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]

Technology appraisal committee A [06 June 2023]

For public –
contains no confidential information

Chair: Radha Todd

Lead team: Mohit Sharma, Ana Duarte, Richard Ballarand

External assessment group: BMJ

Technical team: Emily Leckenby, Zoe Charles, Janet Robertson

Company: AstraZeneca

Appraisal recap

Additional trial data collected since CDF entry will inform committee decision

April 2021 CDF-entry

- Olaparib+bevacizumab recommended for use within the CDF (maintenance therapy following response to 1L chemo with bevacizumab) when cancer is associated with homologous recombination deficiency (HRD)
- OS end point in PAOLA-1. Uncertain estimates due to data immaturity (DCO1, March 2019)
- Committee agreed that OS data *'promising but survival benefit remains uncertain' (FAD 3.8)*
- Unclear if olap+bev is 'curative', insufficient data to show whether treatment can maintain remission up to 5 years

~2 years

June 2023 CDF-review

- OS data from PAOLA-1 now more mature (final cut off - DCO3: March 2022, data maturity: OS: [redacted]; PFS data maturity: [redacted]; time to second progression or death: [redacted]).
- 61.7 month follow-up; median PFS and OS both reported
- Committee to consider whether olaparib is cost-effective in 1L population based on mature PAOLA-1 data

1L: first-line; **CDF**: Cancer Drugs Fund; **DCO**: data cut off; **OS**: overall survival; **PFS**: progression-free survival

Key issues

There are 6 outstanding key issues, survival modelling has large impact on ICER

Issue	Resolved?	ICER impact
Key issues identified by the EAG		
Use of bevacizumab 15mg/kg as a comparator	Yes	-
Subsequent use of PARPi in the key trial PAOLA-1 not reflective of UK practice	No	Unknown
Company's MCM approach to model PFS is inappropriate	No	Large
Survival overestimated in the model	Partly	Large
HRD+ testing cost in the model is lower than that used in the UK/NHS	No	Small
Additional issues identified by the EAG		
Inclusion of rucaparib/olaparib as subsequent treatment in the model	Partly	Unknown
ITT population used to inform baseline patient characteristics	Partly	Small
Use of NHS reference costs 2020/2021	Yes	-
Bevacizumab price	Yes	-

NICE

HRD: homologous recombination deficiency; **ICER**: incremental cost-effectiveness ratio; **ITT**: intention to treat; **MCM**: mixture cure model; **PARPi**: poly-adenosine-disphosphate [ADP] ribose polymerase inhibitor

Background on ovarian cancer

Late diagnosis is common and can lead to poor prognosis

Epidemiology

- 6,300 new ovarian cancer cases in England every year
- Most cases are in people aged 65 years+

Diagnosis and classification

- Most common location is the ovary itself (92%), but may be in fallopian tubes or peritoneum
- Classified from stage 1-4, depending on how far it has spread. Majority diagnosed late (stage 3 or 4)
- Also grouped by the type of cell affected and graded depending on how abnormal the cells are
- High-grade serous carcinoma is the most common type of ovarian cancer

Symptoms and prognosis

- Symptoms include pelvic/abdominal pain, bloating, feeling full quickly and urinary frequency/urgency
- High rates of recurrence following initial treatment – risk increases with stage
- 5-year survival for ovarian cancer in England is 42.6%; → below the European average

Olaparib tablets (Lynparza, AstraZeneca)

Marketing authorisation	Indicated for '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. Inhibiting the PARP pathway allows DNA damage to accumulate and limits the options for DNA repair, ultimately resulting in tumour cell death
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 commercial access agreement is in place for olaparib. This arrangement is confidential and will be discussed in part 2 of the meeting.

