NICE National Institute for Health and Care Excellence

Olaparib for treating newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, after response to first-line platinum-based chemotherapy

Lead team presentation

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Company: Astra Zeneca
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Key clinical issues

1. SOLO1 included 82% of people with complete remission and 18% with partial remission. People with residual disease at 2 years could continue olaparib beyond 2 years.
   - What percentage would continue treatment after 2 years in UK clinical practice?
2. SOLO1 data are immature and median PFS in the olaparib arm has not been reached. A PFS benefit of 3 years+ for olaparib is predicted. No statistically significant OS benefit has been shown
   - To what extent would a progression-free survival benefit be expected to translate into OS?
   - Has olaparib been shown to be curative?
3. Currently patients receive a PARP inhibitor once in the treatment pathway and no evidence is available for retreatment. In SOLO1 XXX of patients in the olaparib arm and XXX in the placebo arm had a PARP inhibitor following disease progression.
   - What would be the treatment pathway if olaparib was recommended?
   - Is it reasonable to assume that people will receive a subsequent PARP inhibitor to the same extent as in SOLO1 trial?
4. The company uses the Edinburgh Ovarian Cancer Database to externally validate the modelled survival in the routine surveillance arm.
   - Does it reflect the population eligible for olaparib in the UK first line maintenance setting?
   - Would patients diagnosed today, with currently available treatments, have the same outcomes as in the database?

Olaparib (Lynparza, AstraZeneca)

- Olaparib is a poly-ADP-ribose polymerase (PARP) inhibitor which inhibits PARP proteins involved in DNA repair.

Marketing authorisation	On 26th April, 2019, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for olaparib 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. It will be introduced as a tablet formulation. Olaparib already has a marketing authorisation for maintenance treatment of relapsed ovarian cancer, as a tablet formulation and also a capsule formulation, which is likely to be phased out. NICE Technology Appraisals guidance 381 recommends olaparib capsules for people with BRCA1/2 ovarian cancer after 3 or more courses of platinum chemotherapy.
Administration	Administered orally

[redacted]

