Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer after 2 courses of platinum-based chemotherapy

For public

CDF exit review of TA620 – ACM2

Technology appraisal committee A [7 March 2023]

Chair: Radha Todd

Evidence review group: BMJ-TAG

Technical team: Alex Sampson, Jo Richardson, Janet Robertson

Company: AstraZeneca

Appraisal recap

Additional trial data collected since CDF entry will inform committee decision

November 2019

CDF-entry

- Olaparib recommended for 2L use within the CDF (maintenance therapy following 2L chemo)
- 3L+ use recommended for routine commissioning (met end-of-life criteria)
- OS was based on data from Study 19. Participants were heavily pre-treated and had mixed BRCA status - *"not sufficiently robust to approve for routine commissioning"*
- SOLO2 data more relevant, but OS data was immature at the time

December 2022

ACM1: CDF-review

- SOLO2 OS data now mature (~40months additional follow-up data, overall maturity [redacted]%)
- Significant proportion of people in placebo arm of SOLO2 switched to subsequent PARPi
- Both ERG and company base cases adjusted for this switching (in different ways). But committee concluded that neither were suitable for decision making.
- Committee could not determine whether olaparib is cost-effective in 2L population
- Company was asked to provide additional analysis - **no ACD sent out for consultation**

March 2023

ACM2

- As requested by committee, company provided updated cost-effectiveness analysis based on unadjusted OS data for routine surveillance

2L = second-line; 3L+ = third-line or later; ACD = appraisal consultation document; BRCAm = BRCA mutation; CDF = Cancer Drugs Fund; ERG = Evidence Review Group; OS = overall survival; PARPi = PARP inhibitor;

Key issues

Committee conclusions from ACM1

Key Issue	Committee conclusions
Estimation of OS for routine surveillance patients	**Use unadjusted OS data** for routine surveillance arm to reflect pathway at CDF entry (where people would be offered olaparib if PARPi naïve at 3L). Also include following assumptions: • Assume all subsequent PARPi use in SOLO2 is olaparib • Assume all PARPis have similar efficacy and tolerability • Assume all subsequent PARPi use in SOLO2 is limited to 3L
Costs of subsequent olaparib for routine surveillance patients	**Costs of subsequent olaparib should be included** when using unadjusted routine surveillance arm data (as benefits are included)

Issues to consider at ACM2

Key Issue	Impact on ICER
Extrapolation of unadjusted OS data for RS arm	N/A; ERG & company aligned
Inclusion of patients who had [redacted]	Very small

3L = third-line; ACM1 = 1st appraisal committee meeting; CDF = Cancer Drugs Fund; ERG = Evidence Review Group; OS = overall survival; PARPi = PARP inhibitor; RS = routine surveillance;

Background on ovarian cancer

Late diagnosis is common and can lead to poor prognosis

Epidemiology

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

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 (HGSC) 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
- Following recurrence, the treatment goal is typically to manage rather than cure the condition
- 5yr survival for ovarian cancer in England is 42.6%; → below the European average

HGSC = High-grade serous carcinoma

Olaparib tablets (Lynparza, AstraZeneca)

Marketing authorisation	Indicated 'as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy'
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.

PARP = Poly-ADP-ribose polymerase

Decision problem

Only appraising 2L maintenance therapy for people with a BRCAm in this CDF exit review