ADP: adenosine-disphosphate

Decision problem

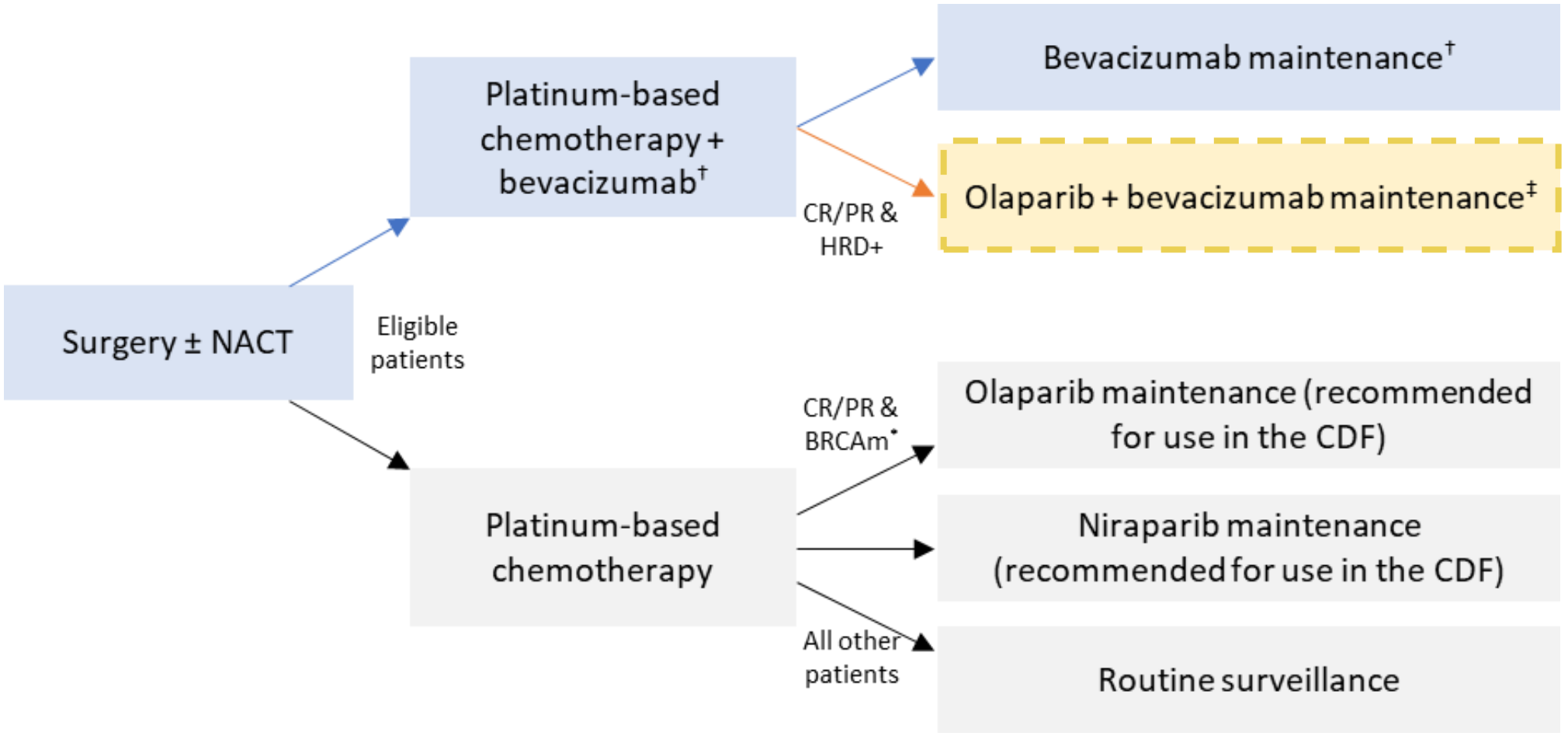
Only appraising 1L maintenance therapy for HRD+ disease in this CDF exit review

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 decision problem deviates from scope by not including routine surveillance as a comparator
- Medical oncologists state increasingly uncommon to have no active treatment in this setting
- EAG's clinical experts agree routine surveillance is not relevant

1L: first-line; **CDF**: Cancer Drugs Fund; **HRD**: homologous recombination deficiency

Treatment pathway: HRD+ Ovarian Cancer



Following disease recurrence, subsequent treatments include:

- Platinum chemotherapy
- Non-platinum cytotoxic drugs
- Targeted therapies (anti-angiogenics, and PARPis)

† For maintenance, bevacizumab monotherapy is only available at 7.5 mg/kg (15 mg/kg dose [as per MA] is not recommended);
‡Bevacizumab 15 mg/kg dose when used with olaparib

NICE

CDF: Cancer Drugs Fund; **CR:** complete response; **HRD:** homologous recombination deficiency; **NACT:** neoadjuvant chemotherapy; **PR:** partial response

