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]

For public –
contains no confidential information

Second committee meeting [ACM2]

Technology appraisal committee A [01 August 2023]

Chair: Radha Todd

Lead team: Mohit Sharma, Ana Duarte, Richard Ballerand

External assessment group: BMJ

Technical team: Emily Leckenby, Zoe Charles, Janet Robertson

Company: AstraZeneca

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ACD: preliminary recommendation

Olaparib with bevacizumab is not recommended, within its marketing authorisation, for maintenance treatment of high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer

Reason the committee made this decision:

- Company's survival modelling using a mixture cure model not justified; concerns regarding the sustained survival benefit observed in the olaparib with bevacizumab arm (DG 3.11)
- EAG survival modelling using 3 knot spline had limitations but more conservative (DG 3.12)

ICER was above acceptable level using EAG's survival modelling and other preferred assumptions on HRD-testing cost and subsequent treatments (DG 3.15)

Consultation responses received from:

- AstraZeneca (company) – **updated base case provided**
- Target Ovarian Cancer (patient/carer group)

Key issues

There are 3 outstanding issues, related to survival modelling and baseline age

Issue	ICER impact
Key issues identified by EAG	
Company's MCM approach to model PFS	Large 
Survival modelling in the model	Large 
Additional issues identified by EAG	
Baseline age in model	Small 

ICER: incremental cost-effectiveness ratio; **MCM**: mixture cure model

RECAP

Decision problem

Intervention	Olaparib in combination with bevacizumab (maintenance treatment)
Population	People with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer: • with complete or partial response after 1L platinum-based chemotherapy plus bevacizumab, and • whose cancer is associated with HRD+ positive status
Comparators	• Bevacizumab maintenance therapy at an 'off-label' dose of 7.5mg/kg (for people that meet the criteria for induction and maintenance treatment with bevacizumab 7.5mg/kg in routine commissioning) • Routine surveillance
Outcomes	• overall survival • progression-free survival • progression-free survival to second progression • time to next line of therapy • adverse effects of treatment • health-related quality of life

- Company did not include routine surveillance as a comparator as uncommon to have no active treatment
- Agreed at ACM1 that routine surveillance not relevant

Olaparib tablets (Lynparza, AstraZeneca)

Marketing authorisation	'Maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency positive status defined by either a BRCA1/2 mutation and/or genomic instability'
Mechanism of action	Poly-ADP-ribose polymerase (PARP) inhibitor which inhibits PARP proteins involved in DNA repair.
Administration	Olaparib tablets are taken orally. Dose: 300 mg (2 x 150-mg tablets) taken twice daily (600 mg per day)
Price	List price for tablets is £2,317.50 per 14-day pack (£4,635 per 28-day cycle) A confidential commercial access agreement is in place for olaparib.

ADP: adenosine-disphosphate

Patient and clinical perspectives

High unmet need for patients with advanced ovarian cancer

Patient perspectives

- Late diagnosis is common and can lead to poor prognosis
- Disease has negative impact on many aspects of life; debilitating treatments affect ability to work or take part in day-to-day life
- Fear of recurrence and further rounds of chemo; accessing PARP inhibitors first line means fewer women will have a recurrence
- Offers targeted treatment for HRD-positive disease - around 50% of people with aOC – who have a poor prognosis and limited treatments

"the latest drugs offer hope and the chance that women with progressive disease can enjoy a better quality of life and longer survival"

Clinical perspectives

- Olap+bev provides clinically meaningful benefits vs current care
- Improvements in OS very challenging so represents a step change
- Adverse effects are frequent but manageable

"very significant improvement in PFS in HRD population, plus significant improvement in OS"

"evidence of absence of benefit in non-HRD population"

NICE **OS:** overall survival; **aOC:** advanced ovarian cancer

Key clinical trial – PAOLA-1

Phase III trial vs placebo, conducted across Europe

Clinical trial design and outcomes

	Trial 1
Design	Phase III randomised, double-blind, placebo-controlled, multicentre study
Population	Adults with advanced (stage III/IV) ovarian cancer in complete or partial response after 1L platinum-taxane chemotherapy with bevacizumab
Intervention	Olaparib 300mg twice daily plus bevacizumab 15mg/kg IV every 3 weeks (47% HRD+)
Comparator(s)	Placebo plus bevacizumab 15mg/kg IV every 3 weeks (49% HRD+)
Duration	Treatment for up to 24 months
Primary outcome	Progression-free survival
Key secondary outcomes	Overall survival, PFS2, TFST, TSST, adverse effects of treatment, HRQoL
Locations	Austria, Belgium, Denmark, Finland, France, Germany, Italy, Japan, Monaco, Spain, Sweden (no UK participants)
Used in model?	Yes

1L: first line; **HRQoL**: health-related quality of life; **IV**: intravenous; **PFS2**: time to second progression or death; **TFST**: time to first subsequent therapy; **TSST**: time to second subsequent therapy

PAOLA-1 results: PFS, DCO3, March 2022

Statistically significant benefit in PFS for olap+bev vs placebo+bev in HRD+ subgroup

Source: Company submission, document B, figure 7

- **Company** reports that Kaplan-Meier curves suggest plateau at ~19% for placebo+bev, and ~46% for olap+bev
- **EAG**: plateau plausible based on observed trial data in the placebo+bev arm but data are not mature enough to confirm existence of plateau in the olap+bev 15 mg/kg arm
- **Question for discussion:** Is there evidence to suggest when a plateau might be observable for the olap+bev 15 mg/kg arm?

