from the fallopian tube and presents after it has spread to the ovary. Ovarian cancer is classified from stage I to stage IV. Advanced ovarian cancer falls within stages III and IV; stage III denotes disease that has spread outside the pelvis into the abdominal cavity and stage IV denotes that distant metastasis to other body organs such as the substance of the liver and the pleura (two thin layers of tissue that protect and cushion the lungs) has occurred. Most people are diagnosed with advanced stage disease. Some people have gene mutations that may increase the risk of ovarian cancer. Mutated inherited genes that increase the risk of ovarian cancer include BRCA 1 and 2.	Thank you for your comment. The background information was updated.
	AstraZeneca UK Ltd	No major comments. NICE is requested to add a reference to support the statement, that "*between 55% and 75% of people whose tumours respond to initial therapy relapse within 2 years of completing treatment*"	Thank you for your comment. This information was taken from previous scopes in ovarian cancer (for example TA611 and 528). As we cannot identify the original

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			reference for this statement, the statement was removed from the scope.
The technology/ intervention	Ovacome Ovarian Cancer Charity	Yes.	Thank you. No action needed.
	Target Ovarian Cancer	Yes.	Thank you. No action needed.
	AstraZeneca UK Ltd	**"The technology" section:** 1. The PAOLA-1 study investigated the efficacy and safety of **olaparib plus bevacizumab maintenance treatment versus bevacizumab plus placebo** (not placebo alone, as suggested by the draft scope). Therefore, we suggest the following revision: *"Olaparib in combination with bevacizumab does not have a marketing authorisation in the UK for maintenance treatment* ***of patients who are in partial or complete response after first-line platinum-taxane chemotherapy with bevacizumab. Maintenance treatment with olaparib plus bevacizumab versus placebo plus bevacizumab was evaluated in a clinical trial in adults with newly diagnosed advanced ovarian, fallopian tube, or peritoneal cancer who were in partial or complete response after first-line platinum-taxane chemotherapy with bevacizumab".*** **"Intervention(s)" section:**	Thank you for your comments. The information section was updated to clarify that bevacizumab was used with first-line chemotherapy. The intervention section was updated to clarify that the intervention was used only in responders.

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		1. As explained above, this proposed indication (pending regulatory approval) is as follows: *"Olaparib in combination with bevacizumab for maintenance treatment of adults with newly diagnosed advanced ovarian, fallopian tube and peritoneal cancer who are in partial or complete response after first-line platinum-taxane chemotherapy with bevacizumab"*	
Population	Ovacome Ovarian Cancer Charity	Yes.	Thank you. No action needed.
	Target Ovarian Cancer	Yes.	Thank you. No action needed.
	AstraZeneca UK Ltd	As explained above, only those patients who were in complete or partial response after completing first-line platinum-taxane chemotherapy and bevacizumab, were included in the PAOLA-1 study. Therefore, we suggest the following revision: *"Women with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial response) after completing first-line platinum-taxane chemotherapy with bevacizumab".*	Thank you for your comment. The population was updated to clarify that only newly diagnosed people are considered in the scope.
Comparators	Ovacome Ovarian Cancer Charity	Yes.	Thank you. No action needed.
	Target Ovarian Cancer	Yes.	Thank you. No action needed.

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	AstraZeneca UK Ltd	1. As shown in the study design schematic, only those patients who were in partial or complete response after completing first-line platinum-taxane chemotherapy with bevacizumab were randomised to either olaparib plus bevacizumab or placebo plus bevacizumab treatment in the PAOLA-1 study. Therefore, platinum-based chemotherapy is not a comparator, rather a prerequisite, for this indication. We request wording on comparators is revised to reflect this. 2. Although no treatments are currently available in NHS England routine commissioning in the maintenance setting, patients are able to access bevacizumab maintenance therapy through the Cancer Drugs Fund (BlueTeq form number: BEV8_v1.3 [current version]; related NICE evidence summary: ESUOM21). Importantly, this indication was first made available in 2013 through the "old" Cancer Drugs Fund, and subsequently transitioned to the Cancer Drugs Fund in its current form. On this basis, it is not covered under NICE's position statement, which explicitly states that "*products recommended for use in the Cancer Drugs Fund **after 1 April 2016** should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals*". **Bevacizumab maintenance therapy for advanced ovarian, fallopian tube, or peritoneal cancer has been available in NHS England since 2013 and is part of standard clinical practice. It should, therefore, be included as a comparator therapy in this appraisal.**	The scope was updated to also include an analysis of platinum-based chemotherapy with bevacizumab (7.5 mg/kg every 3 weeks) followed with bevacizumab maintenance therapy for people who would receive bevacizumab in the CDF.

