Single Technology Appraisal

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 [Review of TA693] [ID4066]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from** AstraZeneca

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Target Ovarian Cancer

   There were no comments on the Draft Guidance received through the NICE website.

3. **External Assessment Group critique of company response to the DG**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination, and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca UK

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct, or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted] [redacted], AstraZeneca UK

Comments on the draft guidance

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Consideration of the evidence base** AstraZeneca UK (AZUK) appreciate the opportunity to consult on the draft guidance for this appraisal and thank the NICE committee and EAG for a productive discussion during the committee meeting on the 6th of June 2023. While we are disappointed that a negative draft recommendation has been issued, we are pleased that many key issues have been resolved at this stage of the appraisal, including acknowledgement of the unmet need in this setting and the importance of maintaining access for patients, alignment on the appropriate cost of homologous recombination deficiency (HRD) testing to include in the economic model, and the conclusion regarding the negligible expected efficacy impact of poly adenosine diphosphate-ribose polymerase (PARP) inhibitor retreatment in the PAOLA-1 trial. However, AZUK would like to highlight some omissions and factual inaccuracies with respect to how the key evidence base was presented at the committee meeting (i.e. in the committee slides), and subsequently incorporated into the draft guidance document, as outlined below:

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	Appropriate presentation of evidence at the committee meeting
	
	We would first like to point out that several of the committee slides did not correctly present or accurately summarise the evidence which was submitted throughout the course of this appraisal, omitting justifications or context which is important for decision making. For example:
	
	• On slide 25 of the committee meeting presentation, it is stated that the company chose to fit a mixture cure model (MCM) to the PAOLA-1 progression-free survival (PFS) data considering that "… *all standard parametric fitted curves underpredict long-term PFS on SoC*." As outlined in our company submission document, and further elaborated upon in our response to both the EAG clarification questions and technical engagement, the MCM was adopted to most accurately reflect the compelling body of evidence on the potential for long-term remission in advanced ovarian cancer (aOC), both from external empirical data as well as longer follow-up data from the PAOLA-1 and SOLO-1 clinical trials. Although it is true that standard parametric models result in clinically implausible extrapolations, this was not the primary reason for adopting the MCM.
	
	  ○ Instead, and aligned with the guidance in NICE DSU technical support document 14 (1), a modelling approach was selected to account for the proportion of patients that experience long-term remission in aOC, something which standard parametric models fail to capture. In this scenario, a MCM is considered the most appropriate approach as it enables reflection of this survival trajectory by representing the patient population as a combination of both long- and short-term survivors. The committee slides failed to present this rationale and the supporting evidence described above which we believe is important context for the committee's decision making.
	
	• On slide 26 there are factual inaccuracies regarding the explanation of the workings of the MCM. It says that the MCM approach "… *assumes patients enter long-term survival trajectory equivalent to the general population at 5 years*." However, as raised by the AZ health economist during the committee meeting, this is incorrect; the MCM does not define the time point at which patients who are progression-free are considered long-term survivors. Rather, the model utilises the underlying characteristics of the dataset to estimate the proportion of patients who may achieve long-term remission, and it is these 'cure fractions' that influence the shape of the respective survival curves.
	
	  ○ Although it is true that for those patients considered 'cured' in the MCM their risk of progression is set to zero, this does not mean that patients are assumed to be free from experiencing survival events; it is simply set equal to all-cause mortality. In fact, the estimated cure fractions for the bevacizumab only and olaparib + bevacizumab arms are lower ([redacted] and [redacted], respectively) compared with the observed five-years PFS rates of 19.2% and 46.1%, respectively, in PAOLA-1, and were confirmed by the clinical experts to align with the proportion of patients who achieve long-term remission in their clinical practice. The MCM therefore does not inherently predict a cure or plateauing effect at 5 years, but appropriately predicts a slow, but decelerated, trend in long-term PFS that is to be expected in a cohort of aOC patients, regardless of the therapy patients received in the first-line (1L) maintenance setting.
	
	  ○ Furthermore, the slide says that the EAG considered it "… *more appropriate to model any relevant remission point using OS arm/data*." Again, although an MCM can be implemented for modelling OS, in this scenario applying such an approach to OS would ignore the long-term progression-free status of these patients (i.e. such an approach would allow progressed patients to achieve long-term remission within the model, despite the fact that there is no evidence to suggest that patients with aOC

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	remain 'curable' after experiencing a disease progression), and lead to contradicting cure fractions and non-convergent long-term extrapolations. Although we welcome valid and constructive critique from the EAG on the health economic modelling approaches, we believe that by presenting these factual inaccurate statements the committee was given a biased interpretation of the MCM and its appropriateness for modelling the PAOLA-1 data. • In addition to the factual inaccuracies discussed above, the slides also omitted relevant scenario analyses that were submitted by AZUK for the committee's consideration as part of our response to technical engagement; importantly, the scenario analysis that adopts a 3-knots spline model with a fixed 7-year cure fraction for PFS. This scenario, which adopts the same 3-knots spline model as preferred by the EAG but assumes that the risk of progression for patients who remain progression-free at 7 years reverts to all-cause mortality, estimates long-term PFS and overall survival (OS) rates and provides an alternative approach to that estimated by the MCM and the standard 3-knots spline model. By omitting this additional scenario analysis from the committee meeting slides the committee was not given a comprehensive range of survival modelling options to choose from and thus were presented with only two modelling approaches. We believe that the discussion on the survival extrapolations could have been more informative if other clinically plausible scenarios had been presented during the meeting. • Finally, we would like to highlight that in our view the committee slides did not present an impartial view of the key issues following technical engagement, with many slide headings imparting a negative judgment on the company's base case assumptions which did not reflect the totality of the evidence base or validation provided throughout the appraisal process, e.g. "*MCM approach used to model PFS inappropriate*" (slides 26–28) and "*Company base case generates implausible survival predictions*" (slides 30–21). While we appreciate this was intended to reflect the EAG's perception of the key issues we remain concerned that this had an impact on the deliberations during both Part 1 and Part 2 of the committee meeting and curtailed a balanced discussion. • Based on the points above, we remain concerned that the committee was not given a fair or full picture of the relevant evidence in order to make a fully informed decision. We thank NICE for their time in discussing some of these concerns during the consultation on Thursday 6th July 2023 and their commitment to addressing these during the next committee meeting on 1st August 2023. We hope that deliberate attention will be given to the drafting of the committee slides and kindly request that the additional scenario analyses outlined in this response document are fully presented for the committee to consider. <u>Manner in which committee meeting discussions are reflected in the draft guidance</u> AZUK appreciate the time taken by clinical experts to attend the committee meeting for this appraisal, and to provide their insights on UK clinical practice in aOC. However, we are concerned that much of this valuable contribution has not been duly reflected in the draft guidance document. For example, Section 3.11 of the draft guidance states that the EAG felt that "*there was no observable plateau in the olaparib with bevacizumab PFS curve, which would be expected for a curative treatment"* but does not appropriately reflect the extent to which the clinical experts expressed their disagreement with this interpretation during the committee meeting. Both clinical experts voiced counter-opinions to the EAG interpretation of the PFS curves, explaining that small numbers at risk impact the tail of the curve, and that the 7-year SOLO-1 data should be referred to as an appropriate source which validates the expectation of curative potential in this treatment setting.