Patient perspectives

Current treatments are limited; offers reduced chance of recurrence of disease

Submissions from Target Ovarian Cancer

- Ovarian cancer diagnosis can have negative impact on many aspects of life; debilitating treatments render individuals unable to work or take part in regular day-to-day life
- Many women fear recurrence and feel that there are few options for ovarian cancer; accessing PARP inhibitors first line means more women will not have a recurrence
- Potential availability of olaparib + bevacizumab for those who are HRD+ means expanding access to around 50% of all those with ovarian cancer
- Offers a targeted treatment to those with poor prognosis and limited treatment options
- Increased time between disease progressions means women have a better quality of life with longer intervals without chemotherapy

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

"easy to take, side effects not as bad as chemotherapy

"an amazing drug, but side effects included aching bones, headaches"

Clinical perspectives

Unmet need for patients with advanced ovarian, fallopian tube and peritoneal cancer

- Olaparib + bevacizumab provides clinically meaningful benefits to people with advanced ovarian cancer compared with current care
- Innovative treatment: improvements in overall survival in ovarian cancer are very challenging so represents a step change
- Adverse effects are frequent but manageable; centres have experience of managing bevacizumab and PARP inhibitor toxicity
- PAOLA-1 first trial to show HRD testing could identify a population of patients who do NOT benefit from addition of PARP inhibitor as maintenance therapy
- HRD testing now routine in most large centres, and whole genome sequencing available for all patients via NHS England

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

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

"patients enrolling in clinical trials tend to be younger and of better performance status… but real world experience is that technology is acceptable and well tolerated"

Equality considerations

None highlighted by company or EAG

- **Company**: Olaparib with bevacizumab is not likely to raise any equality or equity issues
- **EAG**: no equality issues raised
- **Clinical expert:**
  - Sample of tumour sent for HRD testing – patients being treated at centres where this is not routinely undertaken will be disadvantaged
  - No age restrictions in PAOLA-1 trial – the age of participants ranged from 26 to 87
  - Recommendations will have no differential impact according to a patient's race
  - Recommendations will not affect any protected characteristic other than sex
  - Recommendations will not have an adverse impact on disabled people
- **Patient experts:**
  - May impact people with learning disabilities, people who have English as a second language or who have low levels of literacy; can struggle to access treatments if they don't fully understand treatment options and choices
  - Limited access to centres that routinely carry out HRD testing may disadvantage patients