NICE **DCO**: data cut off; **HRD**: homologous recombination deficiency; **PFS**: progression-free survival

PAOLA-1 results: Overall survival, DCO3, March 2022

Statistically significant benefit in OS for olap+bev vs placebo+bev in HRD+ subgroup

Company report sustained overall survival benefit for olap+bev over placebo+bev

EAG agreed there was a statistically significant benefit in overall survival for patients treated with olap+bev vs placebo+bev

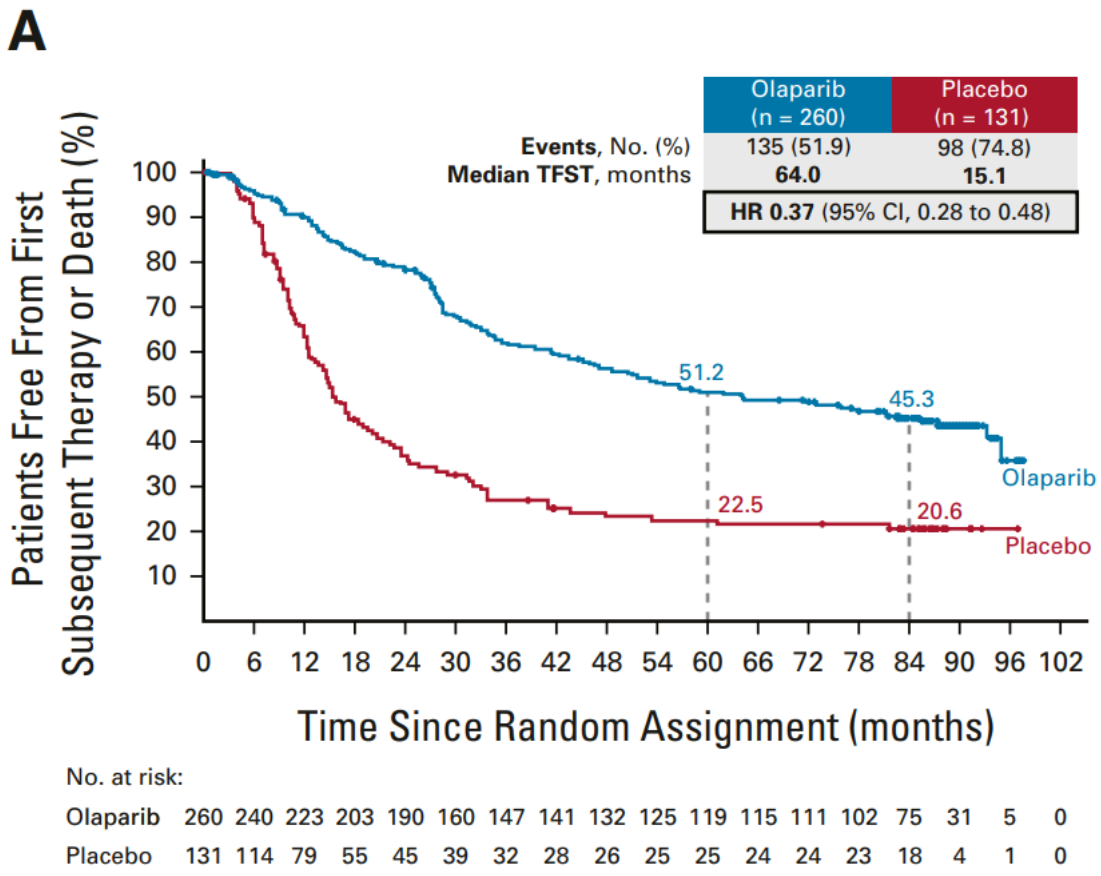
Source: Company submission, document B, figure 8

NICE **DCO**: data cut off; **HRD**: homologous recombination deficiency; **OS**: overall survival

