Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line chemotherapy

For Public – CON information redacted

CDF exit review of TA598 – ACM1

Technology appraisal committee A 16 January 2024

Chair: Radha Todd

Lead team: Jacqueline Tomlinson, Dominic Pivonka, Richard Ballerand

External assessment group: Liverpool Reviews & Implementation Group (LRiG)

Technical team: Raphael Egbu, Sally Doss, Janet Robertson

Company: AstraZeneca

Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line chemotherapy

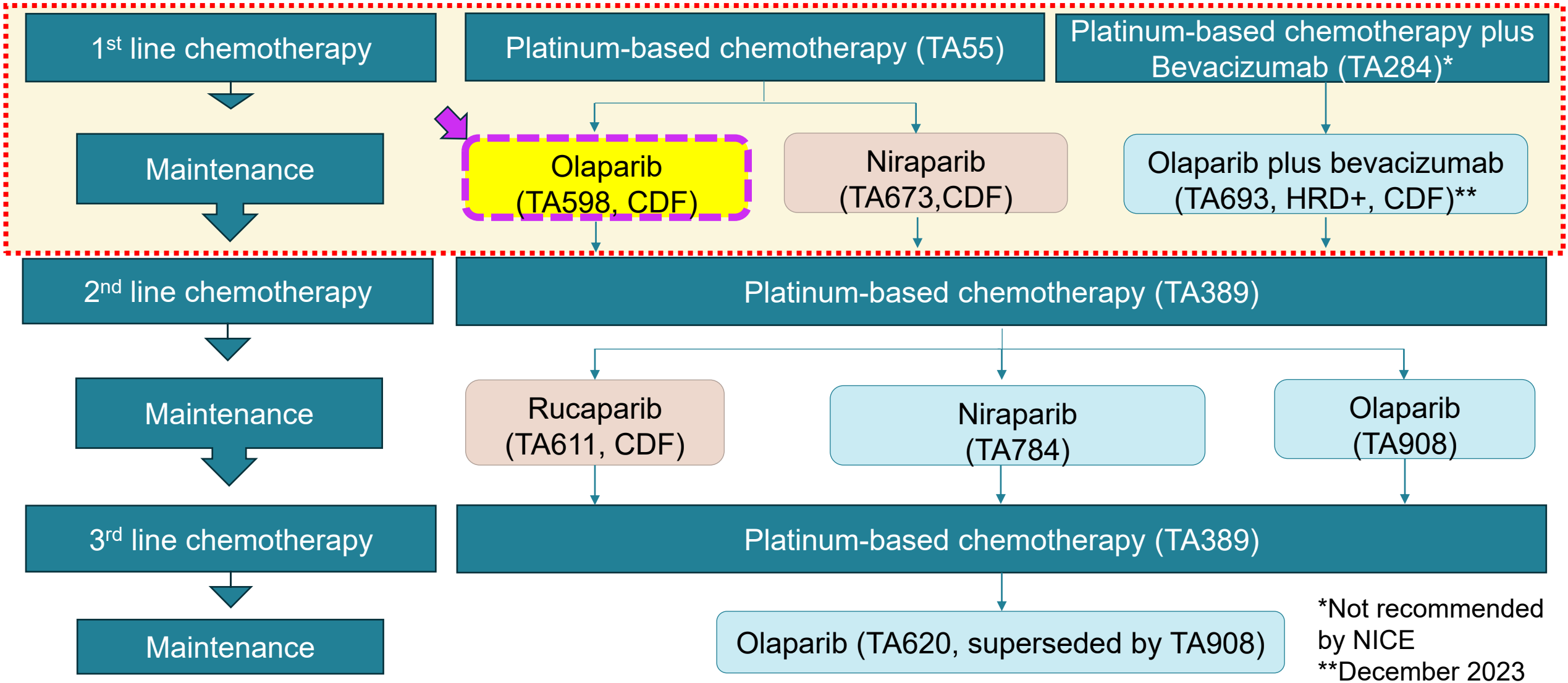
- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Treatment pathway: BRCAm positive ovarian cancer

Available through CDF

Routine commissioning



*Not recommended by NICE
**December 2023

NICE

Does the pathway represent NHS practice? (PARPi retreatment not permitted in the NHS)

BRCAm, BRCA mutation, CDF, Cancer Drugs Fund, HRD, homologous recombination deficiency

Appraisal recap (see slide 30)

Previous slide

Patient perspectives

Ovarian cancer impacts quality of life, early treatment would be beneficial

Submissions from Ovacome and Target Ovarian Cancer

- Can be very isolating given the rarity compared with some other cancers
- Carers of people with ovarian cancer live in similar isolation, not knowing others with the disease
- Impacts quality of life particularly because most people are diagnosed when the cancer has spread (stage 3)
- Currently no first-line maintenance treatment is available for routine use, this leads to additional concerns for people diagnosed
- Anxiety about recurrence and exhausting treatment options is common
- Early treatment would promote greatest benefit and reduce chances of becoming platinum resistant

"Not knowing when or if the disease will recur can be emotionally draining and debilitating"

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

"I found it [olaparib] generally very tolerable after the first few weeks and so worthwhile persevering"

Clinical perspectives

Effective targeted treatment could be beneficial for reducing tumour recurrence

Submissions from Royal College of Pathologists

- Tumour recurrence is a significant challenge with ovarian cancer
- Effective targeted treatment that has less side effects compared with conventional chemotherapy is a needed addition
- Studies show olaparib has potential to significantly improve progression free survival
- Administered orally and has relatively tolerable side effects, this presents improvements to current practice