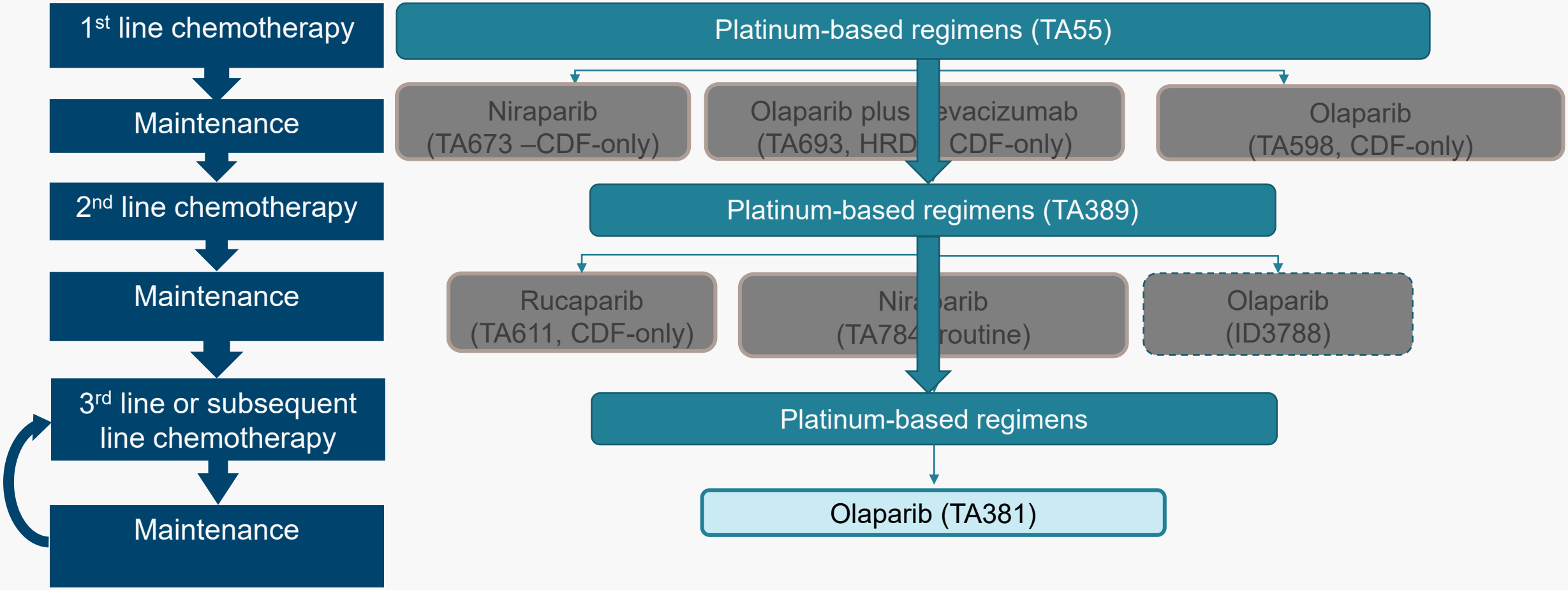
	As per CDF Terms of Engagement
Population	People who have platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or peritoneal cancer that is in response (complete or partial) to second-line platinum-based chemotherapy, and who have a confirmed BRCAm →*narrower than olaparib marketing authorisation*
Comparators	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

TA620 recommended 3L+ use for routine commissioning (met end of life criteria), and 2L use in the CDF. Therefore this CDF review is only considering 2L use.

2L = second-line; 3L+ = third-line or later; BRCAm = BRCA mutation; CDF = Cancer Drugs Fund

Pathway at the time of CDF entry: BRCAm+ Ovarian Cancer

Olaparib after third line platinum was the only PARPi in routine commissioning



CDF review needs to consider pathway at time of CDF entry when using this process for exit (no rescope)

NICE = not routinely available at time of CDF entry

BRCAm = BRCA mutation; CDF = Cancer Drugs Fund; HRD = Homologous recombination deficiency; PARPi = PARP inhibitor
Olaparib = olaparib tablets, unless otherwise specified

Expert perspectives

Olaparib extends survival and helps people live a normal life

Patient expert contributions from Ovacome, Ovarian Cancer Action, Target Ovarian Cancer

- The prospect of recurrence “casts a shadow” over people’s lives
- As most people will eventually become platinum resistant, extending PFS is hugely important, both physically and psychologically
- Olaparib has manageable side effects and can be taken at home
- Vital that those who weren’t offered a PARPi 1L have this opportunity 2L