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Outcomes	Ovacome Ovarian Cancer Charity	Yes, as long as health-related quality of life takes into account the psychological benefit of having maintenance therapy where none existed before. The time after treatment whereby women are under routine surveillance can be psychologically very hard to cope with. Having a choice of maintenance treatment and continued input from oncology teams offers a significant psychological benefit as well as physical health benefits.	Thank you for your comment. No action needed.
	Target Ovarian Cancer	Yes – it is important that indicators such as progression free survival and overall survival are taken in the context of few treatment advances in recent years for ovarian cancer. In particular the challenge of establishing overall survival data and the time this can take and using progression free survival as an interim proxy	Thank you for your comment. No action needed.
	AstraZeneca UK Ltd	We agree that the outcomes listed capture important benefits and risks associated with olaparib plus bevacizumab maintenance therapy. However, we wish to clarify that “progression-free survival 2” (or PFS2) is measured from randomisation and is the “time from randomisation to the earliest of the progression event, subsequent to that used for the primary variable PFS or death” (not progression-free survival on next line of therapy, as indicated in the NICE scope).	Thank you for your comment. The PFS2 definition was updated.
Economic analysis	Ovacome Ovarian Cancer Charity	No comments.	-
	Royal College of Pathologists	The tumour needs to be tested for mutation status. This requires pathologist and laboratory input and this needs to be considered in the cost of the treatment.	Thank you for your comments. The consideration of the cost of diagnostics tests

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		The time needed for this tissue retrieval and tumour quantity assessment needs to be built into the pathway.	was added to the scope.
	AstraZeneca UK Ltd	The economic analysis will follow the NICE reference case. A lifetime time horizon is appropriate in this setting to capture all differences in costs or outcomes between the technologies being compared.	Thank you for your comment. No action needed.
Equality and Diversity	Ovacome Ovarian Cancer Charity	No comments.	-
	Target Ovarian Cancer	Ovarian cancer is more common in women over 50 and cancer is considered a disability under the Equality Act 2010. Therefore age, gender and disability are all relevant protected characteristics for the purpose of this appraisal.	Thank you for your comment. If appropriate, the impact of any recommendation for olaparib combination with bevacizumab on people who share protected characteristics will be considered. Scope unchanged.
	AstraZeneca UK Ltd	No equality considerations identified at this stage.	Thank you for your comment. No action needed.
Other considerations	Target Ovarian Cancer	HRD testing is not currently available in the NHS so there would be associated costs in identifying HRD status.	Thank you for your comments. The consideration of the

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			cost of diagnostics tests was added to the scope.
	AstraZeneca UK Ltd	None that have not been covered elsewhere.	Thank you for your comment. No action needed.
Innovation	Ovacome Ovarian Cancer Charity	Yes. The PAOLA-1/ENGOT-ov25 trial has demonstrated the effectiveness of this treatment regime in offering first line maintenance treatment which extends progression free survival. This is vital for a patient group which faces a high probability of recurrent disease. Our members feel this is vitally needed both in terms of treatment choices and psychological benefit.	Thank you for your comments. No action needed.
	AstraZeneca UK Ltd	As explained in the context of "Timing issues", the PAOLA-1 study included patients regardless of surgical outcome or *BRCA1/2* mutation status, demonstrating the **clinical benefit of olaparib plus bevacizumab maintenance therapy in a broad real-world patient group**. The median duration of progression-free survival (PFS) in the olaparib plus bevacizumab arm of the PAOLA-1 study (22.1 months, versus 16.6 months in placebo plus bevacizumab arm) is **unprecedented** in this setting, in a population of women who were not selected by surgical outcome or biomarker status. **This improvement is especially noteworthy against a comparator arm of bevacizumab + placebo.**	Thank you for your comments. The extent to which the technology may be innovative will be considered in any appraisal of the technology. We encourage companies to submit all relevant and available evidence for consideration. No action needed.

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		Although designed to evaluate the efficacy and safety of olaparib plus bevacizumab maintenance therapy in a biomarker unselected population, the PAOLA-1 study provided important insights into the benefit of PARP-inhibition in women whose tumours are deficient in the homologous recombination repair pathway – the most "faithful" (error-free) mechanism DNA double-strand break repair in human cells and in which the BRCA1/2 proteins play an important role. A pre-planned subgroup analysis of the PAOLA-1 study showed that maintenance treatment with olaparib plus bevacizumab reduced the risk of progression or death by 67% versus bevacizumab maintenance alone, in women whose tumours were deficient in homologous recombination repair, including, but not limited to, mutations in *BRCA1/2* genes. Median PFS duration in this group of women was greater than three years (for olaparib plus bevacizumab, versus ~18 months for placebo + bevacizumab). This is an important finding that shows a benefit of PARP inhibition in the context of a broader range of deficiencies in homologous recombination repair, beyond just the *BRCA1/2* genes. Going forwards, these data are likely to impact on treatment decisions / clinical practice in the UK, especially in the context of NHS England's ambition to leverage molecular diagnostics and genomic testing to ensure that patients can receive the **most appropriate and targeted treatment** for their cancer. AstraZeneca is committed to collaborating with NHS England and its relevant stakeholders, to ensure that new and clinically meaningful biomarker testing can be routinely used to	

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		improve patient outcomes in the UK (building on our experience from EGFR and tumour BRCA testing). The PAOLA-1 study thus marks a step-change in terms of: - the efficacy demonstrated for olaparib plus bevacizumab versus placebo plus bevacizumab in a broad population of women unselected by surgical outcome or biomarker status - demonstrating the benefit of PARP inhibition not just in tumours that are *BRCA1/2* mutated, but in those that have other defects or signs that indicate them deficient in the homologous recombination repair pathway.	
Questions for consultation	AstraZeneca UK Ltd	No further comments.	-
Additional comments on the draft scope	Ovacome Ovarian Cancer Charity	Where to fit in NICE pathway for ovarian cancer: Management of advanced (stage II-IV) ovarian cancer.	Thank you for your comment. If olaparib in combination with bevacizumab maintenance therapy is recommended, the NICE pathways will be updated accordingly.

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

None.