Additional evidence cited by company: SOLO-1

SOLO-1 compares olaparib monotherapy with placebo, 7-years of follow up

SOLO-1 Progression free survival

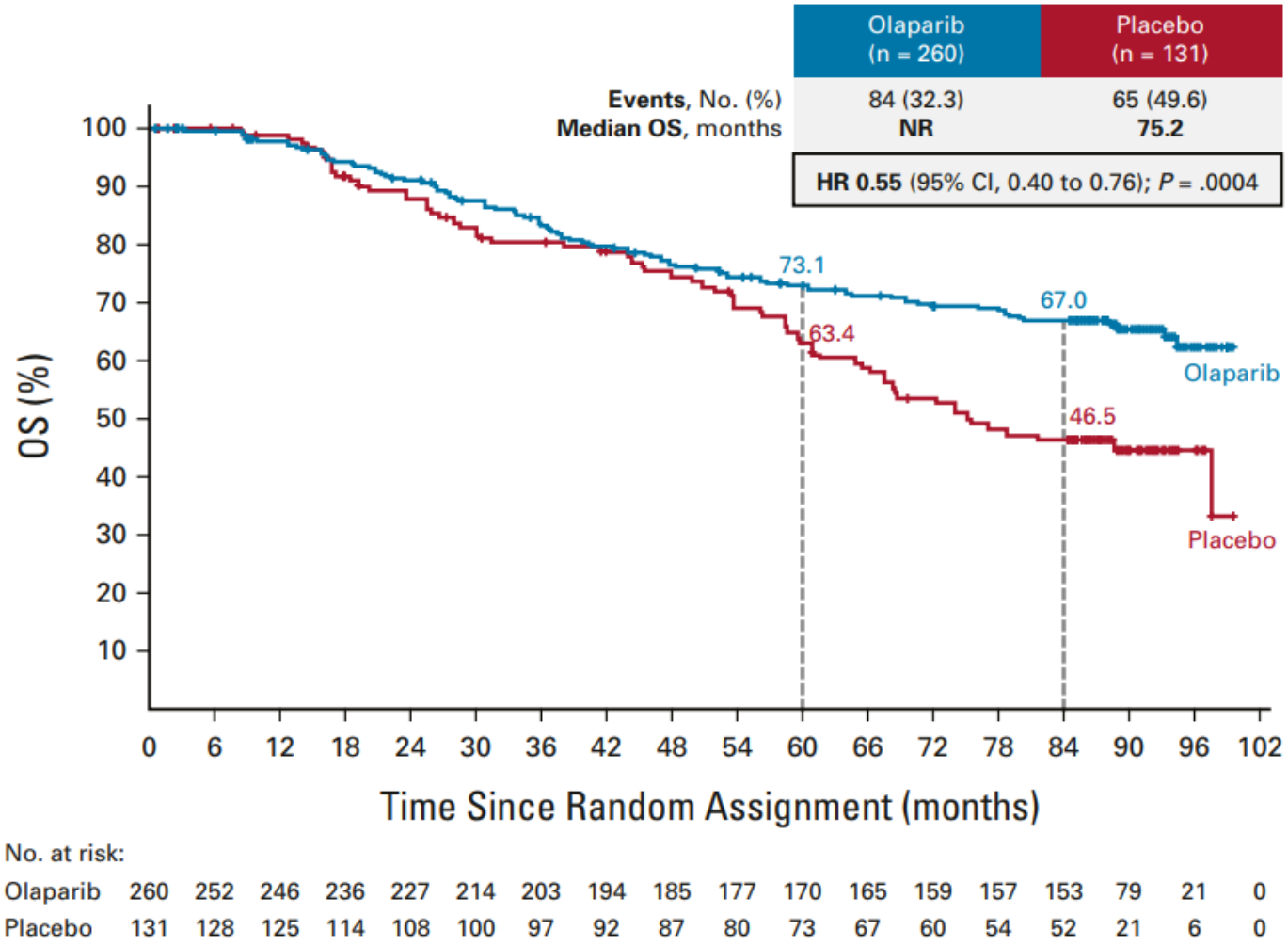


- Company states that SOLO-1 data is compelling evidence for potential for long-term remission in advanced ovarian cancer
- Clinical experts also consider SOLO-1 to be an appropriate source which validates the expectation of curative potential in this treatment setting
- EAG disagrees with assessment that SOLO-1 shows a plateau in olaparib arm – most clearly demonstrated in the PFS curve where:
  - patients continue to experience events until the end of 96-month follow up period
  - patients on olaparib have events at a higher rate than those on bevacizumab from year 3

PFS: progression-free survival

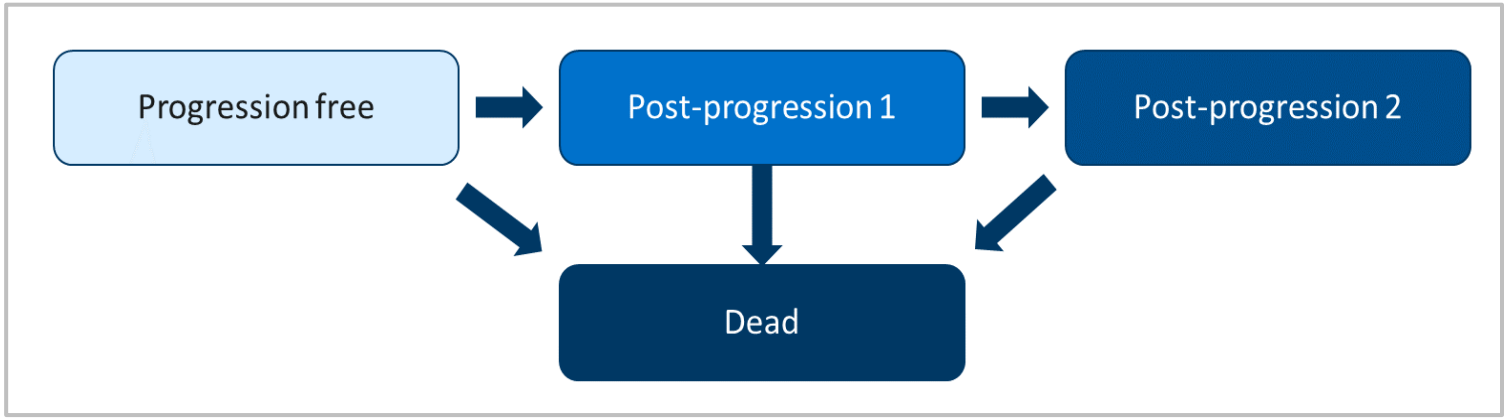
Additional evidence cited by company: SOLO-1