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 [Review of TA693]

Draft guidance comments form

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	Furthermore, where clinical expert input has been cited in the draft guidance, it appears to have been done so selectively, without due reflection of the totality and context of their input. For example, Section 3.11 of the draft guidance states that "*Clinical experts said that it would be plausible for 5–10% of people to be alive 30 years after diagnosis, which is lower than the company's survival estimates*". The 5–10% estimate appears to have been taken from the technical engagement response of one of the clinical experts (page 576 of the committee papers); however, the draft guidance fails to mention important context around this statement which the same clinical expert made within the same technical engagement response. For example, on page 575 of the committee papers they state that "*the MCM models are more in keeping with real clinical practice*", and that "*the EAG standard parametric models are too pessimistic…when data suggest that there is a genuine plateau (or near-plateau). The SOLO-1 7-year data strongly support this concept*". By omitting these points from the draft guidance, we are concerned that the expert input received during the committee meeting has not been accurately reflected. The draft guidance seems to conclude that the committee meeting discussions generally favoured the EAG approach, stating that the company's mixture cure modelling approach was "not justified", but making a much less definitive judgment on the appropriateness of the EAG approach. <u>Other minor factual inaccuracies in the draft guidance</u> • **Publicly available data:** Sections 3.7 and 3.8 of the committee guidance state that the outcomes of PFS and OS, respectively, at 5 years are not publicly available. The company notes that these data were published in The Annals of Oncology in May 2023 (2); as such, these publicly available data can be reported in the draft guidance.
2	**<u>Validation of appropriate survival modelling approach</u>** • One of the key points of discussion during the committee meeting was the clinical plausibility of the survival extrapolations. We thank the committee Chair for allowing a constructive discussion on this topic and for giving the clinical experts the opportunity to share their input on the potential for long-term remission in aOC, referencing their experience in clinical practice and other data sources such as the SOLO-1 trial. However, based on the discussions during the committee meeting, as well as the evidence submitted in our initial company submission, our response to the EAG clarification questions and technical engagement, we do not believe the conclusions reflect the totality of the evidence base presented. • As discussed during the committee meeting, there is ample evidence to support the concept of long-term remission in aOC, and thus the adoption of a MCM as the appropriate modelling approach for this appraisal. The clinical experts provided valuable insights on their experience of treating patients with aOC and referenced both the PAOLA-1 and SOLO-1 trials to confirm that the potential for long-term remission or 'cure' in this disease area is now well-established. When reviewing the extrapolated survival curves from the MCM vs. the EAG's 3-knots spline model, they commented that it is illogical to accept a plateauing effect for PFS for aOC patients who receive bevacizumab-only maintenance therapy, but not for the combination of bevacizumab with olaparib, particularly given that PAOLA-1 has demonstrated superior clinical outcomes with the combination regimen. Both clinical experts also felt that the MCM generates more realistic and clinically plausible long-term PFS estimates, and that the estimated OS rates were generally aligned with their expectation in clinical practice. • Considering this input from clinical experts, the comprehensive clinical evidence base supporting the concept of cure in aOC, and the technical recommendations set forth in

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 [Review of TA693]

Draft guidance comments form

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	NICE DSU TSD 14 (1), we maintain that the MCM approach is the most appropriate modelling method for this appraisal. We would like to reiterate that the EAG's preferred 3-knots spline model has no valid grounds for adoption, fails to capture the potential for long-term remission and does not reflect the expected additional clinical benefit of adding a PARP inhibitor to bevacizumab. Importantly, the 3-knots spline model generates long-term survival estimates which were confirmed by the clinical experts to be too pessimistic and do not reflect the plateauing effect seen in recent empirical studies in aOC. • However, to address some of the committee's concerns around the long-term survival extrapolations that are generated by the MCM approach, we have explored several additional scenario analyses in which the long-term survival predictions are adjusted; these are presented in the Appendix of this response document. In all these scenarios, the potential for long-term remission in advanced OC is appropriately incorporated in the modelling approach, but the standardised mortality rate (SMR) is altered to reflect different relative mortality risk in this patient group vs. the general population. An increased relative mortality risk versus the general population would capture any long-term mortality implications of cancer treatment and its side effects, as well as any increased lifetime mortality risk experienced by patients with germline *BRCA* mutations. • This adjustment results in a slightly higher tapering of the PFS and OS rates towards the end of the extrapolated curves and addresses the critique that by equalising OS to PFS when the respective curves cross, the long-term survival rates remain relatively high over time. Importantly, all of the scenarios model a [redacted] and [redacted] survival rate for the olaparib + bevacizumab arm at 25 and 30 years respectively (Table 5), which was the most contentious point of discussion during the meeting and confirmed by the clinical experts to be aligned with their survival expectation in clinical practice. Furthermore, incorporating increased rates of standardized mortality as scenario analyses also addresses the concern raised during the committee meeting that patients who are diagnosed with an advanced stage cancer at age ~58 likely have a higher mortality risk over time, and that this should be appropriately reflected in the economic model. • In addition to the three scenarios with higher SMRs (1.4, 1.6 and 1.8), we are also presenting a fourth scenario in which we adopt the 3-knots spline model but incorporate the potential for long-term remission by implementing a crude 7-year 'cure' assumption. This scenario was initially presented in our response to technical engagement as an alternative to the MCM and the EAG's 3-knots spline model. It also generates long-term PFS rates ([redacted] at 20 years for the olaparib + bevacizumab arm) that were considered reasonable although conservative by clinical experts, stating that patients' risk of recurrence generally reduces to negligible levels at 5 years instead of 7 years of remaining progression-free. The similar long-term PFS estimates between this scenario and the MCM also demonstrates the stability and appropriateness of adopting an MCM versus implementing a crude cure assumption to reflect the potential for long-term remission over time. • We feel that these scenarios adequately address the committee's concerns on the long-term survival predictions and offer a valid alternative to the EAG's standard 3-knots spline model. We would therefore like to request for these scenario analyses (Table 3), together with their landmark PFS and OS rates (Table 4 and Table 5), to be presented at the second committee meeting on 1st August 2023, allowing the committee to make a fully informed decision.

