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

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	AstraZeneca	We suggest that the wording of the remit should be updated to align more closely with the marketing authorisation for olaparib in this indication. The current wording of the remit omits the fact that the indication is limited to patients with HRD-positive tumours. We propose the following updated wording: "To appraise the clinical and cost effectiveness of olaparib in combination with bevacizumab as maintenance treatment of adult patients with advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD)-positive status."	Thank you for your comment. The remit can be broad but the population has been changed to reflect that olaparib is for those with cancers that are HRD-positive.
	Target Ovarian Cancer	The remit should include that the treatment is only available to those who are HRD positive	Thank you for your comment. The remit can be broad but the population has been changed to reflect that

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			olaparib is for those with cancers that are HRD-positive.
Timing Issues	AstraZeneca	No comment. We accept the timelines for this appraisal which have been proposed by NICE.	Thank you for your comment. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	We suggest the following minor adjustments to the 'Background Information' section, relating to HRD status and bevacizumab use: **HRD status** The marketing authorisation for the "PAOLA-1 indication" is limited to patients with HRD-positive tumours; we therefore suggest to briefly introduce the relevance of HRD status in advanced ovarian cancer in this section. Specifically, published data shows that ~50% of high grade serous ovarian cancer (HGSOC) tumours exhibit homologous recombination deficiency (HRD), which is the main high-fidelity pathway of DNA double-strand break repair in human cells. Importantly, HRD-positive tumours are highly sensitive to cytotoxic chemotherapy as well as targeted PARPi therapy such as olaparib.2,4-5 Women with HRD-positive disease generally achieve significantly longer progression-free survival (PFS) and overall survival (OS) after first-line chemotherapy and are thus prognostically different to those with HRD-negative disease.	Thank you for your comment. The background information has been updated to reflect the comments made.

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		Bevacizumab use The final paragraph on page 1 on the use of bevacizumab in advanced OC is incomplete. As per Section B (NICE & NHSE approved cancer drugs/indications routinely funded by NHSE from 1st April 2016) in the National Cancer Drugs Fund List, bevacizumab in advanced OC is approved for the following indications: i. In combination with 1st line chemotherapy as induction treatment at a dose of 7.5 mg/kg (Blueteq form reference “Bev3”) ii. In combination with 1st line chemotherapy as induction treatment at a dose of 15 mg/kg (Blueteq form reference “Bev9”) iii. As monotherapy maintenance treatment after completion of induction chemotherapy at a dose of 7.5 mg/kg (Blueteq form reference “Bev10”) Please note that baseline funding for all three indications has been available since April 1st, 2021.	
	Target Ovarian Cancer	The information provided is accurate.	Thank you for your comment. No action needed.
The technology/ intervention	AstraZeneca	The “intervention(s)” section of the draft scope currently references both the induction and maintenance treatment phases in advanced OC which we believe is incorrect. The intervention for this appraisal should only include the maintenance phase to reflect the marketing authorisation for olaparib in this indication and account for changes in the treatment landscape in recent years. At the time of the original scope for this appraisal in 2020, the intervention was extended beyond the PAOLA-1 indication to cover the upstream	Thank you for your comment. The intervention section has been updated to reflect maintenance treatment only.

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		implications of adding bevacizumab 15 mg/kg to first-line platinum-based chemotherapy (as this was not yet recommended for routine commissioning in this setting). However, as outlined in our comments to the "Background Information" section above, bevacizumab is now approved and routinely funded in baseline commissioning by NHSE as an induction treatment for advanced OC at both the 7.5 mg/kg and 15 mg/kg dose, as well as maintenance treatment after completion of induction chemotherapy at a dose of 7.5 mg/kg.7 This is reflected in current clinical practice, with a review of the English Blueteq data on new patient starts in advanced OC until September '22 showing that physicians now prescribe bevacizumab as an induction treatment in combination with chemotherapy at both the 7.5 mg/kg and 15 mg/kg dose.9 It is therefore not appropriate to extend the description of the intervention to include the use of upfront bevacizumab. Instead, the appropriate intervention for this CDF exit appraisal should be aligned with the marketing authorisation for olaparib in the PAOLA-1 indication, which specifically focuses on maintenance treatment, i.e.:1 "Olaparib in combination with bevacizumab (15 mg/kg) as maintenance treatment for patients who are in complete or partial response following completion of first-line platinum-based chemotherapy with bevacizumab"	
	Target Ovarian Cancer	Yes	Thank you for your comment. No action needed.
Population	AstraZeneca	**Population** The population is well-defined, we have no further comments.	Thank you for your comment. The subgroups have been