Overall survival: olaparib monotherapy vs. placebo, 7-years of follow up



Company's model overview

Four-state partitioned survival model, same used in TA693



Probability	Calculated using
Alive, free from disease progression	Cumulative PFS curve
Alive, free from second progression	Cumulative PFS2 curve
Having first progression	Difference between cumulative PFS2 and cumulative PFS
Having second progression	Difference between cumulative OS and cumulative PFS2

- Technology modelled to affect QALYs by:
  - Increasing progression free survival
  - Increasing overall survival
  - Increasing adverse event rates
- Technology modelled to affect costs by:
  - Its higher unit cost than current treatments
  - Lower subsequent treatment costs
  - HRD testing costs
  - Lower health-state related resource use costs (monitoring/consultation)
  - Higher continued monitoring costs associated with increased survival
  - Delayed end of life costs from increased survival

Source: EAG report, page 59

HRD: homologous recombination deficiency; **OS**: overall survival; **PFS**: progression-free survival; **PFS2**: time to second progression

Consultation responses

NICE National Institute for Health and Care Excellence

Consultation responses to draft guidance

Comments received from:

- Patient group – Target Ovarian Cancer
- Company - AstraZeneca

Consultation response: Target Ovarian Cancer

Concern about lack of treatment options after 1st line treatment

- No first line maintenance treatments in routine commissioning, can only access after a relapse
- Disease usually returns after first line treatment: at this point treatment is no longer curative and each recurrence and subsequent round of chemotherapy increases the chance of platinum resistance, when very few treatment options remain/prognosis is extremely poor
- Receiving news that cancer has returned can be more devastating than initial diagnosis

Personalised treatment

- Most people who would benefit from personalised treatment will not be able to access it
- Olap+bev is for HRD+ (~50% of people with aOC), whereas olaparib monotherapy is only for BRCA+ (~15% of people with aOC), currently through Cancer Drugs Fund

Quality of life

- Recommendation doesn't reflect the value that olap+bev has on quality of life:
- "returned to work… able to do some gentle exercise… starting a bit more intense activities in the gym"
- "finished bevacizumab June 2023, now on olaparib… CA125 has been between 5-7 for a long time now"

aOC: advanced ovarian cancer

Company response and EAG critique

NICE National Institute for Health and Care Excellence

Company response overview re key issues at ACM1

Key Issue	Committee conclusion	Company draft guidance response
Approach to survival modelling (DG 3.11/3.12)	• Company's modelling of PFS using a MCM was not suitable for decision making • EAG's approach using a 3-knot spline also had limitations but was more conservative	• Maintains use of MCM but included other scenario analyses for consideration by committee
Baseline age in model (DG 3.6)	• Not considered as choice of baseline age had negligible impact on ICER	• Maintains baseline age of 58.1 years from PAOLA-1 HRD+ pop instead of EAG's preference to use age 61.0 from SACT data
HRD+ testing cost (DG 3.4)	• Cost used by the company reflected the cost to be used in clinical practice	• No change – **no further discussion required**
Rucaparib/olaparib as subsequent treatments (DG 3.13)	• EAG's approach using niraparib as the subsequent PARP inhibitor in its base case was appropriate	• Company base case updated to include niraparib as sole subsequent PARP inhibitor – **now aligns with EAG**

Survival modelling: recap on approaches used

Differences in survival modelling have the greatest impact on cost effectiveness

Assumption	Company base case	EAG base case
PFS modelling	MCM, log-logistic	3-knot spline
OS modelling	Standard parametric, lognormal, with general population mortality adjustment for BRCA+ patients in long-term remission. OS curve was set to equal PFS once the 2 curves crossed.	Standard parametric, lognormal, with general population mortality adjustment for BRCA+ patients in long-term remission. OS curve was set to equal PFS once the 2 curves crossed