"PARP inhibitors represent a significant addition in management of BRCA-mutated advanced ovarian cancer"

"Oral administration of the drug means that its use does not require a hospital setting"

Key issues

ICER impact:
Small= <£1k/QALY
Large= >£4K/QALY

Overview of key issues

Issue	Resolved?	ICER impact
Does SOLO-1 treatment pathway reflect NHS treatment pathway?	No – for discussion	Unknown
• What is the appropriate model for estimating progression-free survival? • What is the most appropriate method for modelling overall survival? • Which data cutoff should be used to generate survival estimates?	No – for discussion	Unknown
Which estimate is plausible for modelling mean time on PARPi treatment in the placebo arm?	No – for discussion	Large
Is a discount rate of 1.5% applicable?	No – for discussion	Large
Should olaparib treatment cost be based on average or a fixed dose?	No – for discussion	Small

Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line chemotherapy

- ❑ Background and key issues
- ✓ **Clinical effectiveness**
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- ❑ Summary

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Key clinical trial

Additional SOLO-1 data of up to 7 years collected and presented in this review

Clinical trial design and outcomes

Baseline characteristics (see slide 35)

	SOLO-1
Design	International, phase 3, randomised, double-blind, placebo-controlled trial
Population	People with newly diagnosed FIGO stage (III-IV) BRCA-mutated ovarian cancer who were in response (complete or partial) following first-line chemotherapy
Intervention	Olaparib
Comparator	Placebo
Duration	Ongoing →
Primary outcome	PFS
Key secondary outcomes	OS, PFS2, TFST, TSST, HRQoL, and AEs
Locations	15 countries, including 22 people treated in the UK
Used in model?	Yes

Data cut-off	Date	Follow-up
DCO1	17 May 2018	Median PFS follow-up: 41 months (3.4 years)
DCO2	5 March 2020	5 years from last patient recruited
DCO3	7 March 2022	7 years from last patient recruited

- Treatment continued until disease progression
  - Placebo group allowed to switch to olaparib following progression
- After 2 years people with complete response stopped treatment
- People with partial response could continue treatment beyond 2 years

AE, adverse events; DCO, data cutoff; FIGO, International Federation of Gynaecology and Obstetrics; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy

SOLO-1 trial PFS results (primary outcome)

PFS KM plot (7 years, DCO3, March 2022)

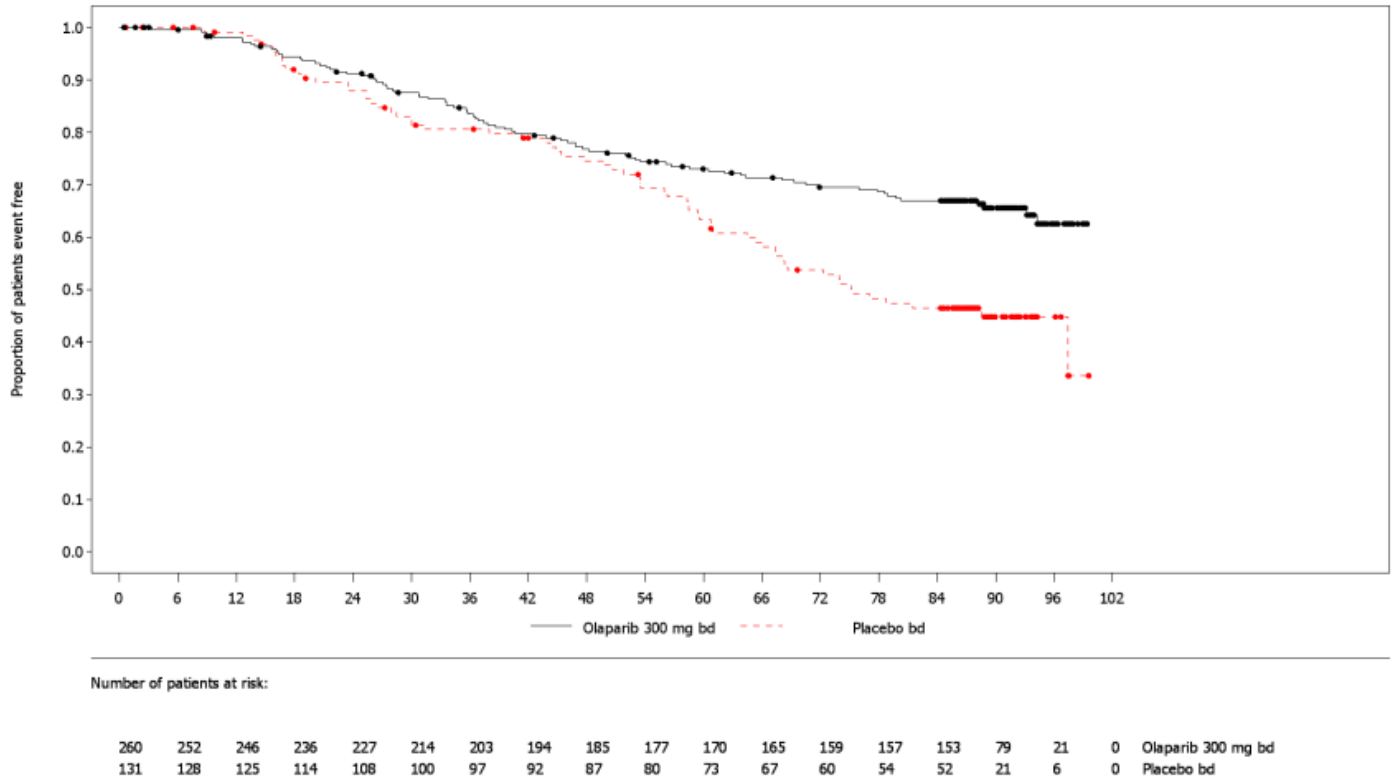
	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	[redacted]	[redacted]
Median PFS, months	[redacted]	[redacted]
HR (95% CI); P	NR	