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		Subgroups In the PAOLA-1 clinical trial, PFS was investigated in pre-specified exploratory subgroup analyses across different subgroups, including tBRCA status. Data from these subgroup analyses show that the clinical benefit of olaparib in combination with bevacizumab maintenance therapy was seen in all HRD-positive patients regardless of tBRCA status, i.e., tBRCAm or non-tBRCAm/tBRCAwt (DCO1, 22 March 2019). This is an important result which addresses a key area of unmet clinical need, by demonstrating that the benefit of olaparib + bevacizumab maintenance can be achieved in all HRD-positive tumours irrespective of BRCAm status, and that all such patients can benefit from this early combination maintenance approach at a time when the likelihood of achieving long-term remission is at its highest. Therefore, subgroup data by BRCA mutation status as outlined in the draft scope is unlikely to be informative to this appraisal and should be removed from the scope.	removed from the scope.
	Target Ovarian Cancer	Yes	Thank you for your comment. No action needed.
Comparators	AstraZeneca	We would like to provide the following comments on the two proposed comparators in the draft scope: **Platinum-based chemotherapy followed with routine surveillance:** At the time of the original appraisal, it was considered relevant to compare versus platinum-based chemotherapy followed by routine surveillance as these patients could have been considered eligible to receive bevacizumab in addition to their first-line chemotherapy treatment. This decision was driven	Thank you for your comment. Platinum-based chemotherapy has been removed from the scope. Bevacizumab maintenance therapy (at a dose of 7.5mg/kg) and routine surveillance

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		by the fact that bevacizumab in combination with first-line chemotherapy was only available in the CDF and not considered standard clinical practice. In effect, both the comparator and intervention were extended beyond the PAOLA-1 regimen to cover the upstream implications of adding bevacizumab 15 mg/kg to first-line platinum-based chemotherapy. Given induction treatment with bevacizumab in combination with chemotherapy is now routinely funded in baseline commissioning, the intervention and thus the comparator should only include the maintenance setting (as outlined in "The technology/intervention" section above). In current clinical practice patients who receive platinum-based chemotherapy followed by no active treatment in the maintenance setting, i.e., routine surveillance, are explicitly not comparable to those who would be considered eligible for the PAOLA-1 regimen as they have not received bevacizumab in the induction setting. This population therefore falls outside the existing marketing authorisation for the PAOLA-1 regimen and should be removed from the scope. It could be argued that "routine surveillance" remains a relevant comparator following initiation with bevacizumab in combination with chemotherapy in the induction setting although this is highly unlikely in clinical practice. Feedback from medical oncologists confirm that it has become increasingly uncommon for patients to receive no active treatment in the maintenance setting, i.e., routine surveillance only, particularly if they received bevacizumab in the induction setting. It follows that the proportion of patients who would discontinue bevacizumab between the induction and maintenance settings – and remain eligible for treatment with the PAOLA-1 regimen – is negligible and not reflective of current clinical practice. In conclusion, both (i) platinum-based chemotherapy followed by routine surveillance and (ii) platinum-based chemotherapy in combination with	remain as comparators at this stage. Stakeholders can provide justification around the most appropriate comparators and the committee will consider this during the appraisal.

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		bevacizumab followed by routine surveillance are not relevant clinical comparators for this decision problem and should be removed from the final scope. **Platinum-based chemotherapy with bevacizumab (7.5 mg/kg every 3 weeks) followed with bevacizumab maintenance therapy** Please refer to our comments above with respect to the fact that induction treatment with bevacizumab in combination with chemotherapy is now routinely funded in baseline commissioning, and that the focus of the comparator should therefore be on the maintenance setting only. We therefore suggest that the cost effectiveness analysis as part of this appraisal should begin at the point of successful completion of this induction phase and should focus only on a comparison vs. bevacizumab in the maintenance setting. It is also important to consider the appropriate dose of bevacizumab to which our comparison ought to be anchored. We understand that bevacizumab as a monotherapy maintenance treatment is currently only approved at a dose of 7.5 mg/kg rather than the 15 mg/kg dosing specified in its EMA marketing authorisation used in the PAOLA-1 trial. However, we suggest that similar to the original appraisal for this indication in 2020 the cost-utility analysis in this appraisal should provide a comparison versus both dosing options (i.e., bevacizumab 15 mg/kg and 7.5 mg/kg maintenance treatment). Such an approach aligns with the PAOLA-1 design, as well the scopes of previous technology appraisals of maintenance treatment strategies for women with newly diagnosed advanced ovarian cancer, including TA598 (olaparib) and TA673 (niraparib).12,13 To conclude, the two comparators relevant to this CDF exit appraisal are therefore:	