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trial – PAOLA-1

Phase III trial vs placebo, conducted across Europe, no UK participants

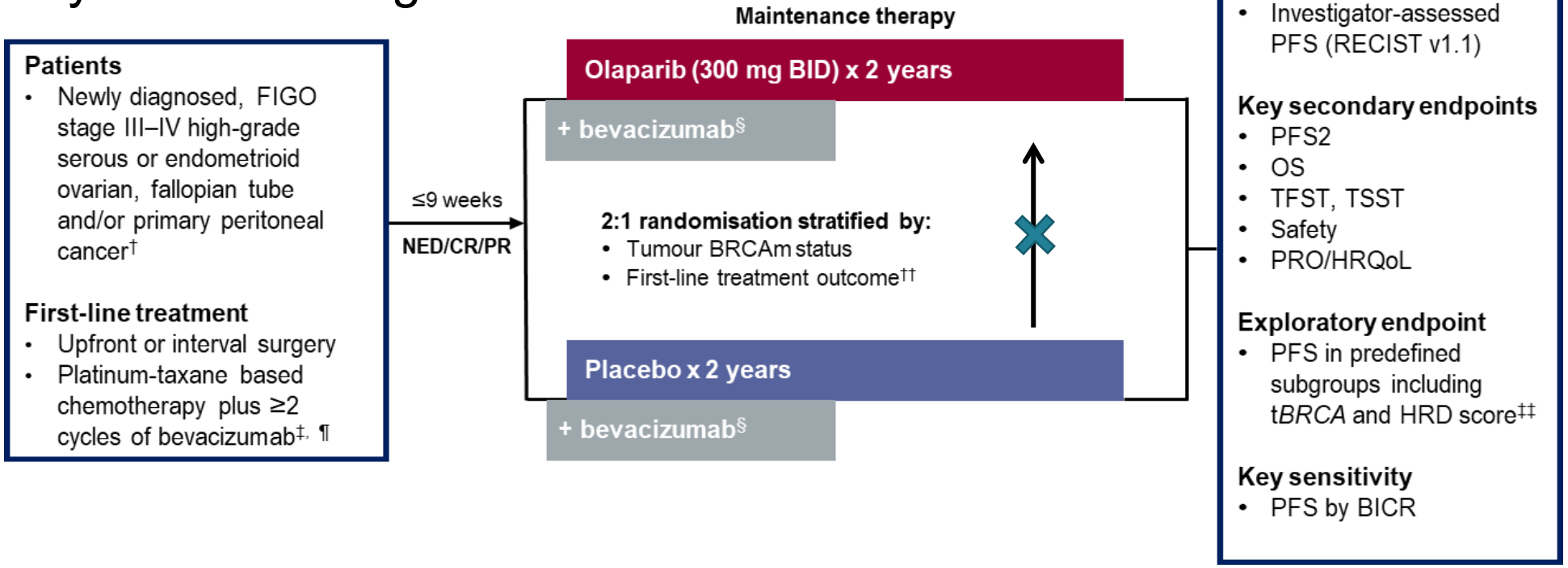
Clinical trial design and outcomes

	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 study design

Possibility of re-challenge



Source: Company submission, document B, figure 5

- Crossover to olaparib not permitted; however after discontinuation of intervention, patients could receive other treatments (including PARPi) at the investigators' discretion
- Subsequent treatments included platinum chemotherapy, non-platinum cytotoxic drugs, and targeted therapies such an anti-angiogenics and PARPi

NICE

BICR: blinded independent central review; **BID**: twice daily; **CR**: complete response; **FIGO**: International Federation of Gynaecology and Obstetrics; **HRD**: homologous recombination deficiency; **HRQoL**: health-related quality of life; **OS**: overall survival; **NED**: no evidence of disease; **PARP**: poly-ADP ribose polymerase; **PFS**: progression-free survival; **PFS2**: time to second progression; **PR**: partial response; **PRO**: patient reported outcome; **TFST**: time to first subsequent therapy; **TSST**: time to second subsequent therapy

Key issue: Subsequent use of PARPi in PAOLA-1

Subsequent use of PARPi in PAOLA-1 not reflective of UK practice

Background

- Retreatment with PARPis not recommended but occurred in [redacted] of olap+bev arm and [redacted] of placebo+bev arm; unclear impact on survival
- EAG requested analysis splitting patients into those who had re-challenge vs those who did not
- EAG provided scenario where subsequent treatments in trial were costed in model

Company

- Negligible impact on efficacy and cost effectiveness; retreatment only occurred in small proportion of patients
- Exploratory analysis conducted into effect on OS: data censored at PARPi initiation compared to unadjusted OS data; [redacted]
- Analysis requested by EAG not approp as would break randomisation, introducing more bias/uncertainty
- EAG's scenario analysis not relevant as doesn't reflect clinical practice

EAG: remains unclear if retreatment with PARPi had an impact on PAOLA-1 clinical effectiveness results

Other considerations

- Clinical expert: OreO study showed stat. sig. improvement in PFS for olaparib vs placebo after prior PARPi maintenance, but retreatment with PARPis is not recommended in UK practice

What conclusions can be drawn about the likely impact of retreatment on the effectiveness results?

ICER: incremental cost-effectiveness ratio; OS: overall survival; PARP[i]: poly-ADP ribose polymerase [inhibitor]

Rucaparib and olaparib as subsequent treatments

Recommended in relapsed setting via CDF but used commonly in NHS

Background

- Company model includes rucaparib as most common subsequent PARPi ([redacted] R:N:O)
- Removed by EAG from model on NICE's advice
- Only niraparib is available through routine commissioning after 2L chemo, olaparib after 3L
- 6.4.10 of NICE manual: a recommendation with managed access is not considered established practice
- Inclusion at discretion of NICE AD; based on timing of exit and extent to which medicine is considered SoC

Company

- NICE no longer excludes CDF medicines as subsequent treatments; appropriate to include to reflect SoC
- Rucaparib has [redacted] market share of PARPis based on NHSE real-world data (new patient starts in relapsed setting (across all lines) Oct 2021 to Sept 2022; [redacted] rucaparib.
- If rucaparib is excluded, then olaparib should be excluded on same basis