NICE

DCO, data cutoff; HR, hazard ratio; KM, Kaplan-Meier; NR, not reported; PFS, progression-free survival

SOLO-1 trial OS results (secondary outcome)

OS KM plot (7 years, DCO3, March 2022)



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	NR	75.2
HR (95% CI); P	0.55 (0.40, 0.76); P=0.0004*	

*P<0.0001 required to declare statistical significance

EAG: Compelling rationale for sudden change in OS at month 42 not provided. OS may not be reliable

Company: Robust and accurate clinical rationale difficult to provide

SACT OS data not used in the company model (see slide 39)

NICE

DCO, data cutoff; HR, hazard ratio; KM, Kaplan-Meier; NR, not reached; OS, overall survival

Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line chemotherapy

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ✓ **Modelling and cost effectiveness**
- ❑ Other considerations
- ❑ Summary

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Key issue: Treatment sequence unclear

ICER impact: Unknown

Proportion of people who followed NHS treatment pathway in SOLO-1 is unclear

Background

- Retreatment with PARPi is not the current NHS practice
- In SOLO-1, subsequent PARPi was received by people in the olaparib (31.1%) and placebo (59.8%) arms
- Company model sets subsequent treatment in the olaparib arm as 0%

Company

- Not feasible to provide sequence data, statistically inappropriate
- Results are generalisable and PARPi retreatment unlikely to impact SOLO-1 results

EAG comments

- Unclear what proportion of people in the placebo arm received PARPi after response to second-line platinum chemotherapy (→EAG estimates around 30% did not follow this pathway) or without response to chemotherapy
- Requested company update model to allow subsequent treatment cost to be calculated for all health states and to allow PARPi treatment cost to be included after 2L and 3L platinum-based chemotherapy
  - → Company update does not link PARPi treatment with subsequent platinum chemotherapy
  - → Company update does not capture placebo treatment cost in the PSA
- Eligibility for subsequent treatment based on constant non-fatal PFS and PFS2 events → overestimates costs
- EAG explored subsequent treatment with two scenarios: (i) exponential decrease in people eligible for subsequent PARPi over [redacted]-year period (ii) clinical expert estimates (see slide 47)

NICE

Does SOLO-1 subsequent treatment pathway reflect NHS practice?
How should subsequent treatment be modelled for olaparib and placebo arms?

Pathway (see slide 3)

ICER impact: Unknown

Key issue: Appropriate survival estimates (1/2)

Company used MCM for extrapolating progression-free survival

Background

- Company considers olaparib to maintain cure for some people (due to survival curve plateauing)
- Its base case uses MCM to estimate PFS while standard parametric models were used for OS and PFS2
- Different data cutoffs were also used for PFS, PFS2 (DCO2), and OS (DCO3)

Company

- Clinical opinion suggests people who have not progressed within 5 years will likely remain in remission
- Preferred model distribution based on statistical fit (AIC and BIC) and clinical opinion
- MCM not considered for PFS2 because olaparib curative potential only expected in first-line setting
- DCO2 data used for PFS due to trial protocol change for people who discontinued or are in remission
  → Reduced visit from 12 weeks to 24 weeks; tumour assessment only when clinically adjudicated
- Additional cure models requested by the EAG was provided and validated by clinical opinion
  → Only statistically plausible models were selected and validated by clinicians, due to time limitation
- Using MCM for PFS2 and OS had limited impact on the ICERs

AIC, Akaike information criterion; BIC, Bayesian information criterion; DCO, data cutoff; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival

Model structure (see slide 41)

Company and EAG PFS extrapolation

MCM used by company and EAG for estimating long-term PFS

Company preferred extrapolation for PFS curves

Uses DCO2

Company base case
log-logistic

EAG alternative extrapolation for PFS curves

Uses DCO3

EAG alternative
Generalised Gamma

Survival assumptions

- PFS2 constrained to be greater than or equal to PFS
- OS constrained to be greater than to PFS2
- SOLO-1 OS hazard constrained to be greater than or equal to general population OS hazard