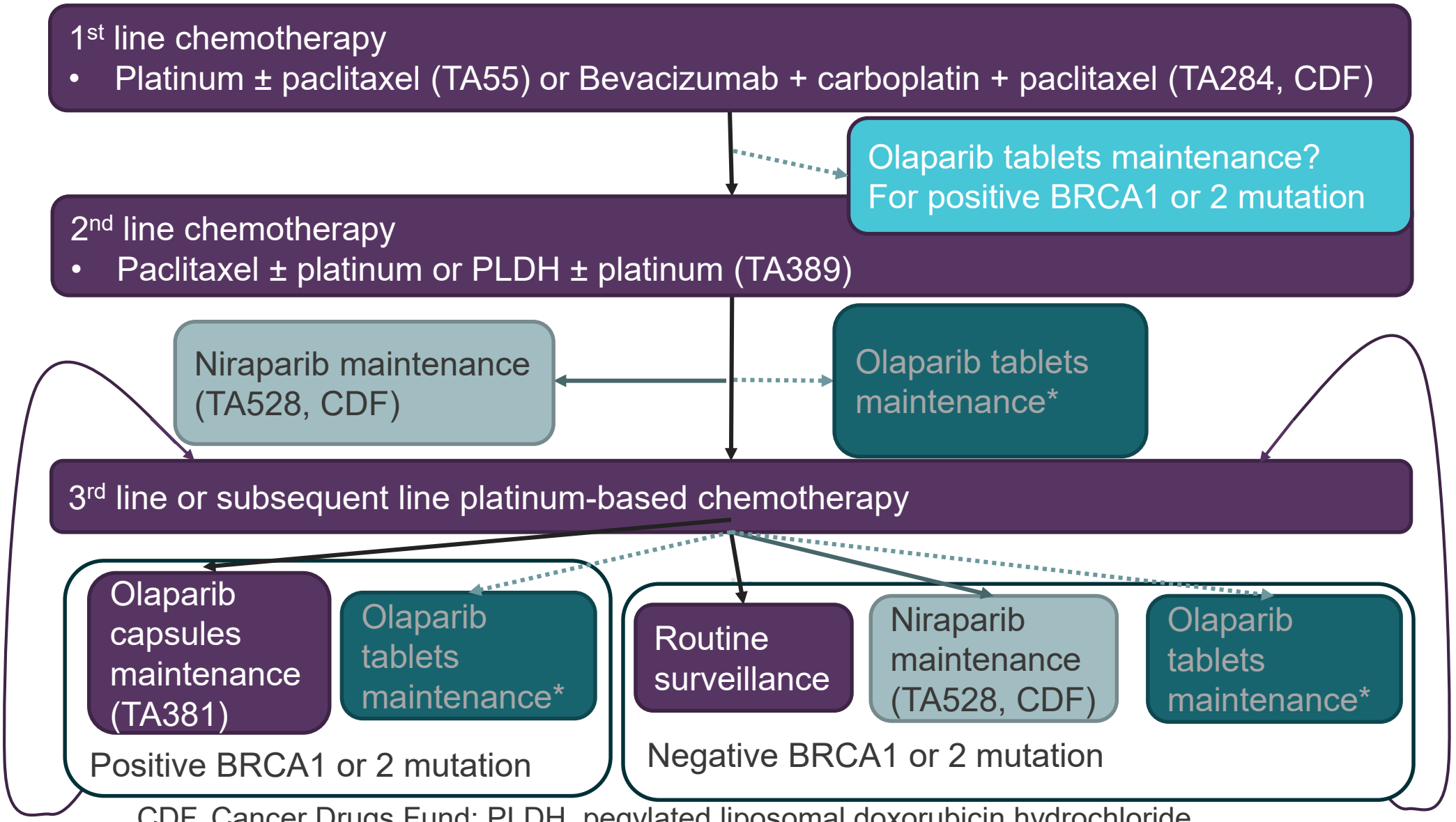
Stopping treatment at 2 years

- The company's proposed marketing authorisation indicates olaparib should stop after 2 years and should only continue if there is evidence of residual disease and patients are likely to derive further benefit.
- In SOLO1 18.1% of patients were in partial response and therefore had residual disease after first-line platinum-based chemotherapy in the olaparib arm and XXX continued treatment after 2 years
- Positive CHMP opinion was issued on 26th April, but no 2 year stopping rule was included
- The number of patients continuing on olaparib after 2 years may affect the cost effectiveness

What percentage of UK patients are likely to continue treatment with olaparib beyond 2 years?

[redacted]