EAG

- Requested confirmation from NICE; decision to exclude both rucaparib and olaparib from base case
- Niraparib to be used as subsequent PARPi
- Provided scenario analysis using updated olaparib price following CDF-exit

CDF: Cancer Drugs Fund; **PARP**: poly-ADP ribose polymerase; **SoC**: standard of care

Key issue: PAOLA-1 baseline characteristics

Company age from HRD+ population, other characteristics from ITT data

Baseline characteristics used in model

Parameter	Company	EAG
Age	58.1 (HRD+)	61 (SACT)
Weight	[redacted]	
Height	[redacted]	
Body surface area	[redacted]	
Serum creatinine	[redacted]	
GFR	[redacted]	

Source: EAG report, table 25

Company

- HRD+ values unavailable for weight/height/serum creatinine
- Changing these parameters: negligible impact on ICER
  - EAG agrees
- SACT age inappropriate; doesn't reflect trial: baseline characteristics should reflect source of evidence on which efficacy, costs and utilities are based

EAG comments

- Baseline age in SACT is more representative of the UK aOC pop

Is the baseline age from the HRD+ population of PAOLA-1 or from SACT more appropriate?

aOC: advanced ovarian cancer; **HRD**: homologous recombination deficiency; **GFR**: glomerular filtration rate; **ICER**: incremental cost-effectiveness ratio; **ITT**: intention to treat; **SACT**: systematic anti-cancer therapy

PAOLA-1 results: Progression-free survival, DCO3 vs DCO1

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

DCO3, HRD+ subgroup, March 2022

	Olap+bev 15mg/kg (n=255)	Placebo+bev 15mg/kg (n=132)
Progression free survival, HR	[redacted] (95% CI: [redacted], p value not reported)	
Median duration of PFS	[redacted] months (95% CI: [redacted])	[redacted] months (95% CI: [redacted])
Number of PFS events	[redacted] PFS events ([redacted]% data maturity)	

Source: Company submission, document B, page 51

DCO1, HRD+ subgroup, March 2019

	Olap+bev 15mg/kg (n=255)	Placebo+bev 15mg/kg (n=132)
Progression free survival, HR	0.33 (95% CI: 0.25, 0.45)	
Median duration of PFS	37.2 months (36.0, NR)	17.7 months (15.8, 19.9)
Number of PFS events	179/387 PFS events (46% data maturity)	

Source: TA693 Company submission, document B, table 7

NICE **CI**: confidence interval; **DCO**: data cut off; **HR**: hazard ratio; **HRD**: homologous recombination deficiency; **NR**: not reported; **PFS**: progression-free survival

PAOLA-1 results: Progression-free survival, DCO3, March 2022

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

- 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 the existence of a plateau in the olap+bev 15 mg/kg arm

Source: Company submission, document B, figure 7

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

PAOLA-1 results: Overall survival, DCO3 vs DCO1

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

DCO3, HRD+ subgroup, March 2022

	Olap+bev 15mg/kg (n=255)	Placebo+bev 15mg/kg (n=132)
Overall survival, HR	[redacted] (95% CI: [redacted])	
Median overall survival	[redacted] months (95% CI: [redacted])	[redacted] months (95% CI: [redacted])
% alive after 5 years	[redacted]%	[redacted]%
Number of OS events	[redacted] PFS events ([redacted]% data maturity)	

Source: Company submission, document B, page 52

DCO1, HRD+ subgroup, March 2019

	Olap+bev 15mg/kg (n=255)	Placebo+bev 15mg/kg (n=132)
Overall survival, HR	[redacted] (95% CI: [redacted])	
Median overall survival	[redacted] ([redacted])	[redacted] ([redacted])
% alive after 5 years	-	-
Number of OS events	[redacted] ([redacted]% data maturity)	

Source: TA693 Company submission, document B, table 7

NICE **CI**: confidence interval; **DCO**: data cut off; **HR**: hazard ratio; **HRD**: homologous recombination deficiency; **NR**: not reported: **OS**: overall 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