NICE **MCM**: mixture cure model; **PFS**: progression-free survival

Modelling of PFS: EAG and company curves

EAG: use of MCM unjustified; prefers 3-knot spline

Company: MCM log-logistic

EAG: 3-knot spline

MCM: mixture cure model; **PFS**: progression-free survival

Source: provided by EAG following PMB

Modelling of OS

EAG: OS curves capped by PFS curves; company base case generates implausible survival predictions

Company base case: PFS, PFS2 and OS (MCM-loglogistic, capped PFS2 and OS)

[redacted]

Source: EAG report, figure 14

EAG base case: PFS, PFS2 and OS (3-knot splines, capped PFS2 and OS, general popn mortality adjusted (assumes general popn. mortality for progressed-free population at 20yrs for olap+bev, 15yrs for placebo+bev)

[redacted]

Source: EAG report, figure 16

MCM: mixture cure model; **OS**: overall survival; **PFS**: progression-free survival; **PFS2**: time to second progression

Company consultation response (1)

Company believes there were some omissions and inaccuracies in how key evidence was presented at ACM1, including:

- **Appropriate presentation of evidence at the committee meeting**
  - The rationale for adopting an MCM
  - The workings of the MCM
  - Not all relevant scenario analyses presented e.g., 3-knot spline model with fixed 7-year cure fraction for PFS
  - Slides did not present an impartial view of the key issues
  - Overall, company concerned that committee not given a complete picture of the relevant evidence

- **Manner in which committee meeting discussions are reflected in the draft guidance**
  - Valuable contribution of clinical experts not reflected in guidance
    - Section 3.11 of the DG states the EAG felt "*there was no observable plateau in the olaparib with bevacizumab PFS curve, which would be expected for a curative treatment*"
    - Both clinical experts voiced counter-opinions to the EAG's interpretation of the PFS curves, stating small numbers at risk impact the tail of the curve, and 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
    - Where clinical expert input is cited in the DG, it has been done selectively, omitting important context

Justification for MCM: Company consultation response (2)

- **Company adopted MCM to most accurately reflect compelling body of evidence on potential for long-term remission in aOC, from external empirical data & longer follow up data from PAOLA-1 & SOLO-1**
  - Although true that standard parametric models resulted in clinical implausible extrapolations, this was not the primary reason for adopting the MCM
  - Company selected a modelling approach (aligned with DSU TSD 14) to account for proportion of patients that experience long-term remission in aOC; this is not captured when using standard parametric models
  - MCM is most appropriate approach as it enables reflection of survival trajectory by representing the patient population as a combination of both long- and short-term survivors

- **Company argues that MCM doesn't define the time point at which those who are progression-free become long-term survivors**
  - Rather, the model utilises underlying characteristics of the dataset to estimate proportion of patients who may achieve long-term remission; these "cure fractions" influence the shape of respective survival curves
  - Patients considered 'cured' in the MCM have risk of progression set to zero, but this does not mean they are assumed to be free from experiencing survival events; set equal to gen pop all-cause mortality
  - Estimated cure fractions for bevacizumab only and olap+bev arms are lower than 5-year PFS rates in PAOLA-1 ([redacted] vs 19.2%, and [redacted] vs 46.1%)
  - MCM does not inherently predict a cure or plateauing effect at 5 years but predicts a slow decelerated trend in long-term PFS that is expected in a cohort of aOC patients regardless of 1L maintenance therapy

NICE

aOC: advanced ovarian cancer; **DSU TSD:** Decision Support Unit technical support document; **MCM**: mixture cure model; **PFS**: progression-free survival

Justification for MCM: Company consultation response (3)

- **Company believes EAG's proposal to model any relevant remission point using OS data is inappropriate**
  - Ignores long-term progression-free status of patients and allows progressed patients to achieve long-term remission, despite no evidence to suggest patients with aOC are 'curable' after disease progression
    - leads to contradicting cure fractions and non-convergent long-term extrapolations