Clinical expert contributions from Royal College of Pathologists, British Gynaecological Cancer Society and UCL Cancer Institute

- Olaparib is effective at delaying disease progression and life expectancy has dramatically improved since PARPis became widely available
- Small proportional of people have exceptional benefit, remaining on olaparib >5 years without further progression (around 20%)
- Although the number of people eligible for a PARPi at 2L is reducing, there remains a need (e.g. PARPi may not have been available/suitable following the first course of chemo)

“Olaparib has transformed my life. It has extended my life by 5 wonderful years. My family and I are forever grateful for this life changing drug. ”

“Maintaining women on outpatient treatment with remote consultations and delaying the need for intravenous chemotherapy has been invaluable”

“Real world studies mirror the benefits seen in clinical trials”

1L = first-line; 2L = second-line; PARPi = PARP inhibitor; PFS = Progression Free Survival

Update since Cancer Drugs Fund entry

Committee agreed company has adhered to the ToE in general

	Original source	Updated source	Committee conclusion ACM1
Overall survival source	Study 19	SOLO2, adjusted to account for high subsequent PARPi use in placebo arm which would overestimate OS.	Prefer unadjusted OS data
Progression-free survival source	Study 19	SOLO2 using radiological disease progression	Appropriate
Time to treatment discontinuation source	Study 19	SOLO2	Appropriate
Baseline characteristics	Study 19	SOLO2	Appropriate
Subsequent treatments	Study 19	SOLO2 final analysis	Appropriate
Time horizon	30 years	50 years	Appropriate

ACM1 = 1st appraisal committee meeting; OS = overall survival; PARPi = PARP inhibitor; ToE = Terms of engagement;

RECAP

Key clinical trials

Mature OS data for people with BRCA mutation now available to support CDF review

	Study 19 (used for CDF entry)	SOLO2 (used for CDF review)
Population	Patients with platinum sensitive relapsed ovarian cancer, who are in response to platinum chemotherapy, **irrespective of BRCA mutation status** (retrospective subgroup analysis of BRCAm)	Patients with platinum sensitive relapsed ovarian cancer **with BRCA mutation**, who are in response to platinum chemotherapy
Intervention	Olaparib, 400 mg capsules twice daily (N = 136)	Olaparib, 300 mg tablets twice daily (N = 196)
Comparator	Placebo (n=129)	Placebo (n=99)
Outcomes	• Progression-free survival • Time to first subsequent treatment • Time to second subsequent treatment • Overall survival • Health-related quality of life • Adverse events	• Progression-free survival • Progression-free survival to 2nd progression • Time to first subsequent treatment • Time to second subsequent treatment • Overall survival • Health-related quality of life • Adverse events
Median follow-up (OS)	• 6.5 years	• 65.7 months for olaparib • 64.5 months for placebo