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 [Review of TA693]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 18 July 2023. Please submit via NICE Docs.

	• Finally, as the topic of discussion on the scenario analyses above will remain on the clinical plausibility of the survival extrapolations, we believe clinical input would be valuable to support the committee in teasing apart these issues and evaluating the new scenarios which we have provided. This position was reflected in our ask to NICE to consider re-inviting the clinical experts for the second committee meeting on 1st August 2023 to further support discussions.
3	**Appropriate baseline age in the economic model** Although not directly raised or discussed during the committee meeting, we would like to take this opportunity to reiterate that the EAG's preferred assumption of adopting the baseline age (years) from the Systemic Anti-Cancer Therapy (SACT) data is inappropriate. Baseline characteristics adopted in the economic analysis should retain consistency with the most relevant source of evidence, i.e., the PAOLA-1 trial, on which other key parameters are based (e.g., efficacy, treatment duration, utilities). We recognise that this does not have a meaningful impact on the estimated ICER and that it is appropriate to explore such an analysis as a scenario, however, adopting it as a base case parameter could lead to internal inconsistency in the economic analysis and bias interpretation of the outcomes. As such, we maintain the baseline age of the PAOLA-1 HRD population in the clinical trial is the most appropriate parameter and is utilised in the additional scenario analyses we present in the Appendix of this response document.
4	**Approach to managing uncertainty** In their draft guidance consultation document, NICE conclude that due to "*multiple uncertainties within the clinical and economic evidence, especially relating to the survival modelling approach*", they consider that an acceptable incremental cost-effectiveness ratio (ICER) would need to be "*comfortably below £30,000 per QALY gained*". AstraZeneca acknowledge that a reduction in the ICER threshold is one approach which the NICE committee can use to acknowledge decision uncertainty when making a recommendation. However, in this instance it is important to note that when considering the most significant unresolved uncertainty in this appraisal (survival modelling approach), the committee have already incorporated the EAG's approach in their preferred assumptions, which clinicians felt to be "*too pessimistic*", with no biological rationale to support the faster decline in OS in the olaparib + bevacizumab arm, and which the committee themselves acknowledged to be conservative. When considering uncertainty, it is inappropriate to both lower the ICER threshold, as well as select the most conservative set of economic modelling assumptions, as this can be considered as "double counting". This is reflected in Section 6.2.33 of the NICE manual (3) which states that "*when considering uncertainty, the committee should… consider the risks to the NHS of using the technology, based on the most plausible ICER".* Considering the clinical expert input on the approach to survival analysis, and the other factors outlined above, AstraZeneca do not believe that the draft guidance reflects a true consideration of the most plausible ICER, and that the NICE committee position with respect to managing uncertainty is therefore unduly conservative. Furthermore, Section 6.2.35 of the NICE manual (3) also states that "*uncertainty will be considered proportionately for the evaluation context (including, for example, the type of technology, evaluation, or population)*". With this in mind, it should be highlighted that the evidence base for olaparib in aOC is widely hailed by the medical community as a "*breakthrough in ovarian cancer treatment*" (4), considering the demonstration of clinically meaningful OS benefits after 5 years follow up in the PAOLA-1 trial, and 7 years follow-up in the SOLO-1 trial, particularly given that OS data for many other PARP inhibitors in this setting remain immature. Since entering the Cancer Drugs Fund (CDF) in 2021, the maturity of OS data from the PAOLA-1 trial has increased

NICE National Institute for Health and Care Excellence

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 [Review of TA693]

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	from 16.3% (5) (Data cut-off [DCO]: 22nd March 2019) to 41.9% (2) (DCO: 22nd March 2022), resolving much of the uncertainty about long-term clinical outcomes. We therefore believe that the extent of uncertainty present in this appraisal has been overstated and would ask the NICE committee to consider the true level of uncertainty considering this important context.
5	**Benefits not captured in the economic model** The draft guidance states that any benefits not captured in the economic model should be acknowledged when considering the most appropriate ICER threshold for this appraisal. AstraZeneca would like to highlight the following important benefits which are not captured in the ICER, and ask the committee to consider these during decision-making: • The full cost of HRD testing was incorporated in the economic model. However, given that the results of a HRD test include BRCA1/2 mutation status, HRD testing effectively replaces the need for somatic BRCA testing in UK clinical practice. The NHS cost-saving of reducing somatic BRCA testing rates is not captured in the economic model. Furthermore, the wider benefits of HRD testing in aOC are not captured in the economic model. HRD testing allows clinicians to understand the genetic driver of their patients' disease, including BRCA1/2 mutation status, which can inform prognosis and optimal management, as well as the need for germline testing, cascade testing, and care for family members identified to be carriers. • Ovarian cancer is a severe disease which can often affect young women, and therefore has a particularly high impact on their families and carers. Prolonging the time in which a patient remains progression-free, and improving their chance of achieving long-term remission represents a significant benefit for families and carers which is not captured in the economic model.

Insert extra rows as needed.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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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 [Review of TA693]

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Appendix

Based on the discussion in the committee meeting and feedback on some of the base case assumptions in the draft guidance, we have made some minor changes to our base case cost-effectiveness analysis in preparation for the second Appraisal Committee Meeting (ACM); these changes are presented in Table 1.