Management of advanced platinum-sensitive ovarian cancer



CDF, Cancer Drugs Fund; PLDH, pegylated liposomal doxorubicin hydrochloride

** ID1296 Olaparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer appraisal currently paused*

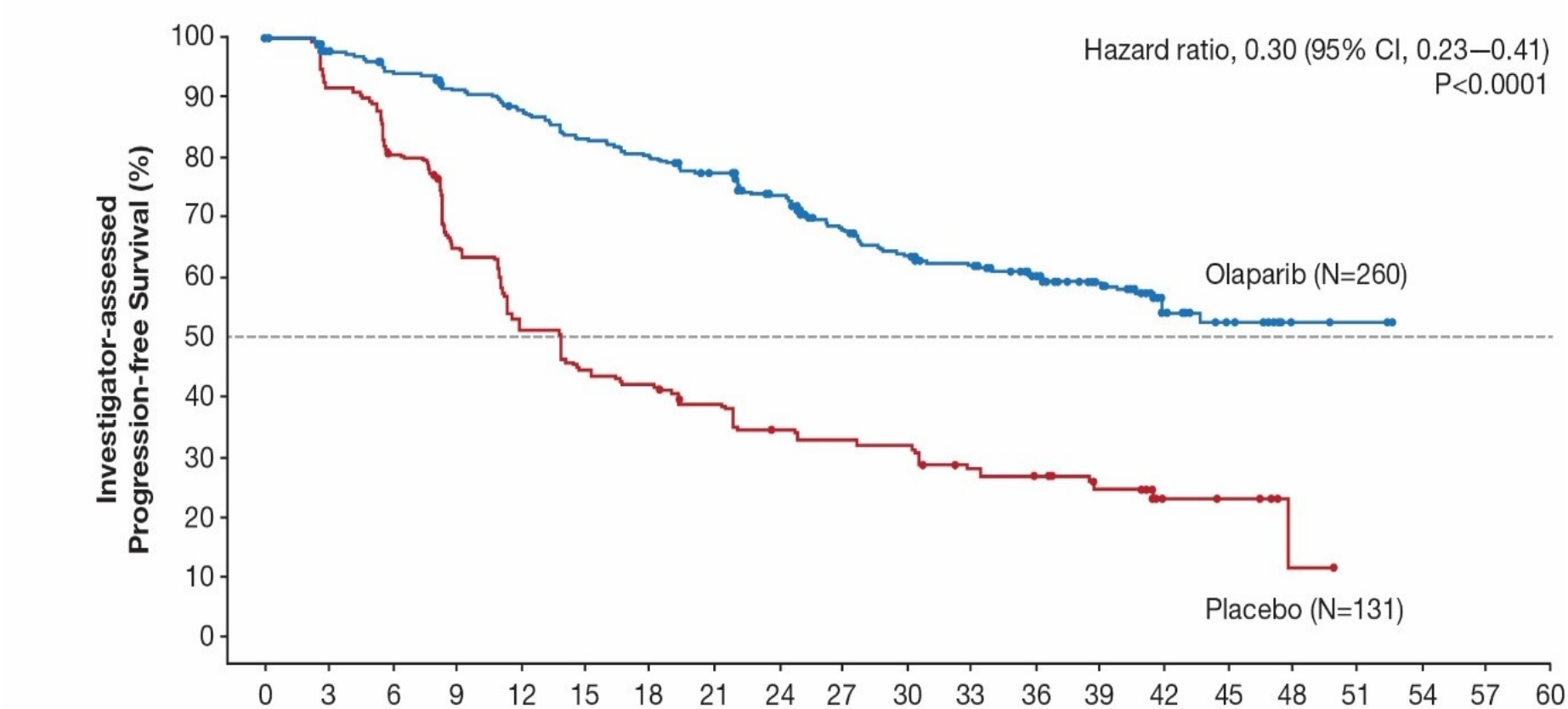
Patient and carer perspectives (Target Ovarian Cancer, Ovarian Cancer Action)

- BRCA-mutated ovarian cancer has a considerable impact on Quality of Life
- As do surgery & chemotherapy (standard treatment) and hospital visits
- “It is like living on a cliff edge…Another 3 years… Will I live another 3 years?”
- Once disease recurs, women know that curative treatment is no longer an option
- Currently there is no first line maintenance treatment available
- Olaparib would be the first PARP inhibitor for first line treatment.
- Olaparib taken orally and at home, as a life extending treatment
- “Not as brutal as chemotherapy. Less side effects…live a relatively normal life…(Olaparib) has given me an additional 23 months of life …I wouldn’t have had.”

Clinical trial evidence – SOLO1

Trial design	RCT comparing olaparib (tablet formulation) with placebo (N=391) Treatment until disease progression or for up to 2 years. At 2 years patients with CR stopped treatment if the disease had not progressed. Those with evidence of residual stable disease could continue treatment Crossover not permitted. Subsequent therapy with platinum and PARP inhibitor as maintenance therapy permitted.
Population	People with newly diagnosed FIGO stage III or IV BRCA-mutated high-grade ovarian cancer after first-line platinum-based chemotherapy and one attempt at debulking surgery. At study entry 82% of patients were in complete response and 18% were in partial response.
Key results	**Primary endpoint PFS**: Statistically significant improvement in PFS (HR: 0.30 [95% CI 0.23, 0.41], p<0.0001) – at 50.6% data maturity Median PFS:13.8 months in the placebo arm and not reached in the olaparib arm but estimated to be at least 3 years longer than placebo. **Secondary endpoints:** **Second progression-free survival**: Median not reached in the olaparib arm and 41.9 months in the placebo arm; HR: 0.50 [95% CI 0.35, 0.72], p=0.0002 **Overall survival**: Median was not reached at 21% maturity; small numerical benefit, hazard ratio 0.95 (95% CI: 0.60 to 1.53; p=0.8903)

SOLO1 Progression-free survival Kaplan-Meier curves



No. at Risk																					
Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	111	88	45	36	4	3	0	0	0
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0

Source: Figure 4 of Company submission

[redacted]

SOLO1 Overall survival Kaplan-Meier curves

Source: Figure 2 of Company's clarification response; Figure 4 of ERG report

[redacted]

Clinical trial evidence – SOLO1

Key uncertainties

- The extent to which the PFS benefit will translate into an OS benefit.
  - Company: literature indicates that the relationship between PFS and OS is 1:1 or could be 1:>2 (Sundar et al., GOG-172 and JGOG-3016)
  - ERG: based on a recent systematic review - modest relationship between the HRs for PFS and OS and moderate association between the medians (Sjoquist et al.)