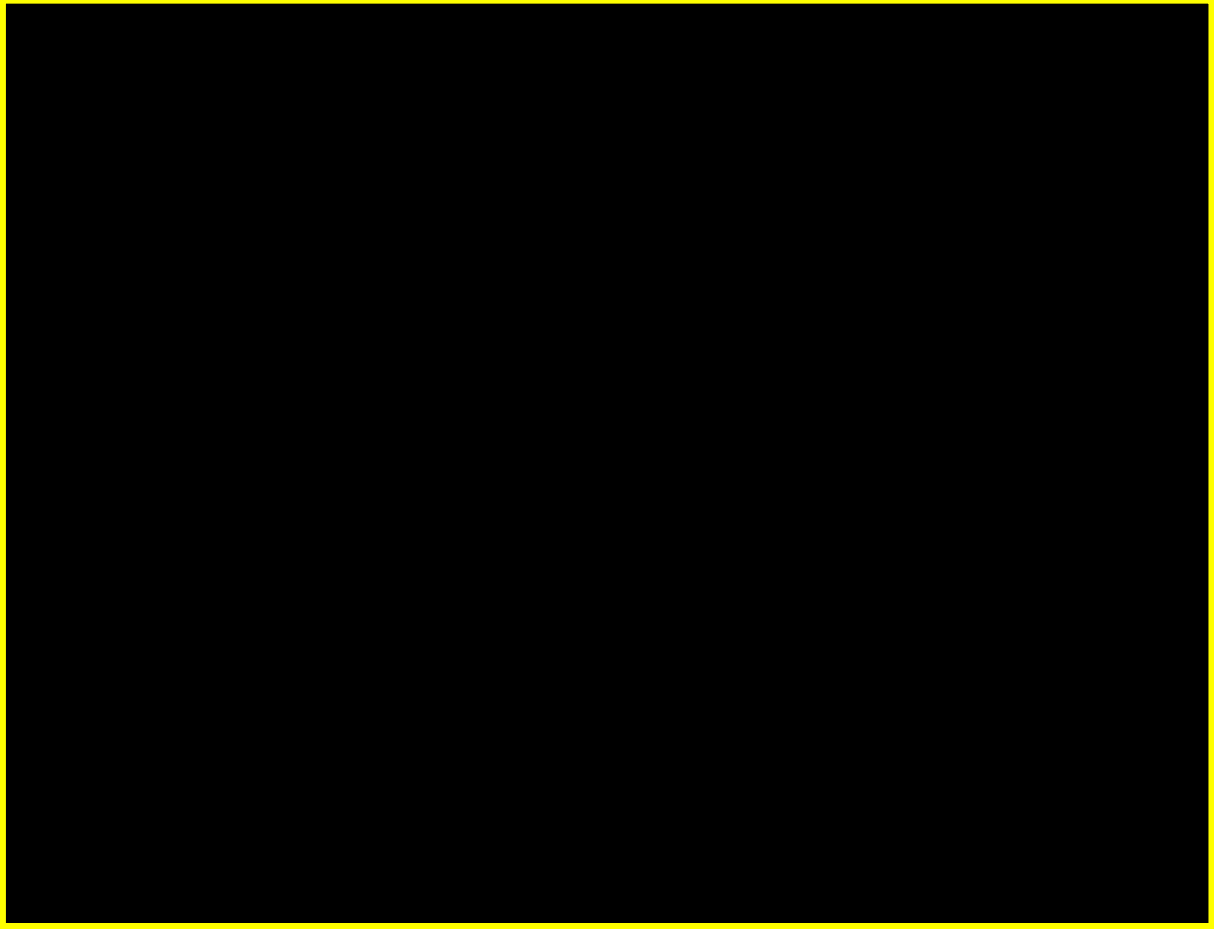
Public Health England systemic anti-cancer therapy (SACT) dataset was secondary evidence source but only has [redacted] patients. Due to short data collection time no outcomes were reported, so not included in updated model.

BRCAm = BRCA mutation; CDF = Cancer Drugs Fund; OS = overall survival;

Clinical data: Progression Free Survival

Olaparib significantly extends progression free survival in second-line maintenance setting

Investigator-assessed progression-free survival



	Olaparib (N=110)	Placebo (N=62)
Events, n/N (%)	[redacted]	[redacted]
Median time to event, months (95% CI)	[redacted]	[redacted]
PFS benefit, months	[redacted]	
HR (95% CI);	[redacted]	

- Median time to progression benefit of [redacted] months with olaparib vs. placebo
- PFS endpoint was met at primary analysis, so this data is from the primary analysis (Sept. 2016 DCO)

