NICE National Institute for Health and Care Excellence

Rucaparib for maintenance treatment of recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy

Lead team presentation

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Company: Clovis Oncology
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Key clinical issues

1. Is ARIEL3 broadly representative of clinical practice?

2. Rucaparib increased progression-free survival (PFS) in ARIEL3 but overall survival (OS) data are immature and median OS has not been reached

   - is it appropriate to use the olaparib trial Study 19 to predict OS for rucaparib? Is there a class effect for PARP inhibitors?
   - are the populations of ARIEL3 and Study 19 (olaparib) broadly comparable?

3. What are the most relevant populations for the decision problem?

   – is it appropriate to focus on the ITT population or to consider subgroups based on BRCA mutation status and line of therapy, and incorporate different efficacy estimates into the modelling?

4. For the comparison of rucaparib with olaparib in the BRCAm 3L+ population for whom NICE currently recommends olaparib:

   – is the company's assumption of clinical equivalence in PFS between rucaparib and olaparib appropriate?

[redacted]

Rucaparib

Marketing authorisation	Maintenance treatment of adults 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
Administration & dose	Administered orally Dose: 600mg (2x300mg) taken twice daily (1,200mg per day)
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
Commercial arrangements	Patient Access Scheme (PAS) approved by Department of Health

Current NICE recommendations for PARPi

<u>Current indication</u> - maintenance treatment after second and subsequent line chemotherapy:

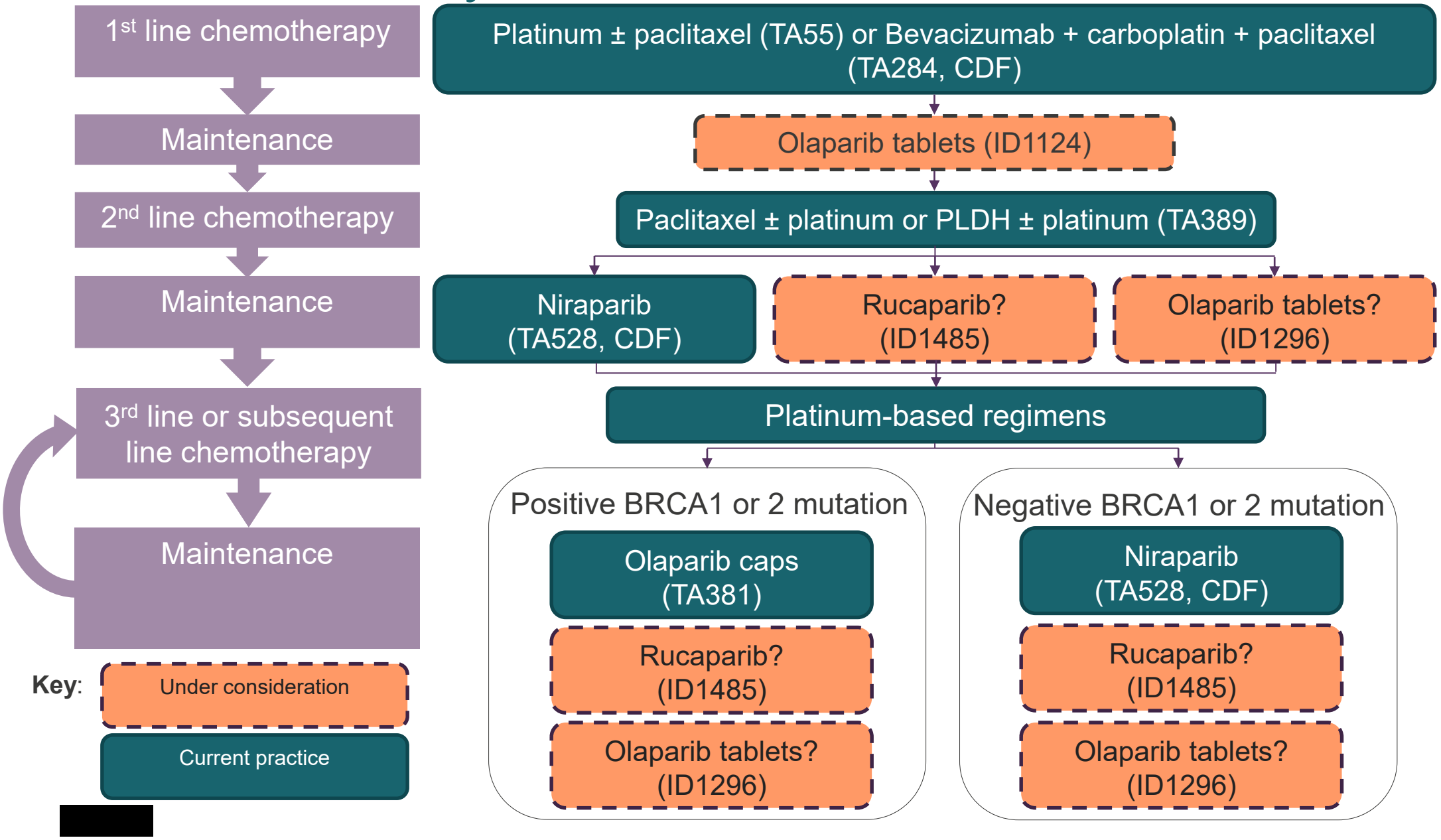
- TA 381 recommends olaparib capsules for adults with BRCA mutation-positive disease who have had 3 or more courses of platinum based chemotherapy
  - appraisal of olaparib tablets after 2 or more lines of platinum currently in progress (ID1296)
- TA 528 recommends niraparib for use within the CDF after 2 or more rounds of platinum; recommendations exclude BRCA mutation-positive population who have received 3 or more previous lines of chemotherapy and are eligible for olaparib capsules