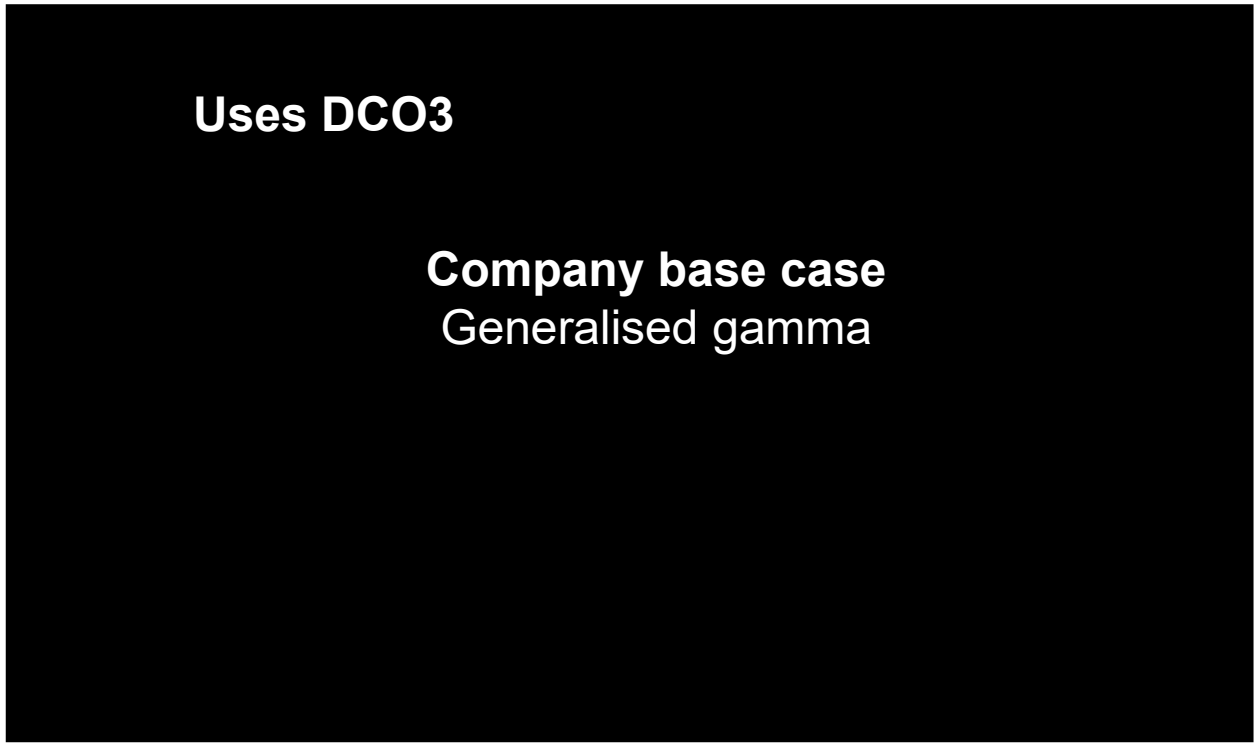
DCO, data cutoff; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival

Company and EAG OS extrapolation

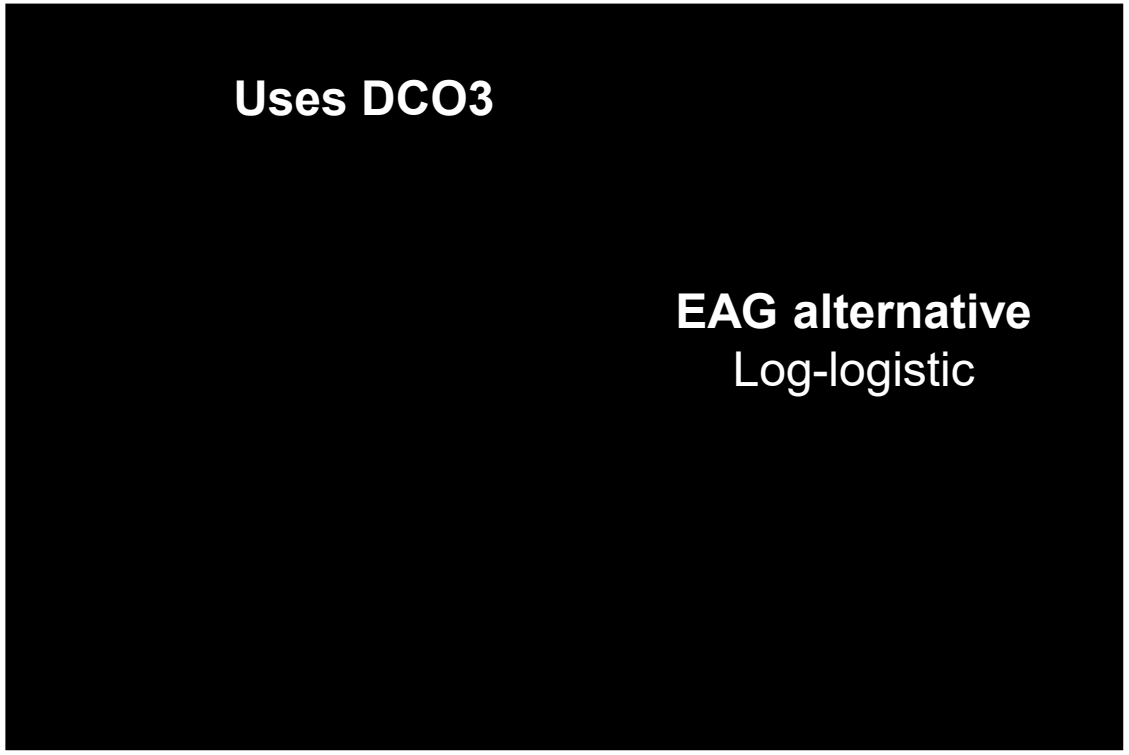
Standard parametric model used by company for estimating long-term OS

EAG prefers MCM

Company preferred extrapolation for OS curves



EAG alternative extrapolation for OS curves



Survival assumptions

- PFS2 constrained to be greater than or equal to PFS
- OS constrained to be greater than to PFS2
- SOLO-1 OS hazard constrained to be greater than or equal to general population OS hazard

DCO, data cutoff; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival

ICER impact: Unknown

Key issue: Appropriate survival estimates (2/2)

EAG raised concerns around mixing model types and data cutoffs

Model structure (see slide 41)

EAG comments

- Prefer use of the same data cutoff to ensure consistency and reduce need for extrapolation
- Using a mix of MCM and standard parametric model is problematic
- If PFS is estimated using MCM, the PFS cure fraction should be applied to OS and PFS2
  - → SOLO-1 OS definition includes PFS and PFS2
- Company base case models generate illogical estimates, company applied additional constraints to fix these
  - → Suggests models not appropriate
- Based on additional analysis by company, EAG satisfied that the MCMs generate more robust cost effectiveness estimates
- EAG has not chosen preferred survival models because:
  - → Company shortlisted 3 models based on statistical fit (AIC and BIC) which it then presented to clinicians for validation
  - → Company approach risks excluding some models with plausible long-term estimates
  - → EAG would have preferred consideration of long-term estimates ahead of trial data fit

- Which data cutoff should be used for modelling survival?
- Does the committee prefer the use of MCM, standard parametric model, or a mix?
- Is the company's approach to shortlisting models appropriate for estimating survival?