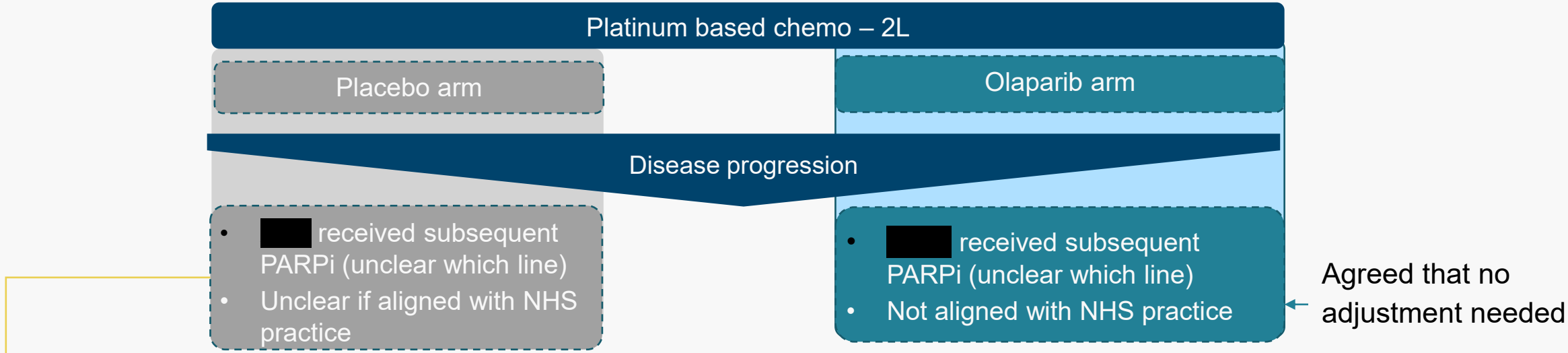
NICE

bd = bis die (twice daily); CI = confidence interval; DCO = data cut off; HR = hazard ratio; PFS = progression free survival;

Treatment switching following progression

Committee prefers to use unadjusted OS data for placebo arm

People in both arms received subsequent PARPi outside of the study (but higher % in placebo arm)*:



Recap from ACM1:

- Company applied treatment switching adjustment to the overall survival data in the placebo arm, to remove benefit of high subsequent PARPi use
- ERG also used adjusted data (but reflected some PARPi use via the choice of extrapolation curve)
- Committee concluded that unadjusted OS data should be used, as it better reflected the pathway at the point of CDF entry. People who are PARPi naïve by 3L would be offered olaparib in NHS.

2L = second-line; 3L = third-line; CDF = Cancer Drugs Fund; ERG = Evidence Review Group; PARPi = PARP inhibitor; OS = overall survival;
**Subsequent PARPi was taken either as maintenance therapy following platinum-based chemotherapy, or as monotherapy.*

Clinical data: Overall Survival

Olaparib extends overall survival in second-line maintenance setting

Placebo unadjusted for subsequent PARPi; Feb 2020 DCO (final)

[redacted]

	Unadjusted	
	Olaparib (N=110)	Placebo (N=62)
Events, n/N (%)	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
OS benefit, months	[redacted]	
HR (95% CI);	[redacted]	

[redacted]

- Unadjusted data shows an overall survival benefit of [redacted] months for olaparib vs placebo and [redacted] reduction in mortality risk

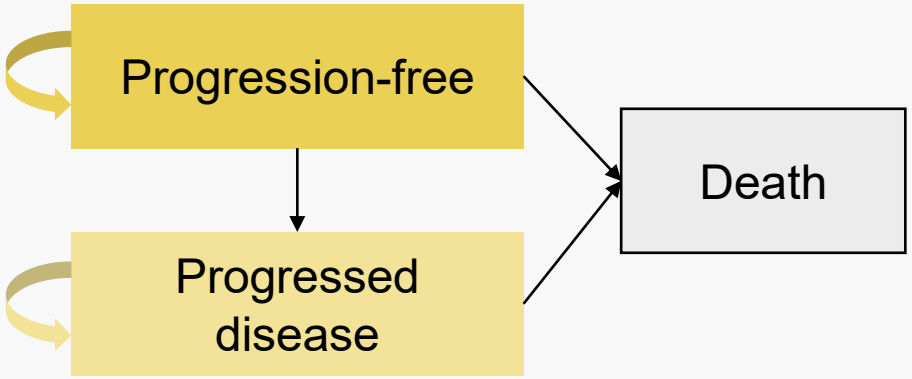
bd = bis die (twice daily); DCO = data cut off; HR = hazard ratio; OS = overall survival; PARPi = PARP inhibitor;