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		1. Bevacizumab maintenance only at a dose of 7.5 mg/kg 2. Bevacizumab maintenance only at a dose of 15 mg/kg	
	Target Ovarian Cancer	Yes	Thank you for your comment. No action needed.
Outcomes	AstraZeneca	Yes	Thank you for your comment. No action needed.
	Target Ovarian Cancer	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.
Economic analysis	AstraZeneca	The economic analysis will follow the NICE reference case. As per the original appraisal a lifetime time horizon is considered appropriate in this setting to capture all differences in costs and outcomes between the technologies being compared.	Thank you for your comment. No action needed.
Equality and Diversity	AstraZeneca	No equality considerations have been identified at this stage.	Thank you for your comment. No action needed.
	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. No action needed.

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Innovation	AstraZeneca	The Phase III PAOLA-1 study, the pivotal clinical trial relevant to this CDF exit appraisal, evaluated the efficacy and tolerability of adding olaparib to bevacizumab maintenance treatment, with the aim of expanding the benefits of PARPi therapy to those women with advanced OC who are considered candidates for bevacizumab treatment in combination with first-line chemotherapy, and improving patient outcomes in this setting. In the HRD-positive patient population, the latest data cut-off (DCO3, 22 Marc 2022) recently presented at ESMO 2022 reported that the addition of olaparib to bevacizumab provided a clinically meaningful improvement in overall survival, reducing the risk of death by 38% versus bevacizumab (based on a HR of 0.62; 95% CI 0.45-0.85) despite PAOLA-1 having 30% Stage IV patients.14 65.5% of patients treated with olaparib plus bevacizumab were still alive at five years versus 48.4% of those treated with bevacizumab alone. Olaparib in combination with bevacizumab also improved median PFS to almost four years (46.8 months) versus 17.6 months with bevacizumab plus placebo and 46.1% of patients treated with olaparib plus bevacizumab remain progression free at five years versus 19.2% of patients treated with bevacizumab alone.14 Considering that the historical five-year survival rate of newly diagnosed patients with advanced OC is 30-50%, this long-term OS and PFS data from the PAOLA-1 further demonstrates the increasingly ground-breaking evidence on the long-term benefit of maintenance treatment incorporating a PARP inhibitor, with approximately two out of three patients still alive in the trial at five years.14 Collectively, these data support the positioning of olaparib added to bevacizumab as the “new standard-of-care” for women with newly diagnosed HRD-positive advanced ovarian cancer, who are in complete or partial	Thank you for your comments. The extent to which the technology may be innovative will be considered during the appraisal. We encourage companies to submit all relevant and available evidence for consideration.

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		response following first-line platinum-taxane chemotherapy and bevacizumab.	
Questions for consultation	AstraZeneca	**Where do you consider olaparib in combination with bevacizumab will fit into the existing care pathway for advanced ovarian, fallopian tube and peritoneal cancer?** Please see an overview of the positioning of the PAOLA-1 regimen in the English treatment pathway for advanced (FIGO stages III-IV) OC in the Appendix. **Is diagnostic testing for BRCA and HRD standard practice in the NHS for people with advanced ovarian cancer?** BRCA and HRD testing are well established in the ovarian cancer clinical pathway and are included on the National Genomic Test directory (M2.5).	Thank you for your comment. No action needed.
	Target Ovarian Cancer	**Where do you consider olaparib in combination with bevacizumab will fit into the existing care pathway for advanced ovarian, fallopian tube and peritoneal cancer?** Olaparib in combination with bevacizumab offers those with ovarian cancer the opportunity access innovative treatment when newly diagnosed. Being able to access treatments as early as possible is very important to those who have been diagnosed. **Is diagnostic testing for BRCA and HRD standard practice in the NHS for people with advanced ovarian cancer?** BRCA testing is now standard practice and is an established part of the genomic testing directory. HRD testing came on stream when the olaparib in combination with bevacizumab was made available on the CDF so while not yet available through the NHS patients report good levels of access.	Thank you for your comment. No action needed.

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Additional comments on the draft scope	Target Ovarian Cancer	Subgroup comparators are listed as those with BRCA mutations, this does not cover the intended patient population of those with positive for HRD	Thank you for your comment. The subgroups have been removed from the scope.

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

Ovarian Cancer Action