EAG comments

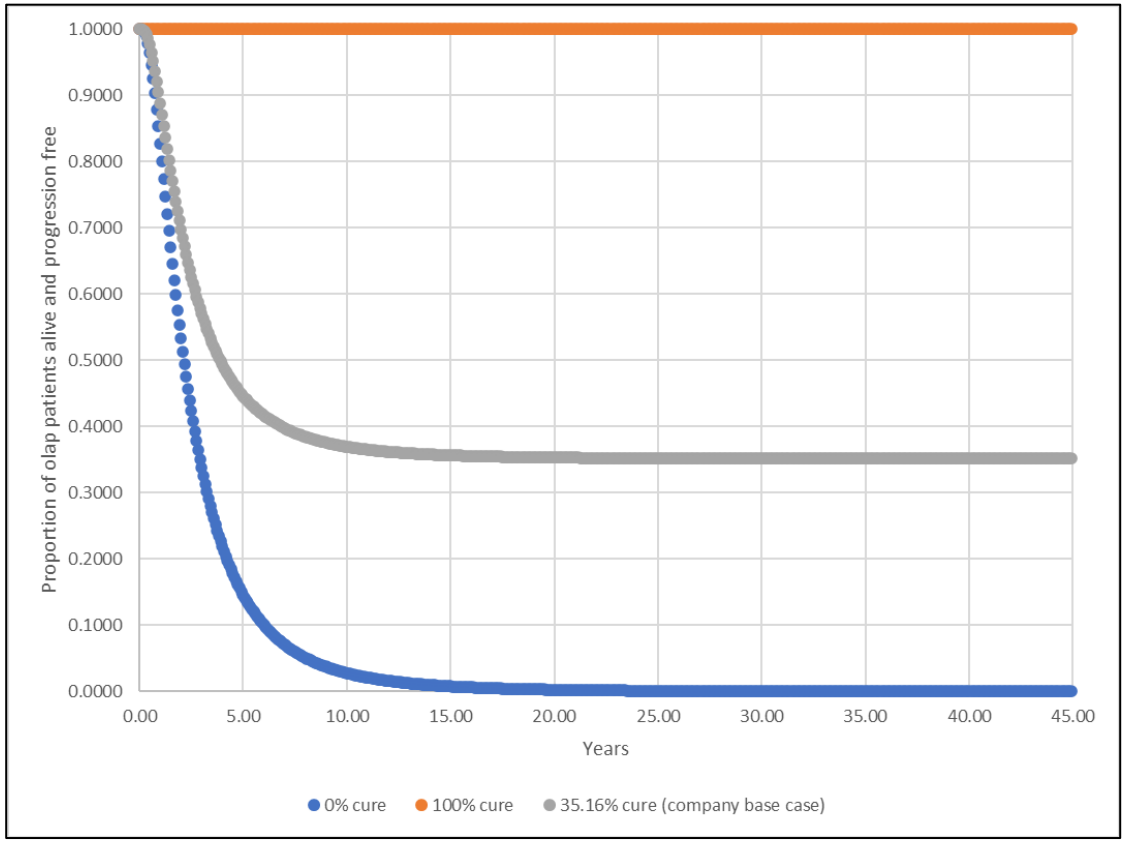
- **Acknowledges confusion around methodological aspects of company's approach to estimating PFS**
  - Modelling approach is described as MCM, but differs from more common approaches to MCMs
  - Usually estimate OS, with goal to depict long-term survivors with risk of death same or close to disease-free
  - Appropriate use of MCM relies on existence of mature survival data with follow up that exceeds anticipated cure time, as well as sufficient number of patients at risk at end of follow up to robustly estimate cure fraction
- **Agrees with company that base-case model does not define time point at which progression-free patients start incurring general population mortality**
  - Also acknowledges that company's model does not force patients' survival trajectory to become same as general population, therefore model does not try to estimate survival for "cured" differently to non-cured
  - Instead, company's model assumes fraction of patients in PFS curve never progress, and only die once general population mortality becomes higher than in the PFS curve
  - Company's final PFS curve is effectively the result of weighting two different PFS curves, one for non-cured patients (fitted with log-logistic model) and one for "cured" patients, which is a constant line through time weighted by proportion of patients estimated to be "cured" in the model ([redacted])
  - Leads to overestimation of PFS and OS ([redacted] alive at 25yrs); EAG maintains spline model as preference

NICE

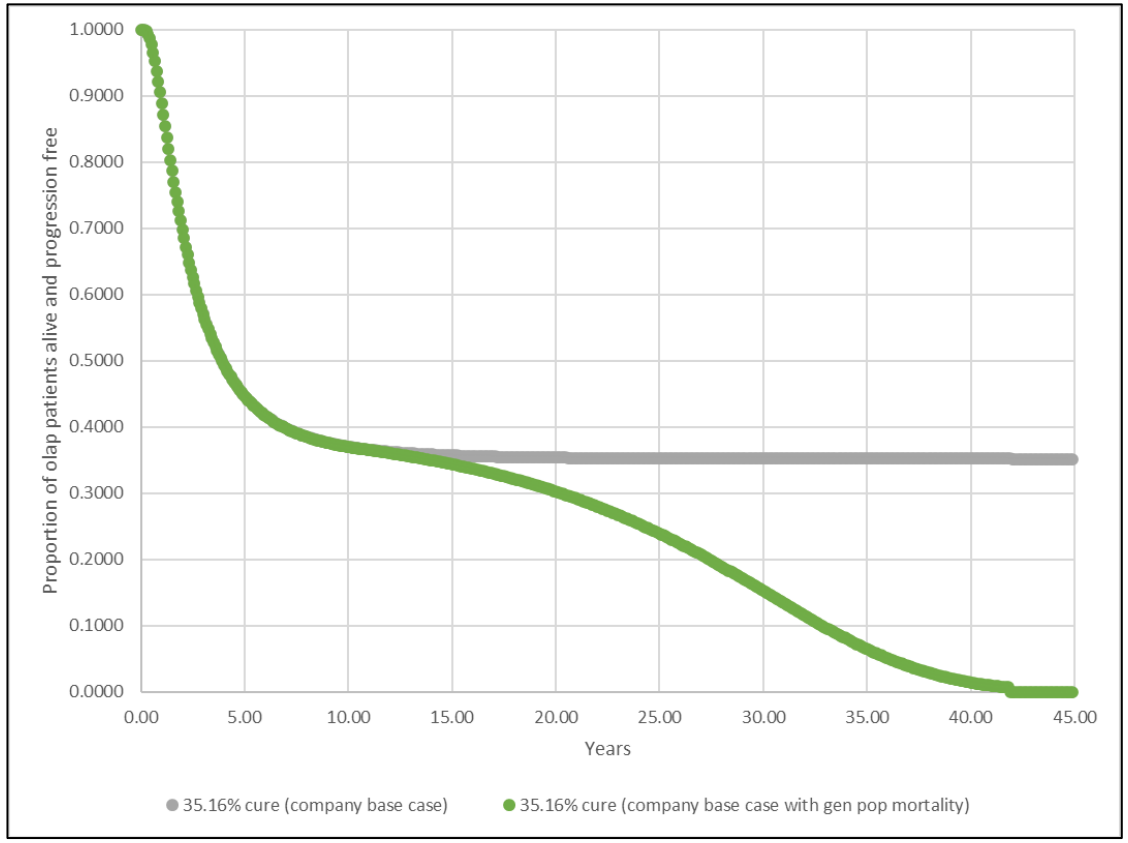
aOC: advanced ovarian cancer; **MCM**: mixture cure model; **OS**: overall survival; **PFS**: progression-free survival