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

Model structure same as CDF entry, but different source for clinical data



Model is based on parametric survival curves for

- progression-free survival (PFS)
- overall survival (OS)
- TTD (used to estimate treatment duration)

Area	Assumptions	Aligned with ToE
Population	People with BRCAm after two courses of platinum-based chemotherapy	Y
Time horizon	50 years	Y
Clinical data source	Investigator-assessed PFS, OS and TTD all taken from SOLO2 (as per CDF exit ToE)	Y
Costs	Extrapolation of TTD data from Sept 2016 DCO.	Y
End of life	Not met	Y

BRCAm = BRCA mutation; CDF = Cancer Drugs Fund; DCO = data cut off; OS = overall survival; PFS = progression free survival; ToE = Terms of engagement; TTD = time to treatment discontinuation;

Summary of base case assumptions at ACM1

Two areas where ERG and company disagreed

	Assumption	Company base case (post TE)	ERG base case	Committee conclusion at ACM1	ICER impact
	Adjustment of OS for subsequent PARPi: olaparib arm	No adjustment required			N/A
Key issue 1 (ACM1)	**Adjustment for subsequent PARPi use in RS OS arm**	Adjusted OS data from SOLO2 with lognormal curve for extrapolation (assumes no 3L PARPi use in RS arm)	Adjusted OS data from SOLO2 with knot spline curve (assumes some benefit from 3L PARPi use in RS arm)	**Use unadjusted data**	Large
	Time-to-treatment discontinuation (TTD) capped to PFS	Capped			N/A
Key issue 2 (ACM1)	**Olaparib 3L costs**	Omitted	Included	**Include**	Small

3L = third-line; ACM1 = 1st appraisal committee meeting; ERG = Evidence Review Group; OS = overall survival; PARPi = PARP inhibitor; PFS = progression free survival; RS = routine surveillance; TE = technical engagement; TTD = time to treatment discontinuation;

Key issue: Extrapolation of unadjusted OS data for RS arm

Company has provided requested analysis but believes it is conservative

Background

- Committee concluded at ACM1 that unadjusted OS data should be used for RS arm
- Committee asked the company to provide:
  - Estimation of overall survival in the RS arm based on unadjusted data from SOLO2.
  - Range of OS extrapolations based on this unadjusted data, with justification for selected curve
  - Updated cost-effectiveness analysis based on unadjusted data (and including 3L costs)

Company response

- Maintain that adjusted OS estimates improves the generalisability of the SOLO2 study by better reflecting UK clinical practice (where very few people are PARPi naïve by 3L)
- At olaparib CDF entry, niraparib was available for 2L use via CDF, so PARPi were part of 2L clinical practice
- Nonetheless, economic model has been updated as per committee's request
- Updated scenario analysis using Study 19 for the RS has also been provided, as it demonstrates a more generalisable estimate of survival and reflects the pathway prior to PARPi use in earlier lines
- Study 19 ICERs are lower than unadjusted SOLO2 as less subsequent PARPi use in RS group ([redacted] vs [redacted])
- Company believes CE estimate of 2L olaparib is likely to fall between the Study 19 scenario and the unadjusted SOLO2 analysis, the unadjusted being most conservative

2L = second-line; ACM1 = 1st appraisal committee meeting; CDF = Cancer Drugs Fund; CE = cost-effectiveness; ICER = incremental cost-effectiveness ratio; OS = overall survival; PARPi = PARP inhibitor; RS = routine surveillance;