AIC, Akaike information criterion; BIC, Bayesian information criterion; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival

ICER impact: Large

Key issue: Time on subsequent PARPi treatment unclear (1/2)

Company used a different trial (SOLO-2) to estimate time on subsequent PARPi

Background

- Company noted that time on subsequent treatment was not collected for SOLO-1
- Model estimated time on subsequent treatment, following progression, in the placebo arm with SOLO-2 data (used in TA908)
  → SOLO-2: olaparib for relapsed ovarian cancer after two or more lines of platinum therapy
- Mean time on olaparib maintenance treatment in SOLO-2 was [redacted] years
- This is longer than the mean time between first and second disease progression estimated in the company model ([redacted] years)

EAG comments

- Following progression, people in the placebo arm will receive chemotherapy then maintenance PARPi until second progression
- Reasonable to assume that time on maintenance PARPi will not exceed mean time between first and second disease progression
- EAG base case uses [redacted] years, this change increases the company's base case ICER by [redacted]

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Olaparib marketing authorisation: Stop treatment after 2 years unless there is evidence of disease and clinical opinion is that further benefit can be derived from continuing treatment

ICER impact: Large

Key issue: Time on subsequent PARPi treatment unclear (2/2)

Company used a different trial (SOLO-2) to estimate time on subsequent PARPi

Company

- SOLO-2 data allows accurate estimates of the proportion of patients on subsequent PARPi
- EAG approach triggers subsequent treatment by PFS curve and is not consistent with SOLO-1 time to subsequent PARPi curve (TTSP)
- Not appropriate to link time in progressed disease state with duration on subsequent PARPi

Time on subsequent PARPi treatment in SOLO-1 not collected

Time to treatment discontinuation curve for 2-L and 3-L PARPi not available for placebo group

PFS and TTSP curve, placebo arm, DCO3

PFS-based: SOLO-1 PFS curve + 4 months of platinum-based chemotherapy initiation added
TTSP-based: SOLO-1 data

Which estimate is plausible for modelling mean time on PARPi treatment in the placebo arm?

PFS, progression-free survival; TTSP, time to subsequent PARPi

ICER impact: Large

Key issue: Appropriate discounting

Company base case applies a lower discount rate of 1.5%

Background

- Company base case applied 1.5% discount rate for costs and health benefits
- NICE process and methods manual states 1.5% can be used in non-reference case if:
  1. The technology is for people who would otherwise die or have a very severely impaired life
  2. It is likely to restore them to full or near-full health
  3. The benefits are likely to be sustained over a very long period.

All 3 criteria must be met

Company

- People who survive beyond 5 years will likely enter long-term remission
- People in remission expected to regain quality of life similar to before diagnosis of ovarian cancer
- Avoiding relapse for 5 years is expected to result in long-term benefit

EAG comments

- Lowest utility value (0.76) used by company does not represent severely impaired quality of life
- Age-adjusted utilities in model lower than general population and does not represent full health restoration
- SOLO-1 data immature, long-term OS still uncertain
  → Using a 3.5% discount rate increases the company's base case ICER by [redacted]

Is a discount rate of 1.5% applicable?

NICE

OS, overall survival

ICER impact: Small

Key issue: Cost of olaparib in the model

Company modelled olaparib dose based on SOLO-1 average, EAG prefers use of recommended dose

Background

- Olaparib available as 100mg and 150mg tablets (recommended total daily dose is 600mg)
- Company model estimates cost of olaparib for first-line maintenance treatment using mean daily dose from SOLO-1 trial: 558 mg
  →Includes dose reduction and interruptions to manage adverse events

Company

- In line with how treatment was received in SOLO-1

EAG comments

- Olaparib only available as 100mg and 150mg tablets so company's lower dose estimate unlikely to be cost saving for the NHS
- EAG applied fixed dose of 600 mg daily for all lines of treatment
- Applying fixed dose in company's model increases the company's base case ICER by [redacted]

Should olaparib acquisition cost be based on SOLO-1 average dose or a fixed dose based on the licence recommendation?

Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line chemotherapy

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Equality considerations

Language differences could impact understanding of treatment options

Risk of disease is higher for some people

Company:

- No equality issues related to the use of olaparib
- People from Ashkenazi Jewish backgrounds have a 10-fold greater risk of BRCA gene mutation
- People with female organs who do not identify as female could have ovarian cancer.

Patient organisation (Ovacome):

- Some people may struggle to access treatments if they do not understand the treatment options this includes people with learning disability and people with English as a second language.

Patient organisation (Target ovarian cancer):

- Some people may find it difficult to undergo genetic (BRCA) testing for religious or social reasons.

Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line chemotherapy

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues

ICER impact:
Small= <£1k/QALY
Large= >£4K/QALY

Overview of key issues

Issue	Resolved?	ICER impact
Does SOLO-1 treatment pathway reflect NHS treatment pathway?	No – for discussion	Unknown
• What is the appropriate model for estimating progression-free survival? • What is the most appropriate method for modelling overall survival? • Which data cutoff should be used to generate survival estimates?	No – for discussion	Unknown
Which estimate is plausible for modelling mean time on PARPi treatment in the placebo arm?	No – for discussion	Large
Is a discount rate of 1.5% applicable?	No – for discussion	Large
Should olaparib treatment cost be based on average or a fixed dose?	No – for discussion	Small

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Time on maintenance PARPi	[redacted] years (SOLO-2 trial)	[redacted] years (company model base case)
Discount rate (costs and QALYs)	1.5%	3.5%
Total daily olaparib dose	558mg	600mg
PFS and PFS2 data cut	DCO2 (5 years data)	DCO3 (7 years data)
Survival extrapolation	OS (DCO3): Standard parametric (g. gamma) PFS: MCM (log-logistic) PFS2: Standard parametric (log-normal)	• Preferred extrapolation not chosen due to modelling concerns raised • Alternative scenario uses- OS (DCO3): MCM log-logistic PFS: MCM (g. gamma) PFS2: MCM (log-normal)

DCO, data cutoff; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival

Cost-effectiveness results

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

EAG preferred assumptions and impact on company base case ICER

How EAG preferred assumptions impact the company base case

Assumption	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
Time on maintenance PARPi	↑	=	↑
Discount rate (costs and QALYs): 3.5%	↑	↓	↑
Total daily olaparib dose: 600 mg	↑	=	↑
DCO3 MCMs for PFS, PFS2, and OS	=	↑	↓
Exploratory analyses: subsequent treatment on progression	↑	=	↑

Arrows indicate the direction and magnitude of change to company's base case. Equal sign indicates no change.

DCO, data cutoff; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; QALY, quality-adjusted life years

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Thank you.

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Supplementary slides

Appraisal recap

Olaparib was previously recommended within the CDF, additional evidence now available to inform committee decision

August 2019 CDF entry

- Recommended for use within the CDF for maintenance treatment after first-line platinum-based chemotherapy (TA598)
- OS results for SOLO-1 trial are immature (21%, DCO1, May 2018) and not statistically significant, leading to considerable uncertainty in the modelling of OS
  → Not resolvable without collection of further OS data
- Uncertainty about proportion of people who will continue treatment beyond 2 years, this could markedly impact treatment cost
- Uncertainty about the use of PARPi after second-line chemotherapy and about PARPi retreatment

January 2024 CDF review

- SOLO-1 OS data of 7 years now available (38% maturity, DCO3, March 2022)
- SACT data also collected
- Committee to consider the cost-effectiveness of olaparib based on the updated evidence

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CDF, Cancer Drugs Fund; DCO, data cutoff; FIGO, International Federation of Gynaecology and Obstetrics; PARPi, poly(ADP-ribose) polymerase inhibitor; OS, overall survival; SACT, systemic anti-cancer therapy

Previous slide

Background on ovarian cancer

BRCA mutation increases ovarian cancer risk, and late diagnosis is common

Epidemiology

- Around 6,100 people were diagnosed with ovarian cancer in England in 2020
- Incidence rate is highest in people aged 75-79

Diagnosis and classification

- Classed as stage 1 to 4 depending on how far it has spread, most people are diagnosed with advanced disease (stage 3 to 4)

  → Stage 3 to 4 means disease that has spread outside of the pelvis

- Mutated inherited gene (BRCA) increases the risk of ovarian cancer

  → People with BRCA-mutated ovarian cancer tend to develop the disease at a younger age

Symptoms and prognosis

- Symptoms include abdominal pain, persistent bloating, urinary urgency, and feeling full quickly
- 5-year survival rate for ovarian cancer in England is 43.8%

Olaparib (Lynparza, AstraZeneca)

Technology details

Marketing authorisation	'As monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) 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.' → Granted by the European Commission (EC) in 2019
Mechanism of action	• Poly(ADP-ribose) polymerase (PARP) inhibitor • PARP enzymes repair damaged DNA in cells including cancer cells • Blocking PARP prevents repair of cancer cells causing their death
Administration	• Taken orally • Recommended dose: 300mg tablets twice daily (total daily dose: 600mg)
Price	• £2317.50 per 14-day pack (56 x 150mg tablets) • £4635.00 per 28-day cycle • A confidential commercial access agreement is in place

Decision problem

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	Adults with BRCA-mutated, advanced, high-grade ovarian, fallopian tube or peritoneal cancer that have responded to first-line chemotherapy without bevacizumab	In line with scope	
Intervention	Olaparib		
Comparators	Routine surveillance		
Outcomes	Include OS, PFS, PFS2, HRQoL (EQ-5D-5L), AE, TFST	In line with scope	Post-progression survival outcomes not generalisable due to differences in subsequent treatment in trial and NHS practice

AE, adverse events; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; TFST, time to first subsequent therapy

SOLO-1 study design

- Newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic *BRCA*m
- ECOG performance status 0–1
- Cytoreductive surgery*
- In clinical complete response or partial response after platinum-based chemotherapy

Olaparib 300 mg bd (N=260)

2:1 randomisation

Stratified by response to platinum-based chemotherapy

Placebo (N=131)

- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

2 years' treatment if no evidence of disease

Primary endpoint

- Investigator-assessed PFS (modified RECIST 1.1)

Secondary endpoints

- PFS using BICR
- PFS2
- Overall survival
- Time from randomization to first subsequent therapy or death
- Time from randomisation to second subsequent therapy or death
- HRQoL (FACT-O TOI score)

BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; FACT-O, Functional Assessment of Cancer Therapy – Ovarian; FIGO, International Federation of Gynaecology and Obstetrics; HRQoL, health-related quality of life; PFS, progression-free survival; RECIST, Response evaluation criteria in solid tumours; TOI, Trial Outcomes Index

SOLO-1 baseline characteristics

Characteristic	Olaparib (N=260)	Placebo (N=131)
Demographic characteristics		
Age, year		
Median	53.0	53.0
Range	29–82	31–84
Race or ethnic group, n (%)		
White	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other	[redacted]	[redacted]
Disease characteristics		
ECOG performance status, n (%)		
0 Normal activity	200 (76.9)	105 (80.2)
1 Restricted activity	60 (23.1)	25 (19.1)
Missing	0	1 (0.8)
Primary tumour location, n (%)		
Ovary	220 (84.6)	113 (86.3)
Fallopian tubes	22 (8.5)	11 (8.4)
Primary peritoneal	15 (5.8)	7 (5.3)
Other	3 (1.2)	0
FIGO stage, n (%)		
Stage III	220 (84.6)	105 (80.2)
Stage IV	40 (15.4)	26 (19.8)
BRCA mutation, n (%)		
BRCA1	191 (73.5)	91 (69.5)
BRCA2	66 (25.4)	40 (30.5)
BRCA1 and BRCA2	3 (1.2)	0
Response to first-line chemotherapy (stratification factor)		
Complete response	213 (81.9)	107 (81.7)
Partial response	47 (18.1)	24 (18.3)

EAG: Broadly reflects population seen in NHS clinical practice

ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics

Other SOLO-1 results

SOLO-1 PFS2, TFST and TSST results (secondary and exploratory outcomes)

	Olaparib N=260	Placebo N=131
PFS2 (DCO2)		
Events, n (%)	80 (30.8)	61 (46.6)
Median PFS2, months	NR	42.1
HR (95% CI)	0.46 (0.33 to 0.65)	
TFST (DCO3)		
Events, n (%)	135 (51.9)	98 (74.8)
Median TFST, months	64.0	15.1
HR (95% CI)	0.37 (0.28 to 0.48)	
TSST (DCO3)		
Events, n (%)	110 (42.3)	80 (61.1)
Median TSST, months	93.2	40.7
HR (95% CI)	0.50 (0.37 to 0.67)	

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DCO, data cutoff; HR, hazard ratio;OS, overall survival; PFS2, second progression-free survival; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy

SACT dataset

SACT OS data reported but not used in the company model

SACT dataset design and outcomes

	SACT dataset
Design	Analysis of SACT dataset
Population	People with BRCA-mutated, platinum-sensitive relapsed high-grade serous ovarian cancer (including patients with primary peritoneal and/or fallopian tube cancer), who are in response (complete or partial) to second-line platinum-based chemotherapy
Intervention	Olaparib
Comparator	N/A
Duration	22.9 months
Primary outcome	OS from first olaparib treatment
Used in model?	No (company: follow up shorter than SOLO-1)

OS, overall survival; SACT, systemic anti-cancer therapy

SOLO-1 and SACT data baseline characteristics

Difference in number of people with response to first-line chemotherapy

		SOLO-1 trial: olaparib arm N=260	SACT data N=[redacted]
Female		260 (100)	[redacted]
Age (years), n (%)	<40	Age band data from the SOLO-1 trial are available, but in a different age grouping to the SACT data. Please see company response to clarification question A6	[redacted]
	40–49		[redacted]
	50–59		[redacted]
	60–69		[redacted]
	70–79		[redacted]
	>80		[redacted]
Performance status at the start of regimen, n (%)	0	200 (76.9)	[redacted]
	1	60 (23.1)	[redacted]
	2	0 (0.0)	[redacted]
	Missing	0 (0.0)	[redacted]
BRCA1 and BRCA2 mutation, n (%)	BRCA1 mutation	191 (73.5)	[redacted]
	BRCA2 mutation	66 (25.4)	[redacted]
	BRCA1 and BRCA2 mutation	3 (1.2)	[redacted]
	Not captured	0 (0.0)	[redacted]
Response assessment at the end of first-line chemotherapy, n (%)	Complete response	213 (81.9)	[redacted]
	Partial response	47 (18.1)	[redacted]
	Not captured	0 (0.0)	[redacted]

EAG: Difference in BRCA type unlikely to impact outcome

EAG: Fewer people with complete response in the SACT group

SACT dataset OS results

Similar OS results for SOLO-1 and SACT dataset

SACT OS KM plot

OS results for SOLO-1 (olaparib only) and SACT at different timepoints

Time point	SOLO-1 trial (DCO3) N=260	SACT dataset N=
6 months		
12 months		
18 months		
24 months		
36 months		

SACT data not used in the company model

DCO, data cutoff; KM, Kaplan Meier; OS, overall survival; SACT, systemic anti-cancer therapy

Company PFS cure model results

Company model results - cure fractions and mean PFS for each fitted PFS cure model (SOLO-1 DCO3)