- In the absence of mature OS data the company used the effect on PFS2 (time from randomisation to second progression) for modelling OS i.e. this predicts the 1:1 relationship between OS and PFS2.
  Clinical experts: PFS2 is an accepted surrogate for OS in case of immature OS data
  ERG: literature suggest that this relationship is weaker.

[redacted]

Issue 4: Subsequent PARP inhibitor use in clinical practice

Background

- Company used data from SOLO1 for modelling subsequent PARP inhibitor use in the economic model (XXX in the olaparib arm and XXX in the placebo arm)
- ERG: subsequent PARP inhibitor use in the routine surveillance arm could be an underestimate because of the availability of niraparib (through the CDF) and olaparib later in the treatment pathway

Stakeholder's comments:

- PARP inhibitors are not routinely commissioned after second line platinum-based chemotherapy but may be in the future:
  - there is an ongoing NICE appraisal for olaparib after 2 lines of platinum-based therapy
  - niraparib is currently available through the Cancer Drugs Fund for this indication
- Currently UK patients only receive a PARP inhibitor once during the treatment pathway
- No evidence available on the effectiveness of retreatment with a PARP inhibitor
- In SOLO1 treatment with olaparib stopped at 24 months and did not continue until disease progression -> tumour sensitivity to PARP inhibitors might be retained after subsequent chemotherapy. This should be tested in a clinical trial

[redacted]

Real World Evidence - Edinburgh Ovarian Cancer Database

- Database containing more than 4000 people with ovarian cancer from South East Scotland since the mid 1980s
- Company used a subgroup of patients diagnosed between 2000-2019 to externally validate the outputs of its economic model for OS in routine surveillance arm
- All patients had BRCA mutated advanced ovarian cancer and 32.6% of patients had received a PARP inhibitor (olaparib, niraparib or rucaparib), either in routine clinical practice, or through PARP inhibitor trials
- Company: database demonstrates that if a patient with newly diagnosed advanced BRCAm ovarian cancer is able to remain relapse-free for more than 5 years after diagnosis- will be a very low probability of recurrence
- ERG: the patient characteristics between SOLO1 and the Edinburgh Database might differ, because the time of diagnosis is unknown in the two datasets. Also subsequent treatment use differs, because much of the data in the Edinburgh Database is from before the introduction of PARP inhibitors.

[redacted]

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   - What would be the treatment pathway if olaparib was recommended?
   - Is it reasonable to assume that people will receive a subsequent PARP inhibitor to the same extent as in SOLO1 trial?
4. The company uses the Edinburgh Ovarian Cancer Database to externally validate the modelled survival in the routine surveillance arm.
   - Does it reflect the population eligible for olaparib in the UK first line maintenance setting?
   - Would patients diagnosed today, with currently available treatments, have the same outcomes as in the database?

[redacted]

Key cost-effectiveness issues

1. The modelled overall survival does not reflect the clinical trial evidence from SOLO1
   - Is it reasonable to use a surrogate outcome, PFS2, to estimate long term OS in the routine surveillance arm instead of the available OS data from the trial?
   - Does the company's OS curve for routine surveillance have face validity?
   - Is the ERG's suggestion to use a sequential model likely to better predict the long-term survival benefit of olaparib?
2. Subsequent PARP inhibitor use in clinical practice:
   - The model structure does not allow exploration of different assumptions about the effectiveness of subsequent PARP-inhibitor use. Are the assumptions of the model regarding subsequent PARP inhibitor use appropriate?
3. Limitation in the model structure:
   - Does the 3 health state model adequately reflect the treatment pathway? Is the 4 health state model more appropriate for decision making, or is an alternative model structure needed, as advocated by the ERG?
4. Piecewise modelling approach to model PFS and OS:
   - Is it appropriate to use only the second half of the KM data for extrapolating PFS and OS?
   - Is the use of a piecewise modelling method justified?