Maintenance treatment after first line chemotherapy:

- Olaparib tablets following first line platinum chemotherapy was considered at the May committee meeting (ID1124)

[redacted]

Management of advanced platinum-sensitive ovarian cancer as of July 2019



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

Patient and carer perspectives (Target ovarian cancer, Ovacome)

- Ovarian cancer negatively impacts many aspects of life (self-esteem, physical and mental wellbeing, body image, mental health…)
- Surgery can have long term effect on abdominal organs and quality of life
- Devastation, shock, disbelief and fear are commonly experienced emotions
- The risk of developing resistance to platinum is high, and treatment for platinum-resistant disease is extremely limited as well as for recurrent disease
- Women are keen to consider options that may extend their time between recurrences, such as rucaparib – Living under the shadow of ovarian cancer and not knowing when the disease will recur can be emotionally draining and debilitating and lead to a lot of anxiety
- Oral treatments reduce hospital visits and financial burden in terms of travel time and potential unpaid leave
- Currently no PARP inhibitor is routinely available second line (only niraparib through CDF)
- " I'm 15 months and still going with rucaparib… delighted with the results and good quality of life on the drug… good break from chemo and most importantly prolonging my life"

Clinical trial evidence – ARIEL3

Trial design	Randomised controlled trial comparing rucaparib with placebo (N=564) Patients had treatment until progression or discontinuation due to other reasons
Population	Adults with platinum-sensitive, high-grade serous or endometrioid ovarian primary peritoneal or fallopian tube carcinoma who received 2 or more platinum-based chemotherapy regimens and had a complete or partial response to the last regimen • **66%** were in **partial** response and **34%** in **complete response** • **63%** of patients had **2 lines (2L)** of platinum; **37%** had **3 or more (3L+)** • **35%** had a **BRCA mutation** (23% germline; 10% somatic) • [redacted]**%** of patients in the placebo arm had a **subsequent PARPi after progression**
Key results	**Primary endpoint**: **PFS as assessed by investigator,** statistically significant improvement in PFS (HR 0.36 [95% CI 0.30,0.45] p<0.0001) Median PFS: 10.8 months in the rucaparib arm and 5.4 months in the placebo arm **Secondary and exploratory endpoints:** **Interim overall survival**: median OS not reached at data cut-off (15 April 2017) and no differences were observed in the KM estimates **Second progression-free survival (PFS2),** statistically significant improvement ([redacted]). Median [redacted] months in rucaparib arm; [redacted] months in placebo arm