PAOLA-1 results: Time to second progression or death, DCO3 vs DCO1

PFS2 is informed by PFS; hazard ratio for PFS2 at DCO3 not reported

DCO3, HRD+ subgroup, March 2022

	Olap+bev 15mg/kg (n=255)	Placebo+bev 15mg/kg (n=132)
PFS2, HR	Not reported	
Median time to PFS2	[redacted] months (95% CI: [redacted])	[redacted] months (95% CI: [redacted])
% patients with 2nd progression	[redacted]%	[redacted]%
Number of PFS2 events	[redacted] PFS events ([redacted]% data maturity)	

Source: Company submission, document B, page 53

DCO1, HRD+ subgroup, March 2019

	Olap+bev 15mg/kg (n=255)	Placebo+bev 15mg/kg (n=132)
PFS2, HR	[redacted] (95% CI: [redacted])	
Median time to PFS2	[redacted] ([redacted])	[redacted] months ([redacted])
% patients with 2nd progression	-	-
Number of PFS2 events	[redacted] ([redacted]% data maturity)	

Source: TA693 Company submission, document B, table 7

NICE **CI**: confidence interval; **DCO**: data cut off; **HR**: hazard ratio; **HRD**: homologous recombination deficiency; **NR**: not reported; **PFS**: progression-free survival; **PFS2**: time to second progression

PAOLA-1 results: Time to second progression or death DCO3, March 2022

PFS2 events based on radiological, CA-125, symptomatic progression, or death

Source: EAG

- Company reports that Kaplan-Meier curves demonstrate PFS benefit delays time to second progression or death (PFS2)
- EAG notes that out of patients with 1st progression, [redacted]% of olap+bev and [redacted]% of placebo+bev had second progression
- Olap+bev unlikely to provide benefit in preventing second progression in those who have already progressed

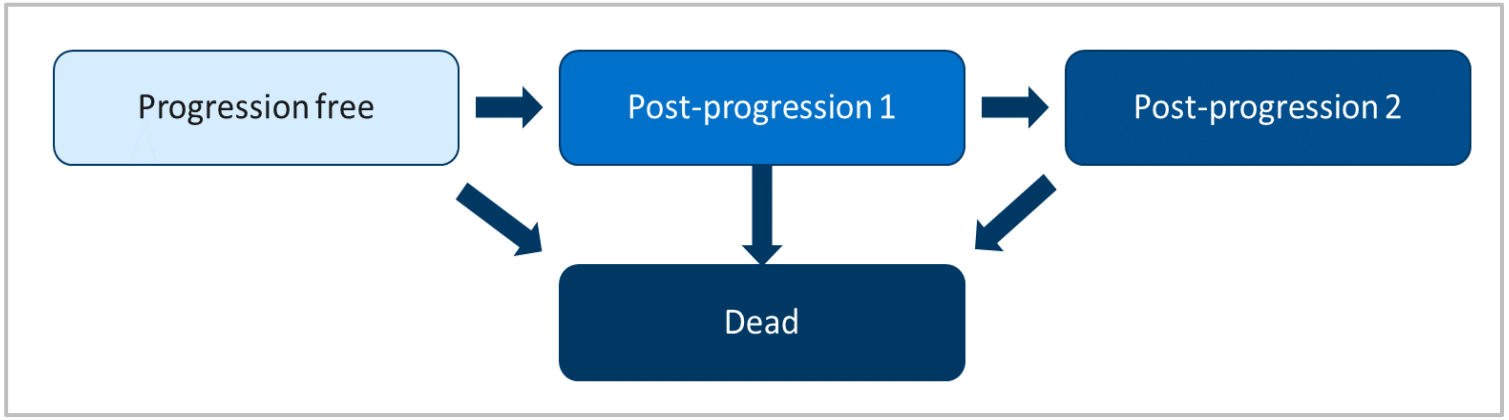
DCO: data cut off; **HRD**: homologous recombination deficiency; **PFS**: progression-free survival; **PFS2**: time to second progression or death

Cost effectiveness

NICE National Institute for Health and Care Excellence

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

NICE

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

Survival curves; progression-free survival

Company chose to fit MCM to PAOLA-1 PFS data; MCM-log-logistic best fit

- **Company:** all standard parametric fitted curves underpredict long-term PFS on SoC
- At 7 and 10 year time-points, all fitted models predict <[redacted] and [redacted] of placebo+bev arm will be progression-free
  - Published evidence shows that up to 23% and ~20% remain progression free at 7 and 10yrs
  - Extrapolated data too pessimistic; concluded parametric models significantly underestimate long-term PFS