[redacted]

Issue 8: Modelling OS in the routine surveillance arm and using PFS2 as a surrogate for OS

Background

- Company: SOLO1 OS estimates are unreliable - immaturity of data and confounding factors such as subsequent PARPi use
- Company: Used PFS2 data as a surrogate for OS in the routine surveillance arm
- ERG: concerns about the company's method - highlighted that OS data in the trial is real data, cannot be implausible and it is the most relevant data to model OS
- ERG: OS benefit for olaparib in the model is not supported by the clinical trial evidence
- ERG's exploratory analysis shows the ICER is very sensitive to changing assumptions around OS extrapolation and limiting the time horizon

Stakeholder comments

Comments from clinical experts:

- PFS2 is an accepted surrogate outcome for measuring benefit in maintenance trial where OS may lag behind PFS data by several years.
- The predicted difference between olaparib and routine surveillance seems reasonable

Comments from company:

- The modelled OS curve for routine surveillance is in line with real-word data from the Edinburgh Ovarian Cancer Database
- Extrapolating the current placebo OS curve would suggest that approximately 60% of patients would remain alive at 10 years in current UK clinical practice, which is clinically implausible as the current 5-year survival rate for this population is less than 20%

[redacted]

Issue 8: Modelling OS in the routine surveillance arm and using PFS2 as a surrogate for OS

Figure 1: Illustration of the modelling approach used by the company for modelling long-term PFS and OS benefit (overlaid with Kaplan-Meier data)

[redacted]

Issue 8: Modelling OS in the routine surveillance arm and using PFS2 as a surrogate for OS

Extrapolation of SOLO1 overall survival compared with Edinburgh Ovarian Cancer Database, subgroup analysis of patients diagnosed between 2000-2019

[redacted] Source: company response to TE, figure 1

Issue 8: Modelling OS in the routine surveillance arm and using PFS2 as a surrogate for OS

Scenario (using 3-state model and 3.5% discount rate)	ICER
Company's base case with the following assumptions used in the routine surveillance arm: • using OS KM data up to 24 months • then the relative effect of placebo versus olaparib, calculated from PFS2 KM data from SOLO1 applied to the parametric curve for olaparib up to 7 years • after 7 years all-cause mortality was used to extrapolate to a lifetime horizon (50 years)	£18,356
ERG exploratory analysis 1: Using SOLO1 OS data in both arms of the model and limit the time horizon to 45 months	£660,497
ERG exploratory analysis 2: Setting the rate of OS events equal in both arms after 2 years (termination of treatment with olaparib)	£27,877
ERG exploratory analysis 3: Exploratory analysis 2 + setting the time horizon to XXX years (when the olaparib OS curve crosses olaparib PFS curve), i.e. assuming no OS benefit for olaparib	£201,580

[redacted]

Issue 4: Subsequent PARP inhibitor use in clinical practice

Background

- Company's model uses evidence from SOLO1, where subsequent PARP inhibitor use following disease progression was XXX in the olaparib arm and XXXX in the placebo arm
- ERG considered that the estimate of subsequent PARP inhibitor use in the routine surveillance arm could be an underestimate because of the availability of niraparib (currently through the CDF) and olaparib later in the treatment pathway
- ERG couldn't assess the effect of changing assumptions around the use of subsequent PARP inhibitors because of limitations in the model structure -> unclear how changes to the assumptions would affect the ICER
- ERG suggests substantial changes to the model structure and the development of a sequential model

Stakeholder comments

- Assumptions in the model around subsequent PARP inhibitor use in SOLO1 are reasonable
- Company considered a sequential model but found there was insufficient data to populate it
- Company conducted additional scenario analyses as a response to consultation.
- ERG warned that changing the assumptions around subsequent PARP inhibitor use only changes the costs and does not affect the benefits generated by the model, which favors olaparib -> ICERs are underestimated

[redacted]