Key issue: Extrapolation of unadjusted OS data for RS arm

Company selected lognormal curve

[redacted]

Model	AIC	BIC
Generalised gamma	**381.92**	**388.31**
Spline	383.73	392.24
Lognormal	385.90	390.16
Log logistic	388.64	392.89
Weibull	393.80	398.05
Exponential	396.47	398.60
Gompertz	397.89	402.15

	Curve selection	2yrs	3yrs	20yrs
Model	lognormal	[redacted]	[redacted]	[redacted]
SOLO2		[redacted]	[redacted]	N/A

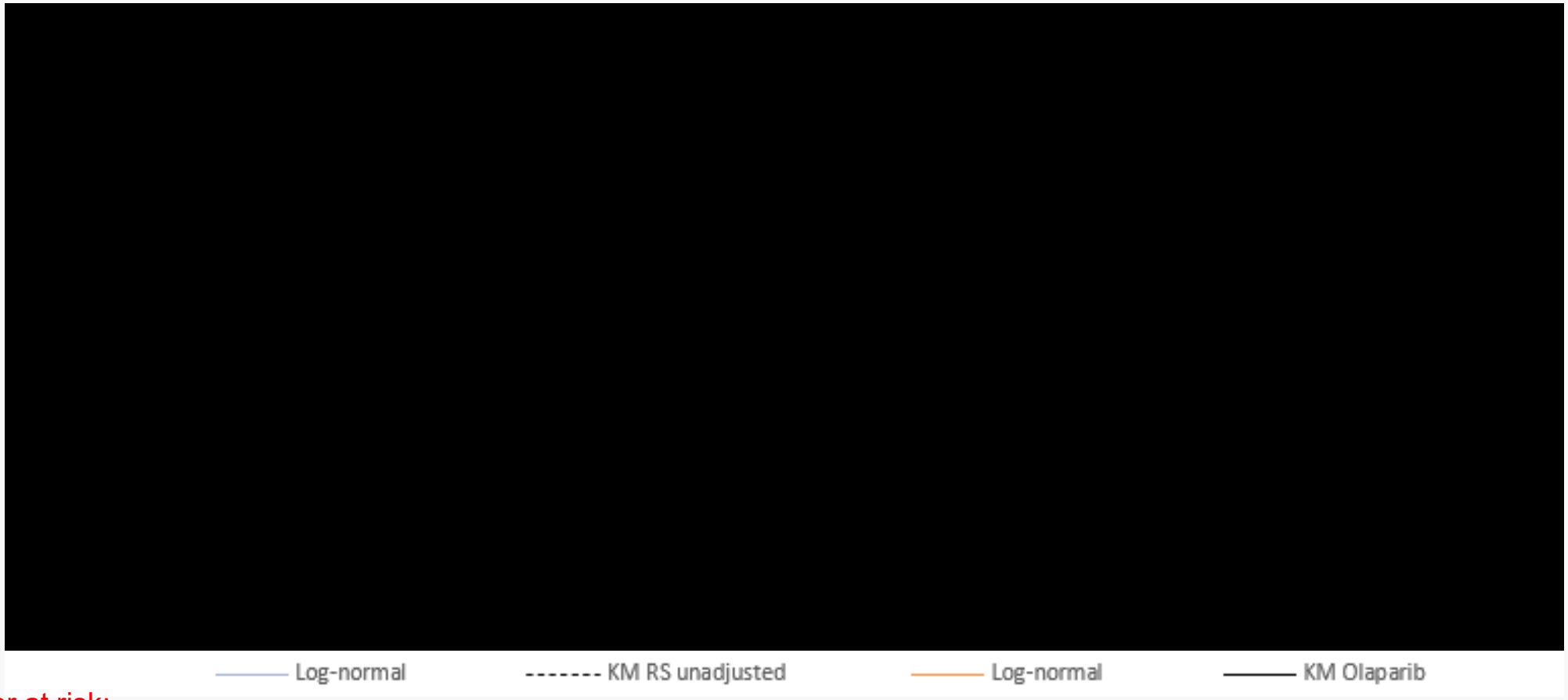
Company

- Selection of lognormal based on statistical goodness-of-fit, visual inspection, external clinical validation, and consistency with olaparib arm
- Log cumulative hazards plot does not support the assumption of proportional hazards, so independent models fitted to each arm ***ERG agrees***
- Weibull, Gompertz ruled out – clinicians said too pessimistic ([redacted] alive at 20yrs) ***ERG agrees***
- Spline and generalised gamma ruled out - RS OS exceeds olaparib OS, which clinicians said is highly unlikely. ***ERG agrees***
- Estimates based on the lognormal curve are conservative and likely represent the upper bound of the cost-effectiveness estimate

3L = third-line; ERG = Evidence Review Group; OS = overall survival; RS = routine surveillance

Company's selected extrapolation curves – RS & olaparib

ERG and company aligned on selection of extrapolation curves



Number at risk:

Olaparib

Placebo

NICE

ERG = Evidence Review Group; KM = Kaplan-Meier; RS = routine surveillance;

Overview of ERG critique

1 remaining area where ERG and company differ, but very small impact on ICER

- ERG says company's response is "mostly appropriate and aligned with the committee preferences"
- Results align with the ERG base case from ACM1 and the scenario using the inverse of the unadjusted OS hazard ratio to produce an unadjusted OS curve for RS (very similar ICERs)
- Company did not include data from [redacted] (these should be included based on assumption that all PARPi use was olaparib). Minimal impact on ICER.
- Noted at ACM1 that Study 19 scenario introduces more uncertainty as population is less relevant for people with a BRCAm than SOLO2

Assumption	Company base case (post-ACM1)	Corrected company base case (post-ACM1)	ICER impact