Source: EAG report, figure 11

- **As a result, parametric MCM model used**
- Concerns raised in original appraisal
  - *"3-year follow up PFS data from PAOLA-1 does not provide sufficient evidence to support assumption that a proportion of patients would be cured at 5 years"*
  - *"Specific cure fractions used in MCM not supported by trial data"*
- Company believes availability of 5-year PFS data shows clear plateauing and PFS rates in line with clinical expectations/evidence
- EAG raised concerns around use of MCM

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

Key issue: MCM approach used to model PFS inappropriate

Use of MCM unjustified; EAG prefer 3-knot spline to model PFS

Background

- **Company:** assumes patients enter long-term survival trajectory equivalent to gen. pop. @ 5yrs
- **EAG:** does not consider that data from PAOLA-1, or external sources, validate the use of cure model in aOC, and considered that company did not present evidence supporting existence of different survival trajectory for patients who can "be cured"
- **Company:** provided spline curves (and MCM with splines) at clarification; **EAG:** argued 3-knot spline model provides good visual fit to PFS KM data, captures 'possible plateau' in placebo+bev arm/provides plausible tails
- **Company**: long-term responders not captured
- **EAG**: more appropriate to model any relevant remission point using OS arm/OS data

Source: EAG report, figure 12

Company response at TE

- Plateauing in placebo+bev arm shows progression-free patients have high chance of long-term remission
- When validating modelling approaches, clinicians felt company approach generated more reasonable estimates

KM: Kaplan-Meier; **MCM**: mixture cure model; **OS**: overall survival; **PARPi**: poly-ADP ribose polymerase inhibitor; **PFS**: progression-free survival

Key issue: MCM approach used to model PFS inappropriate

Use of MCM unjustified; EAG prefer 3-knot spline to model PFS

EAG comments

- Might, in theory, be a plateauing effect in olap+bev arm, but data not mature enough to show this
- Remains unclear how many would enter long-term remission, and how survival differs from general population
- EAG clinical experts unsure if PFS curves would remain separate or would converge over time

Clinical expert: once patient reaches 5 years without progressing, risk of progression very low; EAG model is too pessimistic as assumes an ongoing rate of progression beyond 5 years when data suggest a plateau

Extrapolation of PFS (%)	Time (years)							
Placebo+bevacizumab arm	1	2	3	5	7	10	20	30
KM data: PAOLA-1 placebo+bev	[redacted]							
Company base case; MCM, LL	[redacted]							
EAG base case: 3-knots spline	[redacted]							
Olaparib+bevacizumab arm	[redacted]							
KM data: PAOLA-1 olap+bev	[redacted]							
Company base case; MCM, LL	[redacted]							
EAG base case: 3-knots spline	[redacted]							

Source: Company response to clarification, tables 11 and 12, company response to TE, tables 3 and 4

Which approach to modelling PFS is more appropriate, MCM or 3-knot spline?

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

Key issue: MCM approach used to model PFS inappropriate

Use of MCM unjustified; EAG prefer 3-knot spline to model PFS

Company: MCM log-logistic

EAG: 3-knot spline

[redacted]

Source: provided by EAG following PMB

Which approach to modelling PFS is more appropriate?

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

Survival curves; overall survival

Standard parametric modelling approach used; lognormal curve chosen

- **Company:** OS data modelled up to point where cumulative survival probabilities equal to or less than cumulative survival for PFS2, at which point OS curve would follow trajectory of PFS2/PFS
- Best fitting curve (generalised gamma) generated unlikely crossing timepoints; therefore chose log-normal
  - Crosses at [redacted] and [redacted] years for olap+bev and placebo+bev respectively
- Predicts cumulative probability of OS for placebo+bev from [redacted] at 7 years and [redacted] at 10 years; in line with ovarian cancer studies

- **EAG:** also uses lognormal curve, but differences occur due to differences in PFS modelling

[redacted]

Source: Company's fitted curves, EAG report, figure 14

AIC: Akaike information criterion; **BIC**: Bayesian information criterion; **OS**: overall survival; **PFS**: progression-free survival; **PFS2**: time to second progression or death