Issue 4: Subsequent PARP inhibitor use in clinical practice

Scenario (using 3-state model and 3.5% discount rate)	ICER
Base case: Subsequent PARP inhibitor use is modelled based on SOLO1	£18,445
Assuming that 51%* of patients in routine surveillance arm who progress will receive subsequent treatment with a PARP inhibitor (*estimated to be the maximum % of patients who would receive a subsequent PARP inhibitor)	£9,634
Removing the costs of subsequent PARP inhibitor (XXX) in the olaparib arm	£13,168

[redacted]

Issue 5: Limitation in the model structure

Background

- Company's model is a partitioned survival model with 3 health states (progression free, progressed disease and death)
- ERG: model structure over simplifies the treatment pathway, given that patients can experience multiple disease progressions.
- A sequential model would be more suitable for decision making including a different health state for each chemotherapy line and subsequent maintenance treatment
- Would require data to be used from multiple studies to populate the parameters, as data would need to be obtained for patients at each available therapy line
- The advantage of this model structure is that it could potentially produce estimates of OS that are closer to the data observed in SOLO1
- Changes to the model structure are likely to have a big impact on the ICER, difficult to assess the extent

[redacted]

Stakeholder comments

- Company submitted a 4-health state model, and added a PFS2 health state populated with PFS2 data from SOLO1. For extrapolation, an exponential distribution was used. A utility value of 0.68 was applied for the progression-free 2 health state (informed by TA 381)
- The ERG warned that OS is modelled in the same way as in the 3-health state model and the curves generated by both models do not reflect the clinical trial evidence

Company's base case (3.5% discount rate)	ICER
3-health state model	£18,356
4-health state model	£17,480

Issue 7: Piecewise modelling approach for modelling PFS and OS

Time point	Olaparib arm	Routine surveillance arm
Up to 24 months	Kaplan-Meier (KM) data from SOLO1	
Up to 7 years	Extrapolation based on 2nd half of KM curves, using log-logistic model	**PFS**: Extrapolation based on 2nd half of KM curve, using log-logistic model **OS**: Applied the relative effect of placebo versus olaparib calculated based on PFS2 KM data from SOLO1 to the parametric curve of the olaparib arm
After 7 years	All-cause mortality up to lifetime horizon	

- ERG highlighted that the company did not demonstrate that the empirical hazard changed at 2 years, when treatment stops, to justify its approach
- For illustration also see the figure on slide 17

[redacted]

Issue 7: Piecewise modelling approach to model PFS and OS

Stakeholder comments

- Company: the piecewise modelling is justified and aligned to approaches accepted by NICE in previous appraisals
- Company compared the goodness of fit of parametric models fitted to the full KM curve and fitted to the post-24 months period. The parametric models fitted to post 24-months period provided a superior fit to the data and a more reliable long-term extrapolation of survival
- The results show good agreement with real-world data from the Edinburgh Ovarian Cancer Database
- Looking at the KM curves, there was no change in the shape of the curves after treatment stopped at 2 years
- The 24-months time point is before the median follow-up for PFS of SOLO1, therefore there is enough data to support long term extrapolations
- Scenario analyses show that changing the piecewise modelling approach has small impact on the ICER

[redacted]

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration
2	Generalisability of SOLO1 to UK clinical practice	Response rates observed in SOLO1 are reflective of UK clinical practice	Results of SOLO1 trial are generalisable to UK clinical practice
3	FIGO stage II disease could be included in advanced ovarian cancer	The anticipated MA will not include FIGO stage II ovarian cancer	FIGO stage II disease will not be considered as part of the appraisal
6	Discount rates: Company presented base case results using non-reference case discount rates of 1.5% for costs and benefits	Olaparib could be curative in some people. Real-world survival data suggests that if a patient is relapse-free for more than 5 years after diagnosis, the disease may not recur	Olaparib OS data is too immature for it to be considered curative
9	Company used mean dose of olaparib from SOLO1 in the model instead of the recommended dose in the marketing authorisation.	Tablets are 100mg and 150mg; so this may not have a major impact on cost if price is per tablet. However dose interruptions would potentially lead to fewer tablets being used/reduced cost	Given that the price per tablet of olaparib is the same regardless of dose, in practice the cost per day of treating a patient on a reduced dose is the same as treating a patient on a full dose of olaparib. Therefore, the model should be based on whole tablets rather than average cost per milligram

[redacted]

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