Company's estimated PFS curves presented in EAG's critique

Company's weighted PFS curve used in model and PFS curves for "cured" and non-cured



Company's final PFS curve used in model adjusted by general population mortality multiplied by the SMR, and weighted PFS curve without adjustment



Source: EAG response to company ACD comments, figures 1 and 2

PFS: progression-free survival

Validation of MCM: Company consultation response (4)

- **Company believes there is ample evidence to support concept of long-term remission in aOC**
  - Clinical experts referenced both PAOLA-1 and SOLO-1 to confirm that potential for long-term remission or 'cure' is well-established in aOC
  - When reviewing extrapolated survival curves, they commented that it is illogical to accept a plateauing effect for PFS in patients receiving bevacizumab only, but not for olap+bev
  - Clinical experts felt MCM generated more realistic and clinically plausible long-term PFS estimates, that OS rates were generally aligned with clinical expectations and EAG's model too pessimistic
  - Company argues EAG's model has no valid grounds for adoption: fails to capture potential for long term remission, generates pessimistic survival estimates and doesn't reflect plateauing effect

EAG comments

- In bevacizumab arm, EAG base-case only differs from company base-case by, at most, 2.2% and only at 20 years; observed plateau in bevacizumab arm trial data is informing spline model predictions
- Major difference between company and EAG predictions is in extrapolated part of olap+bev OS and PFS curves; as trial observed olap+bev arm did not show clear plateau, best fitting spline model also does not show a plateau
- EAG reinforces its view that there is not sufficient evidence to model a plateau in olap+bev arm
- Also note that olap+bev is a relatively novel treatment, not been available >10 years, therefore any statements on long-term rate of survivors associated with it remain speculative in nature

aOC: advanced ovarian cancer; **MCM**: mixture cure model; **OS:** overall survival; **PFS**: progression-free survival

Scenario analyses: Company consultation response (5)

- Company maintain MCM approach is most appropriate, but provide additional scenario analyses to address concerns around survival extrapolations:
  - **3 scenarios where standardised mortality rate is altered to reflect different relative mortality risk**
    - Base-case SMR is 1.14, scenarios change this to 1.4, 1.6 and 1.8
    - all model a [redacted] survival rate for olap+bev arm at 25 and 30 years respectively - confirmed by clinical experts to be aligned with their survival expectations
  - **Company also highlighted previous scenario adopting 3-knot spline model but incorporating long-term remission potential by implementing a crude 7-year 'cure' assumption**
    - generates PFS rates of [redacted] at 20 years for olap+bev arm

aOC: advanced ovarian cancer; **MCM**: mixture cure model; **OS:** overall survival; **PFS**: progression-free survival

Comparison of KM data and long-term extrapolation for PFS

	Time (years)					
	1	2	3	5	10	20
Bevacizumab only arm						
KM data PAOLA-1 trial	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Company base-case (MCM, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's base-case (3-knot spline, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + bevacizumab arm						
KM data PAOLA-1 trial	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Company base-case (MCM, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's base-case (3-knot spline, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: MCM, SMR: 1.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: MCM, SMR: 1.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: MCM, SMR: 1.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: 3 knot-spline, 7-year cure, SMR: 1.14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: company response to consultation, table 4