Key issue: Survival overestimated in the model

Company base case generates implausible survival predictions

Background

- OS curves cross PFS curves; from this point mortality for long-term responders is dictated by risk in extrapolated PFS curve, or general pop. mortality if higher
  - MCM PFS curves lead to [redacted] alive in olap+bev arm after 25 years (age 87) – not plausible
- 3-knot spline model for PFS more realistic but may still overestimate survival: [redacted] alive at 30 years
- EAG applies SMR of 1.14 for BRCA+ disease in relation to general pop. mortality: [redacted] alive at 30yrs

Company

- Adopted the increased SMR of 1.14 for BRCA+ patients in its base case
- Compares to UK general pop. mortality for women aged 59: [redacted] alive at age 87, [redacted] at 95, [redacted] at 98
- General pop. survival drops by [redacted] between ~68-78yrs, not feasible to drop [redacted] for olap+bev
- MCM OS estimates more realistic; drop off after 10yrs too high in EAG model compared to general pop.

EAG comments

- Criteria for survival being overestimated in model shouldn't be based on it being lower than in general pop.
- Implausible that company's SMR-adjusted MCM PFS curves lead to [redacted] of patients alive at 30 years

Clinical expert comments

- No reason to expect olap+bev curve to decline at faster rate than placebo+bev between 5-10yrs or 10-20yrs
- Feasible that 5-10% of patients could be alive 30yrs after diagnosis as 15-20% diagnosed aged <55yrs

NICE

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

Key issue: Survival overestimated in the model

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

	Time (years)						
	1	2	3	5	10	20	30
Average age of patients (years)	~59	~60	~61	~63	~68	~78	~88
(based on starting ages of 58 and 61)	~62	~63	~64	~66	~71	~81	~91
General population mortality	99.6%	99.2%	98.6%	97.5%	93.6%	78.7%	43.4%
Adjusted for BRCA (SMR = 1.14)	99.6%	99.0%	98.5%	97.1%	92.8%	76.1%	38.6%
Placebo+bevacizumab arm							
KM data: PAOLA-1	[redacted]						
Company base case; MCM, LN	[redacted]						
EAG base case: 3-knots spline	[redacted]						
Olaparib+bevacizumab arm							
KM data: PAOLA-1	[redacted]						
Company base case; MCM, LN	[redacted]						
EAG base case: 3-knots spline	[redacted]						

Source: Company response to TE, tables 5 and 6

Which survival estimates are most plausible?

LN: lognormal; **MCM**: mixture cure model; **OS**: overall survival; **PFS**: progression-free survival

Key issue: Survival overestimated in the model

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)

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)

Source: EAG report, figure 16

Which survival estimates are most plausible?

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

Key issue: HRD+ testing cost

HRD+ testing cost in the model is lower than that used in the UK/NHS

Background

- Company base-case per-patient HRD testing cost includes [redacted] unit cost of 'in-house lab' HRD test
- EAG notes Myriad MyChoice tests have list price of [redacted]; uses this price in own base-case

Company

- [redacted]
- [redacted]
- Disagree with EAG's view that NHS list price of HRD testing is appropriate; doesn't reflect likely cost
- Revised base case to include a [redacted] cost per HRD test

EAG comments

- Maintains NHS list price should be used in the model until official discount can be confirmed by NHSE

Clinical expert comments

- Myriad test currently most commonly used; however multiple lower-cost options becoming available
- Whole genome sequencing now available for all patients with ovarian high grade serous carcinoma; will remove need for Myriad testing

Which HRD testing cost should be used in the model?

NICE

HRD: homologous recombination deficiency; **NHSE**: NHS England

Summary of company and EAG base case assumptions

Differences in age, survival modelling, HRD test cost and subsequent treatments

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Baseline age	58.0 (HRD+, PAOLA-1)	61.0 (SACT data)
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, crossing MCM PFS curve	Standard parametric, lognormal, with general population mortality adjustment for BRCA+ patients in long-term remission, crossing 3-knot spline PFS curve
HRD+ testing cost	[redacted] – in house cost	[redacted] – Myriad test cost
Rucaparib/olaparib as subsequent treatments	Includes	Excludes

NICE

HRD: homologous recombination deficiency; **MCM**: mixture cure model; **OS**: overall survival; **PFS**: progression-free survival; **SACT**: systemic anti-cancer therapy

Cost-effectiveness results

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

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Thank you.