Table 1. Changes to the company's base case assumptions for the economic model

Model parameter	Original company base case assumption	Company's revised base case assumption post-EAR (*related to key issue number X)*	ICER vs. bevacizumab 7.5 mg/kg*	NMB vs. bevacizumab 7.5 mg/kg*
Original company base case (pre-ACM1, June 2023)			***Dominant***	[redacted]
Baseline age	58.1 years (as per PAOLA-1 HRD-subgroup baseline characteristics)	N/A *We maintain a baseline age of 58.1 years.*	Dominant	[redacted]
Subsequent proportion of PARPi use	[redacted] olaparib, [redacted] niraparib, [redacted] rucaparib	100% niraparib *The committee aligned with the EAG's approach using niraparib as the only subsequent PARP inhibitor in the base-case analysis.*	Dominant	[redacted]
Standardised mortality rate (SMR)	SMR of 1.14	N/A *We maintain an SMR of 1.14 in our base case analysis but present several scenario analyses below in which this rate is increased.*	Dominant	[redacted]
HRD testing costs	[redacted]	N/A [redacted] *was confirmed to be reflective of the expected cost of HRD testing in NHSE during the committee meeting.*	Dominant	[redacted]

*Changes in the ICER and NMB are cumulative with each revision of the company's original base-case assumptions.
Abbreviations: ACM, Appraisal Committee Meeting; EAG, External Assessment Group; HRD, homologous recombination deficiency; ICER, incremental cost-effectiveness ratio; N/A, not applicable; NHSE, National Health Service England; NMB, net monetary benefit; PARPi, poly adenosine diphosphate-ribose polymerase inhibitor; SMR, standardised mortality rate.

The revised base case results based on the changes outlined above are presented in Table 2. Please note that these results are based on the original PAS price for olaparib (a [redacted] reduction from list price) (Table 40 in the Company Submission).

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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 [Review of TA693]

Draft guidance comments form

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Table 2. Company revised base case results (deterministic)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)	NMB
Versus bevacizumab 15 mg/kg								
Bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Versus bevacizumab 7.5 mg/kg								
Bevacizumab 7.5 mg/kg	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Note: Discounted outcomes.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; NMB, net monetary benefit; QALY, quality-adjusted life year.

NICE National Institute for Health and Care Excellence

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 [Review of TA693]

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The following additional scenario analyses were conducted to address some of the key concerns on the clinical plausibility of the survival extrapolations raised during the committee meeting. We would kindly ask for these scenario analyses to be presented, together with their long-term PFS and OS rates, as outlined in Table 4 and Table 5 respectively, at the second ACM on 1st August 2023.

Table 3: New survival modelling scenario analyses

Scenario	Base case value	Scenario analysis value	ICER (£/QALY) vs bevacizumab 15 mg/kg	NMB vs. bevacizumab 15 mg/kg	ICER (£/QALY) vs. bevacizumab 7.5 mg/kg	NMB vs. bevacizumab 7.5 mg/kg
Base case	-	-	**Dominant**	[redacted]	**Dominant**	[redacted]
Survival modelling PFS	MCM (log-logistic), SMR of 1.14	MCM (log-logistic), SMR of 1.4	Dominant	[redacted]	Dominant	[redacted]
		MCM (log-logistic), SMR of 1.6	Dominant	[redacted]	Dominant	[redacted]
		MCM (log-logistic), SMR of 1.8	Dominant	[redacted]	Dominant	[redacted]
		3-knots spline model with a 7-year cure, SMR 1.14	Dominant	[redacted]	Dominant	[redacted]

Abbreviations: 2L, second-line; 3L, third-line; CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MCM, mixture cure model; NMB, net monetary benefit; PFS, progression-free survival; QALY, quality-adjusted life year

NICE National Institute for Health and Care Excellence

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 [Review of TA693]

Draft guidance comments form

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Table 4: Comparison of KM data and long-term extrapolation for PFS with new proposed scenario analyses vs. AZ revised base-case & the EAG's preferred base-case

	Time (years)							
	1	2	3	5	10	20	25	30
Bevacizumab only arm								
KM data PAOLA-1 trial	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
AZ revised base-case (MCM, log-logistic, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's base-case (3-knots spline, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: MCM (log-logistic), SMR of 1.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: MCM (log-logistic), SMR of 1.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: MCM (log-logistic), SMR of 1.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: 3-knots spline model with a 7-year cure, SMR 1.14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + bevacizumab arm								
KM data PAOLA-1 trial	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
AZ revised base-case (MCM, log-logistic, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's base-case (3-knots spline, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: MCM (log-logistic), SMR of 1.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: MCM (log-logistic), SMR of 1.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: MCM (log-logistic), SMR of 1.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: 3-knots spline model with a 7-year cure, SMR 1.14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM: Kaplan-Meier (observed); PFS: progression-free survival.

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Table 5: Comparison of KM data and long-term extrapolation for OS with new proposed scenario analyses vs. AZ revised base-case & the EAG's preferred base-case

	Time (years)							
	1	2	3	5	10	20	25	30
Average age of patients (years)†	~59	~60	~61	~63	~68	~78	~83	~88
General population mortality	**99.6%**	**99.2%**	**98.6%**	**97.5%**	**93.6%**	**78.7%**	**64.1%**	**43.4%**
Bevacizumab only arm								
KM data PAOLA-1 trial	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
AZ revised base-case (MCM, log-logistic, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's base-case (3-knots spline, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: MCM (log-logistic), SMR of 1.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: MCM (log-logistic), SMR of 1.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: MCM (log-logistic), SMR of 1.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: 3-knots spline model with a 7-year cure, SMR 1.14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + bevacizumab arm								
KM data PAOLA-1 trial	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
AZ revised base-case (MCM, log-logistic, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's base-case (3-knots spline, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: MCM (log-logistic), SMR of 1.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: MCM (log-logistic), SMR of 1.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: MCM (log-logistic), SMR of 1.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: 3-knots spline model with a 7-year cure, SMR 1.14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Based on the fact that the average age of patients at initiation of the PAOLA-1 trial was 58.1 years.
Abbreviations: KM: Kaplan-Meier (observed); OS: overall survival

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Target Ovarian Cancer

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	GSK June 2023 £14,000 for the development of patient information guides March 2023 £300 honorarium for a speaking event
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that this draft recommendation does not consider the lack of treatment options those who have completed the 1st line of treatment. There are currently no 1st line treatment

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	options in routine commissioning. Patients can only access a maintenance treatment once they have experienced a relapse. Current standard treatment involves surgery and chemotherapy, with chemotherapy either post-surgery or neoadjuvant. In the majority of cases the disease returns after first line treatment. At this point treatment is no longer curative and each further recurrence and subsequent round of platinum-based chemotherapy a woman goes through increases her chance of becoming platinum resistant; at which point very few treatment options remain and prognosis is extremely poor. For many women, receiving the news that their cancer has returned can be more devastating than the initial ovarian cancer diagnosis which is why widespread access to effective first line treatment must be a priority.
2	We are concerned that the draft recommendation will mean that the majority of those who would benefit from personalised treatment will not be able to access it. Olaparib and bevacizumab in combination is currently available to those who are positive for HRD. This is approximately half of those with advanced ovarian cancer. Olaparib as a monotherapy is currently available in the Cancer Drugs Fund but this is only available to those who have a BRCA mutation which is only around 15 per cent of those with advanced ovarian cancer.
3	We are concerned the recommendation also does not reflect the value that those who have taken the treatment tell us it has on their quality of life. We recently asked those who had taken olaparib and bevacizumab in combination their experiences: *I returned to work in April, and I have been able to do some gentle exercise for a while now, lots of walking, some swimming and yoga, and I am just about starting a bit more intense activities in the gym as well.* *I, finished bevacizumab June 2023 and I'm now on olaparib - my CA125 has been between 5-7 for a long time now.*
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.