MCM: mixture cure model; **PFS**: progression-free survival

Comparison of KM data and long-term extrapolation for OS

	Time (years)					
	1	2	3	5	10	20
Average age of patients	~59	~60	~61	~63	~68	~78
General population mortality	**99.6%**	**99.2%**	**98.6%**	**97.5%**	**93.6%**	**78.7%**
Bevacizumab only arm						
KM data PAOLA-1 trial	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Company base-case (MCM, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's base-case (3-knot spline SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + bevacizumab arm						
KM data PAOLA-1 trial	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Company base-case (MCM, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's base-case (3-knot spline, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: MCM, SMR: 1.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: MCM, SMR: 1.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: MCM, SMR: 1.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: 3-knot, 7-year cure, SMR: 1.14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: company response to consultation, table 5

MCM: mixture cure model; **PFS**: progression-free survival

Comparison of KM data and long-term extrapolation for PFS

	Time (years)							
	1	2	3	5	10	20	25	30
Bevacizumab only arm								
KM data PAOLA-1 trial	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Company base-case (MCM, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's base-case (3KS, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + bevacizumab arm								
KM data PAOLA-1 trial	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Company base-case (MCM, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's base-case (3KS, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: MCM, SMR: 1.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: MCM, SMR: 1.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: MCM, SMR: 1.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: 3KS, 7-year cure, SMR: 1.14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: company response to consultation, table 4

3KS: 3-knot spline; **LL:** log-logistic**; MCM**: mixture cure model; **PFS**: progression-free survival

Comparison of KM data and long-term extrapolation for OS

	Time (years)							
	1	2	3	5	10	20	25	30
Average age of patients	~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]	-	-	-	-
Company base-case (MCM,SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's base-case (3KS, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib + bevacizumab arm								
KM data PAOLA-1 trial	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Company base-case (MCM, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's base-case (3KS, SMR 1.14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: MCM, SMR: 1.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: MCM, SMR: 1.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: MCM, SMR: 1.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: 3KS, 7-year cure, SMR: 1.14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE

LL: log-logistic; **MCM**: mixture cure model; **PFS**: progression-free survival

Scenario analyses: EAG comments

EAG comments

- Scenario analyses using different SMRs are of limited value, all rely on assumption that "cured" fraction of patients in PFS curve do not progress or die at any point in the model, until rate of progression/deaths in PFS curve become lower than rate of deaths observed in general population multiplied by the SMR

Which approach to modelling survival is appropriate?

MCM: mixture cure model; **PFS**: progression-free survival

Baseline age in model: company consultation response

- **Company argues EAG's preferred assumption of adopting baseline age from SACT is inappropriate**
  - Baseline characteristics adopted in model should retain consistency with most relevant source of evidence, i.e., the PAOLA-1 trial, on which other key parameters are based (e.g., efficacy, treatment duration, utilities)
  - Recognise that age does not have a meaningful impact on 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, 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 analysis provided

EAG comments

- EAG maintains that baseline age from SACT is more accurate reflection of UK's eligible aOC population
- EAG has not seen any evidence supporting that age is a potential treatment modifier for relative effectiveness of olap+bev
- Therefore, using a younger population in model (compared to SACT) only increases time period over which olap+bev accrues benefits in the model, biasing the ICER downwards

Which baseline age is appropriate?

HRD: homologous recombination deficiency; **SACT:** Systemic Anti-Cancer Therapy dataset

Uncaptured benefits: company consultation response

Company raised uncaptured benefits as part of consultation response

HRD testing cost

- 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 model
    - Furthermore, the wider benefits of HRD testing in aOC are not captured in the 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.

Impact on families and carers

- 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 - not captured in the model

aOC: advanced ovarian cancer; **BRCA:** Breast Cancer gene; **HRD:** homologous recombination deficiency

Managing uncertainty: company consultation response (1)

Company raised methods for managing uncertainty as part of consultation response

- **DG concludes that due to "multiple uncertainties within the clinical and economic evidence, especially relating to the survival modelling approach" … an acceptable incremental cost effectiveness ratio (ICER) would need to be "comfortably below £30,000 per QALY gained"**
    - Company acknowledge that a reduction in ICER threshold is one approach that can be used to acknowledge decision uncertainty when making a recommendation
    - However, when considering the most significant unresolved uncertainty (survival modelling), the committee have already incorporated the EAG's approach into their preferred assumptions, which clinicians felt was "too pessimistic" and the committee acknowledged to be conservative
    - Inappropriate to lower the ICER threshold as well as select the most conservative set of assumptions - can be considered "double counting"
    - This is reflected in Section 6.2.33 of the NICE manual 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 clinical expert input on the survival modelling approach, company do not believe DG reflects a true consideration of the most plausible ICER – management of uncertainty is unduly conservative

DG: draft guidance

Managing uncertainty: company consultation response (2)

Company raised methods for managing uncertainty as part of consultation response

- Section 6.2.35 of the NICE manual also states that *"uncertainty will be considered proportionately for the evaluation context (including, for example, the type of technology, evaluation, or population)"*
  - 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", 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 from 16.3% (DCO: 22nd March 2019) to 41.9% (DCO: 22nd March 2022), resolving much of the uncertainty about long term clinical outcomes

Company therefore believes 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

aOC: advanced ovarian cancer; **DCO:** data cut off; **OS:** overall survival

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

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