Adjustment for subsequent PARPi use in RS OS arm	Unadjusted, lognormal extrapolation		N/A
Inclusion of patients who had [redacted]	Excluded	Included (and assumed olaparib)	Very small

NICE

ACM1 = 1st appraisal committee meeting; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; OS = overall survival; PARPi = PARP inhibitor; RS = routine surveillance;

Cost-effectiveness results

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

- Committee will consider the company and ERG ICERs once confidential comparator PAS discounts are applied
- In general, interventions where the most plausible ICER is less than £20,000 per QALY gained are considered to be cost effective.
- Above this level, committee will take account of the degree of uncertainty around the ICER and the presence of benefits which may not have been adequately captured in the model
- All ICERs are well above the level usually considered as a cost-effective use of NHS resources

ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; PAS = patient access scheme; QALY = quality-adjusted life year

Key discussion points

- ERG says company's updated analyses is broadly appropriate and has similar results to ERG base case from ACM1
- Only remaining point of difference between company base case and ERG-corrected company base case has very small impact on ICER
- Does committee agree that updated analyses is appropriate for decision making, and which is the preferred ICER?

NICE

ACM1 = 1st appraisal committee meeting; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio;

NICE National Institute for Health and Care Excellence

Thank you.

Overall Survival: Olaparib arm (unadjusted)

Extrapolation of olaparib arm still uses lognormal curve

- Unchanged from ACM1: lognormal

Company:

- Lognormal gives consistent long-term OS estimates when compared with observed data from SOLO2 at 3 and 5 yrs
- Also aligns with clinical expert opinion that [redacted] of patients to remain alive at 20 years

	Curve selection	3yrs	5yrs	20yrs
Model	lognormal	[redacted]	[redacted]	[redacted]
SOLO2		[redacted]	[redacted]	N/A

NICE

ACM1 = 1st appraisal committee meeting; OS = overall survival;