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- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

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EAG response to company ACD comments

July 2023

Source of funding
This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135728

1 Introduction

This document provides the Evidence Assessment Group (EAG)'s critique of the company's response to the appraisal consultation document (ACD) produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of olaparib (Lynparza®, AstraZeneca) with bevacizumab (Avastin®, Roche) 15mg/kg (hereafter referred to as olap+bev) for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer (hereafter referred to as advanced ovarian cancer) after complete response (CR) or partial response (PR) to first-line platinum-based chemotherapy with bevacizumab when the cancer is associated with homologous recombination deficiency (hereafter referred to as HRD+).

Section 2 presents the EAG's critique of the comments made by the company in response to the ACD, the company's updated results are presented in Section 3 and Section 4 presents the EAG's updated base case and scenarios. Comments by the company are discussed according to comment number as per the company's response document to ACD. Table 1 below summarises these comments, including which area of the ACD they relate to and EAG response, as well as reference to which section they are discussed in more detail.

Table 1. Summary of issues covered in company's response to ACD

Comment in company's ACD response		Company response	EAG comment
1	Consideration of the evidence base, factual inaccuracies, and omissions at ACM	The Company wish for several factual inaccuracies to be corrected and relevant information that was omitted to be included.	The EAG acknowledges the inaccuracies in the presentation of the MCM. (see Section 2.1)
2	Validation of appropriate survival modelling approach	The company wishes to emphasise the justification for long term survival	The EAG maintains that the most appropriate method to estimate PFS in the model is with the use of spline models (see Section 2.1 and 2.2)
3	Appropriate baseline age in the economic model	The company maintains that use of the SACT data is inappropriate as it represents an inconsistent source of baseline characteristics	The EAG maintain that the SACT data represents the best source of data to reflect UK patients (see Section 2.3)
4	Approach to managing uncertainty	The company states that it is inappropriate to both lower the ICER threshold, as well as select the most conservative set of economic modelling assumptions	The EAG considers this to be an issue to be resolved by the committee.

5	Use of a discounted price for HRD testing and benefits not captured in the economic model	The company maintained the use of a discount to the list price to the HRD test, The company noted that there are additional uncaptured benefits from changes to HRD testing and further uncaptured benefits for carers.	The EAG agrees with the use of the discounted price for the HRD test. The EAG considers the issue of potentially uncaptured benefits to be an issue to be resolved by the committee (see Section 2.5).

Abbreviations: ACD, appraisal consultation document; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; mITT, modified intention to treat; NMA, network meta-analysis; TE, technical engagement; MCM, mixture cure model.

2 EAG's critique of company's response to ACD

2.1 Comment 1. Consideration of the evidence base.

The company noted that on slide 26 of the ACM slides, the statement that the mixture cure model (MCM) "*assumes patients enter long-term survival trajectory equivalent to the general population at 5 years*" is incorrect. The company clarified that the MCM does not define the time point at which patients who are progression free are considered long-term survivors. Rather, the model utilises the underlying characteristics of the dataset to estimate the proportion of patients who may achieve long-term remission, and it is the trajectory of these patients that influences the shape of the respective survival curves.

The company also stated its disagreement with the EAG's preference to have a MCM based on OS evidence, rather than PFS evidence, and added that "*applying such an approach to OS would ignore the long-term progression-free status of these patients* […] *and lead to contradicting cure fractions and non-convergent long-term extrapolations.*"

Furthermore, the company reported that clinical experts at the ACM voiced counter-opinions to the EAG interpretation of the PFS curves, quoting that the 7-year SOLO-1 data should be used to validate the existence of a plateau in the olap+bev arms and thus, the expectation of curative potential in this treatment setting.

The company reported other concerns regarding what was considered a misrepresentation of the evidence base during the ACM. The EAG does not consider these to be factual inaccuracies that need addressing by the EAG, and therefore, considers these to be issues to be addressed by NICE, and does not discuss these in this report.

EAG comment

On further reflection, the EAG acknowledges that there has been some confusion around the methodological aspects of the company's approach to estimating PFS through what the company considered an MCM approach. Even though the company described their modelling approach as an MCM, in hindsight, the EAG realises that the company's approach differs from the more common approach to MCMs, according to the definition of an MCM provided in Bullement et al. 2019[1] and Othus et al. 2017.[2]

Mixture cure models are usually used to estimate overall survival, as the goal of such approach is to depict long-term survivors whose risk of death becomes the same (or close to) that of a disease-free patient[1,2]. Furthermore, Lambert *et al.* 2007 noted that from the point at which diseased individuals no longer experience excess mortality, patients can be considered "statistically cured" in an MCM. The appropriate use of MCM relies, therefore, on the existence of mature survival data from studies with long follow-up times that far exceed the anticipated point of cure time, as well as sufficient numbers of patients at risk at the end of follow-up in order to robustly estimate a cure fraction.[3]

The EAG agrees with the company's point that their base case model does not define the time point at which patients who are progression free (and considered "cured") start incurring the general population mortality. The EAG also acknowledges that the company's model does not force patients' survival trajectory to become the same as that of the general population (as long as the model internal calculations provide valid estimates i.e., that the rate of death in the general population curve does not exceed the rate of deaths in the PFS curve). Therefore, the company's model does not try to estimate the survival for "cured" patients differently for that of non-cured patients. Instead, the company's model assumes that there is a fraction of patients in the PFS curve who never progress and never die - the company's modelling approach to PFS assumes a cure fraction in the model that is endogenously estimated via the following formula:

$$PFS(t) = \pi \times \dot{PFS}(\mathrm{t}) + (1 - \pi) \times \widetilde{\mathrm{PFS}}(\mathrm{t})$$

where π represents the "cure" fraction with $\widetilde{\mathrm{PFS}}(\mathrm{t})$ and $\dot{PFS}(\mathrm{t})$ representing the probability of patients being progression-free and alive for non-cured and "cured" patients, respectively. The company then assumed that $\dot{PFS}(\mathrm{t})$ is held constant at 100%, therefore assuming that "cured" patients do not progress or die. This simplifies the formula to:

$$PFS(t) = \pi + (1 - \pi) \times \widetilde{\mathrm{PFS}}(\mathrm{t})$$

The company analysed the PAOLA-1 data in the statistical program R (using the flexsurvcure package) to estimate the $\widetilde{\mathrm{PFS}}(\mathrm{t})$ survival curve and to estimate the proportion of patients cured in the model (π).