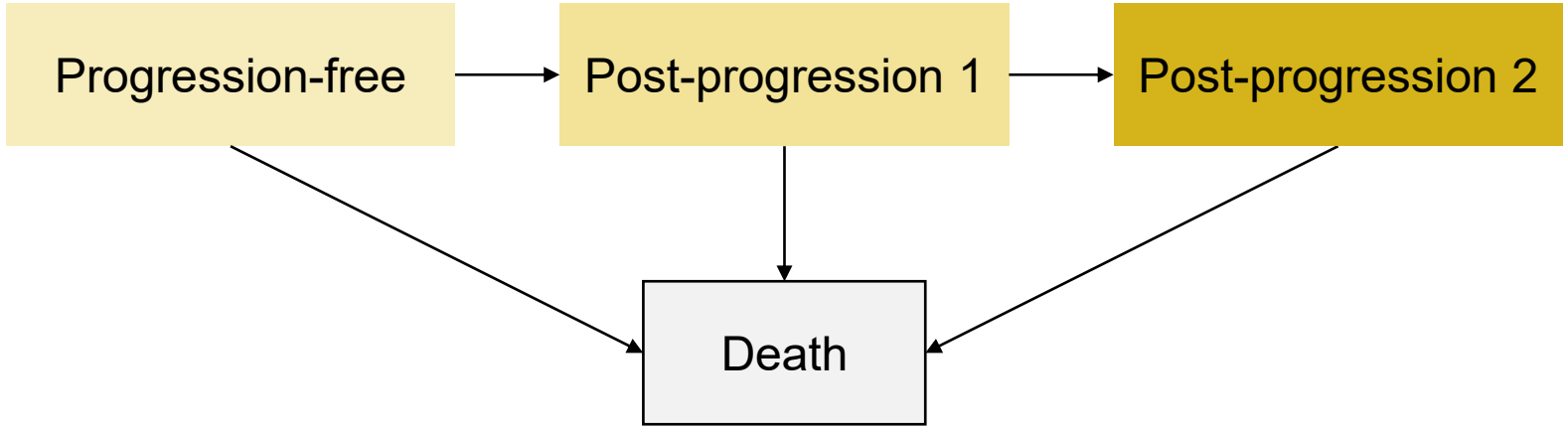
Parametric distribution	Olaparib		Routine surveillance	
	Cure fraction	Mean PFS (years)	Cure fraction	Mean PFS (years)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]

EAG comments

- Routine surveillance (placebo) estimates more plausible due to less variation compared with the olaparib arm

Company's model overview

Model structure: partitioned survival model with four health states



Probability	Calculated by
PD-1	Difference between PFS2 and PFS1
PD-2	Difference between OS and PFS2

- Technology affects **costs** by:
  - Increasing cost of maintenance PARPi treatment after first-line platinum chemotherapy
- Technology affects **QALYs** by:
  - Increasing QALYs in the progression-free health state
- Assumptions with greatest ICER effect:
  - Reducing time on subsequent treatment in the placebo arm
  - Using 3.5% discount rate
  - Applying subsequent treatment costs following progression

PD-1, first disease progression; PD-2, second disease progression; PFS, progression-free survival; OS, overall survival; QALY, quality-adjusted life-year

Summary of company base case OS estimates

Standard parametric OS extrapolations compared with SOLO-1 KM (DCO3)

	Years post-initiation of treatment						
	1	2	3	5	7	10	20
Olaparib							
SOLO-1 KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline (1knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							
SOLO-1 KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline (1knot)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company PFS cure model results (decomposed)

Comparison of PFS KM data and long-term MCM extrapolation, DCO3

Olaparib								
Curve	Population	Years post-initiation of treatment						
		1	2	3	5	7	10	20
KM data	SOLO-1	[redacted]						
Loglogistic	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						
Generalised Gamma	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						
Lognormal	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						

Placebo								
Curve	Population	Years post-initiation of treatment						
		1	2	3	5	7	10	20
KM data	SOLO-1	[redacted]						
Loglogistic	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						
Generalised Gamma	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						
Lognormal	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						

Company OS cure model results (decomposed)

Comparison of OS KM data and long-term MCM extrapolation, DCO3

Olaparib								
Curve	Population	Years post-initiation of treatment						
		1	2	3	5	7	10	20
KM data	SOLO-1	98%	91%	83%	73%	67%		
Lognormal	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						
Loglogistic	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						
Generalised Gamma	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						

Placebo								
Curve	Population	Years post-initiation of treatment						
		1	2	3	5	7	10	20
KM data	SOLO-1	99%	88%	81%	63%	47%		
Lognormal	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						
Loglogistic	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						
Weibull	**Total**	[redacted]						
	Cured	[redacted]						
	Uncured	[redacted]						

How company incorporated evidence into model

Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	SOLO-1
Intervention efficacy	
Comparator efficacy	
Utilities	
Costs	BNF (list price, PAS also available), eMIT
Resource use	NHS reference costs 2021/2022, PSSRU

BNF, British National Formulary; eMIT, Drugs and Pharmaceutical electronic Market Information Tool; PAS, patient access scheme; PSSRU, Personal Social Services Research Unit

Company response to EAG request for MCM

Company preferred PFS and OS extrapolations for the total and uncured population, olaparib arm, DCO3

Company preferred PFS and OS extrapolations for the total and uncured population, placebo arm, DCO3

DCO, data cutoff; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival;

Company and EAG estimates of people receiving second and third-line treatment

Estimated proportion of people receiving 2-L treatment

Treatment	Estimated proportion of patients (%)			
	Olaparib		Routine surveillance	
	Company	EAG alternative	Company	EAG alternative
Total platinum	50	70	38	70
Platinum only	50	70	-3*	10
PARPi maintenance	-	-	38	60
Non-platinum or other	8	20	13	20
No treatment	42	10	49	10

*explanation in company confidential model

Estimated proportion of people receiving 3-L treatment

Treatment	Estimated proportion of patients (%)			
	Olaparib		Routine surveillance	
	Company	EAG alternative	Company	EAG alternative
Total platinum	28	50	23	50
Platinum only	28	50	2	30
Platinum then PARPi	-	-	21	20
Non-platinum or other	44	20	37	20
No treatment	28	30	40	30