Therefore, the company's final PFS curve used in the model is effectively the result of weighting two different PFS curves: one for non-cured patients, $\widetilde{\mathrm{PFS}}(\mathrm{t})$, which was fitted with a log-logistic model; and another for "cured" patients, which is a constant line

throughout time (as patients were assumed to not die or progressed) weighted by the proportion of patients estimated to be "cured" in the model ([redacted]). Figure 1 shows the company's estimated PFS curves for "cured" and non-cured patients, as well as the final weighted PFS curve used in the model. As can be observed, the shape of the weighted PFS curve is entirely informed by non-cured patients, as the PFS curve for "cured" patients is merely a straight line.

Figure 1. Weighted PFS curve used in the model and PFS curves for "cured" and non-cured patients

The CS originally stated that "*when extrapolating beyond PAOLA-1 and the landmark for long-term responders, all-cause mortality using data from the UK (England & Wales) population was used to model the risk of death to reflect the fact that these patients will eventually die from causes other than OC*". However, what this means in the model is that the general population mortality is only applied when the latter exceeds the mortality observed in the PFS or the OS curves.

Therefore, the EAG still considers the company's approach to modelling PFS to be fundamentally flawed as it assumed that "cured" patients never die. The rationale for when this assumption changes and "cured" patients start dying in the model (i.e., when the mortality in the in the general population mortality becomes higher than that in the PFS curve) seems arbitrary. In the model, this happened at [redacted] years, as can be seen in Figure 2, where the PFS curve estimated by the company (grey line, same as in Figure 1) is adjusted by the mortality in the general population survival curve, resulting in the green PFS curve, which is ultimately used in the company's model.

Figure 2. Final PFS curve used in the model adjusted by the general population mortality and weighted PFS curve without the adjustment

Having a weighted PFS curve where it is assumed that [redacted] of olap+bev patients are "cured" and do not progress or die for [redacted] years is likely to lead to an overestimation of the entire PFS curve for olap+bev. This is also true for OS, given that the OS curve crosses the PFS curve at around [redacted] years for olap+bev (Figure 3). From this point onwards, the company's model assumes that mortality for the "cured" and non-cured patients still alive would be dictated by the risk of death in the extrapolated

PFS curve; or by the general population mortality if the latter was higher than the former (which becomes true at year [redacted] in the model). The EAG notes that the shape of the company's base case PFS curve leads to implausible survival predictions of [redacted] of patients being alive at 25 years in the model (when patients would be approximately 87 years old in the company's base case) in the olap+bev arm.

Figure 3. PFS, OS and PFS2 curves used in the company's base case model

[redacted]

Therefore, the EAG preference remains to use a spline model to estimate PFS for both treatment arms of the model. The EAG-preferred spline models do not rely on estimating a cure fraction and importantly, do not rely on assuming that "cured" patients do not die for [redacted] years, as is assumed in the company's base case model. The EAG notes that the spline models estimate a very similar PFS and OS trajectory for bevacizumab patients compared to the company's base case model (bevacizumab arm), however, provide a more conservative estimate for the PFS and OS benefit for olap+bev vs bevacizumab (Figure 4).

Figure 4. EAG-preferred PFS, OS and PFS2 curves

The EAG would also like to note that it disagrees with the assessment that the SOLO-1 data show a plateau in the olaparib arm - the OS data from the SOLO-1 trial are shown in Figure 5 and first and second PFS are shown in Figure 6. This is demonstrated most clearly in the PFS curve which shows that olaparib patients continue to experience events until the end of the 96-month follow-up period, and that olaparib patients are experiencing events at a higher rate than bevacizumab patients from year 3 (even though the absolute number of PFS events is lower in the olaparib arm).

The EAG therefore, maintains its view that there is not sufficient evidence to model a plateau in the olap+bev arm. Both the PAOLA-1 data and the SOLO-1 data[4] show that the rate of progression in the olap+bev arm exceeds that of placebo after year 3 which leaves any potential predicted "cure" time point as uncertain. The EAG acknowledges that it is not implausible that the olap+bev curve could plateau in a similar way to the bevacizumab arm but in absence of data demonstrating when this would happen, the EAG remains of the opinion that the 3-knot spline curves provide a more appropriate modelling approach.

Figure 5. SOLO-1 OS (%) curve

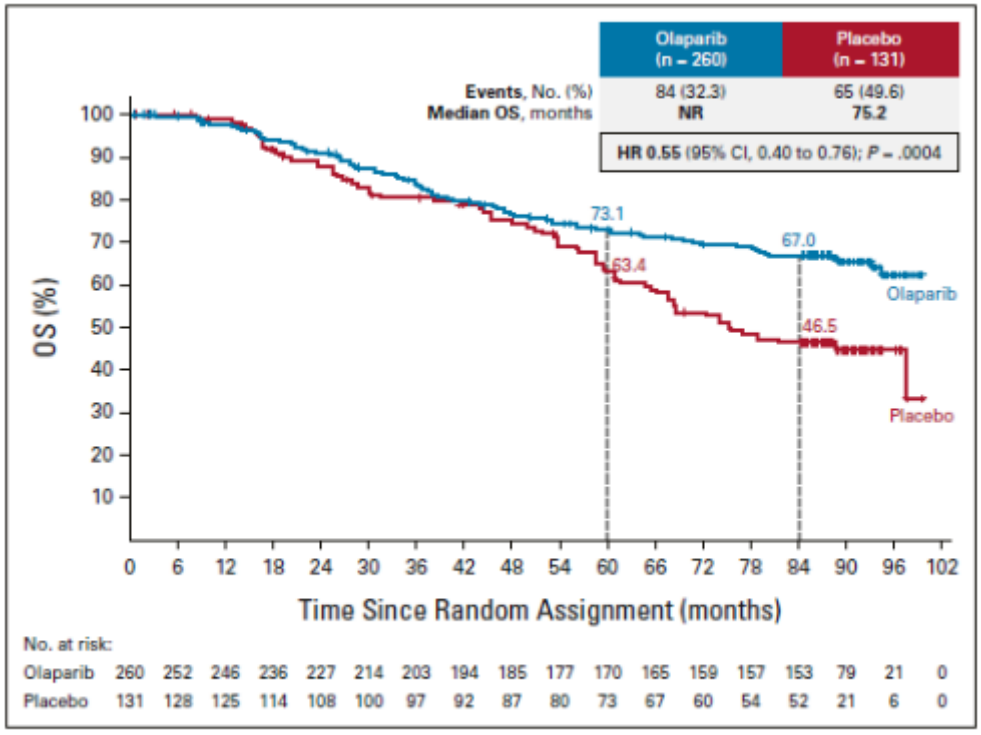

FIG 2. Kaplan-Meier estimates of OS. HR, hazard ratio; NR, not reached; OS, overall survival.

Figure 6. SOLO-1 PFS1 and PFS2 (%) curve

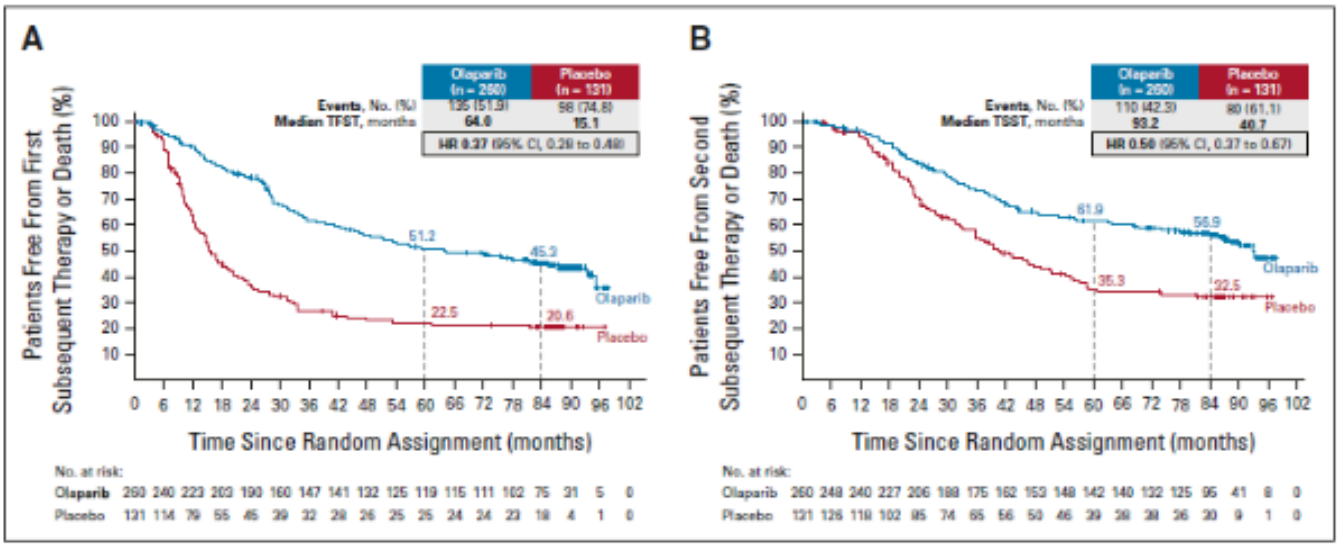

FIG 3. Kaplan-Meier estimates of (A) TFST and (B) TSST. HR, hazard ratio; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death.

2.2 Comment 2. Validation of appropriate survival modelling approach

The company reiterated previous arguments that external sources and clinician expert opinion support modelling a plateau in the survival trajectory for "cured" olap+bev patients. The company also provided additional scenario analysis where the MCM PFS model was combined with different standardised mortality rates (SMRs) to reflect different relative mortality risk in this patient group vs. the general population. The cost effectiveness results of these are presented in section 3.2.

The company reiterated its view that the EAG-preferred spline models do not provide clinically plausible long-term predictions. The company provided landmark tables with their base case, alongside the EAG-preferred splines, and further company's scenario analysis.

EAG comment

The company's scenario analysis using different SMRs are of limited valued, given that these all still rely on the company's assumption that the "cured" faction of patients in the PFS curve do not progress or die at any point in the model, until the rate of progression or deaths in the PFS curve becomes lower than the rate of deaths observed in the general population.

Table 2 and Table 3 report the landmark estimates for OS and PFS, respectively, in the company's and the EAG's models. It should be noted that in the bevacizumab arm the EAG base case spline only differs from the company base case model by, at most, 2.2% and this deviation only occurs at 20 years. This is because the observed plateau in the bevacizumab arm trial data is informing the spline model predictions.

The major difference between the company's and EAG's predictions is the extrapolated part of the olap+bev OS and PFS curves. As the trial-observed olap+bev arm did not show a clear plateau, the best-fitting spline model also does not show a plateau in the extrapolated part of the curve. The EAG reinforces its view that there is not sufficient evidence to model a plateau in the olap+bev arm and that the spline models provide a more conservative estimate for the PFS and OS benefit for olap+bev vs bevacizumab.

Finally, the EAG notes that olap+bev is a relatively novel treatment and has not been available for patients for more than 10 years. Therefore, any statements on the long-term rate of survivors associated with this treatment speculative in nature.

Table 2: Comparison of KM data and long-term extrapolation for OS for company's revised base-case and the EAG's preferred base-case (adapted from Table 5 in company response to ACM)

	Time (years)							
	1	2	3	5	10	20	25	30
Average age of patients (years)†	~59	~60	~61	~63	~68	~78	~83	~88
General population mortality	99.6%	99.2%	98.6%	97.5%	93.6%	78.7%	64.1%	43.4%
Bevacizumab only arm								
KM data PAOLA-1 trial	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
AZ revised base-case (MCM, log-logistic, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's base-case (3-knots spline, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + bevacizumab arm								
KM data PAOLA-1 trial	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
AZ revised base-case (MCM, log-logistic, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's base-case (3-knots spline, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Based on the fact that the average age of patients at initiation of the PAOLA-1 trial was 58.1 years.
Abbreviations: KM: Kaplan-Meier (observed); OS: overall survival

Table 3: Comparison of KM data and long-term extrapolation for PFS for company's revised base-case and the EAG's preferred base-case (adapted from Table 4 in company response to ACM)

	Time (years)							
	1	2	3	5	10	20	25	30
Bevacizumab only arm								
KM data PAOLA-1 trial	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
AZ revised base-case (MCM, log-logistic, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's base-case (3-knots spline, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + bevacizumab arm								
KM data PAOLA-1 trial	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
AZ revised base-case (MCM, log-logistic, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's base-case (3-knots spline, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Based on the fact that the average age of patients at initiation of the PAOLA-1 trial was 58.1 years.
Abbreviations: KM: Kaplan-Meier (observed); OS: overall survival

2.3 Comment 3. Appropriate baseline age in the economic model

The company reiterate their argument that the EAG use of the Systematic Anti-Cancer Therapy (SACT) data to inform baseline age is inappropriate since it represents an inconsistent source of data given that treatment effectiveness in the model is estimated with the PAOLA-1 trial data.

The EAG maintains that the baseline age from the SACT data is a more accurate reflection of the UK's aOC population eligible to receive olap+bev 15 mg/kg. Furthermore, the EAG has not seen any evidence supporting that age is a potential treatment modifier for the relative effectiveness of olap+bev. Therefore, using a younger population in the model (compared to the SACT baseline age which is representative of the UK aOC population) only increases the time period over which olap+bev accrues benefits in the model, thus, biasing the ICER upwards.

2.4 Comment 4. Approach to managing uncertainty

The EAG considers this to be an issue to be resolved by the committee.

2.5 Comment 5. Use of discounted HRD test cost and potential benefits not captured in the economic model

The EAG accepts the use of a discounted HRD test cost in the model. The EAG considers that the potential uncaptured benefits described by the company to be an issue to be resolved by the committee.

3 Company updated results

3.1 Company results

The company only made one change to their original base case submitted at ACM1, presented in Table 3. Full deterministic and probabilistic results from the new company base case are presented in Table 4 and Table 5.

Table 3. Changes to the company's cost-effectiveness model

Model parameter (key issue)	Original company's base case assumption	Company's revised base case assumption post TE	ICER vs bevacizumab	NMB
ACM1 company base-case			**Dominant**	[redacted]
Subsequent treatment: PARPi therapy (key issue 6)	All three PARPis available in the UK in the aOC relapsed setting are included in the economic model, with the following proportions: [redacted] rucaparib, [redacted] niraparib and [redacted] olaparib	100% niraparib The committee aligned with the EAG's approach using niraparib as the only subsequent PARP inhibitor in the base-case analysis	Dominant	[redacted]

Abbreviations: aOC, advanced ovarian cancer; BRCAm, breast cancer gene mutation; EAG, Evidence Assessment Group; EAR, External Assessment Report; HRD, homologous recombination deficiency; ICER, incremental cost effectiveness ratio; IV, intravenous; MCM, mixture cure model; NA, not applicable; NHS, National Health Service; NMB, net monetary benefit; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PFS; progression free survival; SMR, standardised mortality rate; UK, United Kingdom

Table 4. Company's deterministic base case results

Interventions	Total Costs (£)	Total LYG*	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Bevacizumab 7.5mg/kg	[redacted]	[redacted]	[redacted]	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

Table 5. Company's probabilistic base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Bevacizumab 7.5mg/kg	[redacted]	[redacted]	[redacted]				-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

3.2 Scenario analysis

The company provided additional scenarios to address concerns on the clinical plausibility of survival extrapolations with the results shown in Table 6.

Table 6. Results of company scenarios (deterministic)

	Results per patient	Olap+bev	placebo+bev	Inc. value
0	**Company's base case**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			Dominant
	NMB			[redacted]
	NHB			[redacted]
1	**MCM (log-logistic), SMR of 1.4**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			Dominant
	NMB			[redacted]
	NHB			[redacted]
2	**MCM (log-logistic), SMR of 1.6**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			Dominant
	NMB			[redacted]
	NHB			[redacted]
3	**MCM (log-logistic), SMR of 1.8**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			Dominant
	NMB			[redacted]
	NHB			[redacted]
4	**3-knots spline model with a 7-year cure, SMR 1.14**			
	Total costs	[redacted]	[redacted]	[redacted]
	Total QALYs	[redacted]	[redacted]	[redacted]
	ICER			Dominant
	NMB			[redacted]
	NHB			[redacted]

Abbreviations: HRD, homologous recombination deficiency; ICER, incremental cost-effectiveness ratio; LYG, life year gained; NMB, net monetary benefit; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PFS; progression free survival; QALY, quality-adjusted life year; SMR, standardised mortality rate.

4 EAG preferred assumptions

4.1 Deterministic results

The EAG base case now only differs from the company's in the preference for the baseline age used and the method used to estimate PFS (Table 6). Table 8 shows the cumulative impact of each assumption for the EAG base case (deterministic results). In the EAG's base case olap+bev 15mg/kg remains dominant.

Table 7. EAG's preferred assumptions

#	Assumptions	Company approach	EAG approach
1	Baseline age	Baseline age 58	Baseline age 61 years
2	PFS model choice	Cure fraction applied to the PFS curve in both arms	Spline 3 knots for PFS both arms

Abbreviations: EAG, economic assessment group; HRD, homologous recombination deficiency; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MCM, mixture cure model; NHS, national health service; NMB, net monetary benefit; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PFS; progression free survival; QALY, quality-adjusted life year; SMR, standardised mortality rate.

Table 8. EAG's base case (deterministic cumulative impact)

	Results per patient	Intervention	Comparator	Incremental value
0	**Company's corrected base case**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			Dominant
	NMB			[redacted]
	NHB			[redacted]
1	**Baseline age 61 years**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			Dominant
	NMB			[redacted]
	NHB			[redacted]
2	**Spline 3 knots for PFS both arms**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			Dominant
	NMB			[redacted]

	NHB			[redacted]

Abbreviations: Abbreviations: HRD, homologous recombination deficiency; ICER, incremental cost-effectiveness ratio; LYG, life year gained; NMB, net monetary benefit; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PFS; progression free survival; QALY, quality-adjusted life year; SMR, standardised mortality rate.

Table 9. EAG's probabilistic base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Olaparib + bevacizumab 15 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Bevacizumab 7.5mg/kg	[redacted]	[redacted]	[redacted]	-	-		-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

5 References

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