[redacted]

ARIEL3 Progression-free and overall survival

Population	n rucaparib/ n placebo	Median PFS, months (95% CI)		HR (95% CI)
		rucaparib	placebo	
ITT	375/189	10.8 (8.3,11.4)	5.4 (5.3,5.5)	0.36 (0.30,0.45)
BRCA	130/66	16.6 (13.4,22.9)	5.4 (3.4,6.7)	0.23 (0.16,0.34)
BRCA 2L	77/41	[redacted]	[redacted]	[redacted]
BRCA 3L+	53/25	NR	NR	[redacted]
Non-BRCA	245/123	[redacted]	[redacted]	[redacted]

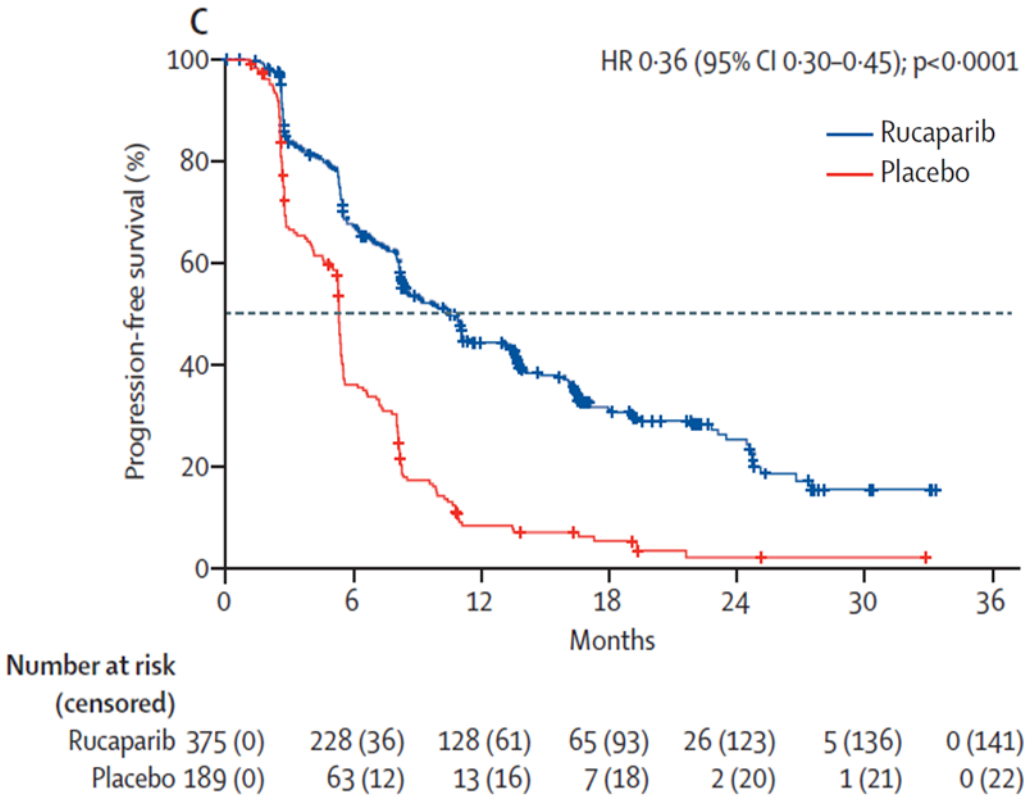
		Overall survival, Events n (%)		HR (95% CI)
ITT	375/189	81 (21.6)	42 (22.2)	[redacted]
BRCA	130/66	[redacted]	[redacted]	[redacted]
BRCA 2L	77/41	[redacted]	[redacted]	[redacted]
BRCA 3L+	53/25	NR	NR	[redacted]
Non-BRCA	245/123	[redacted]	[redacted]	[redacted]

At data cut-off (15 April 2017), median OS was not reached. NR: Not reported

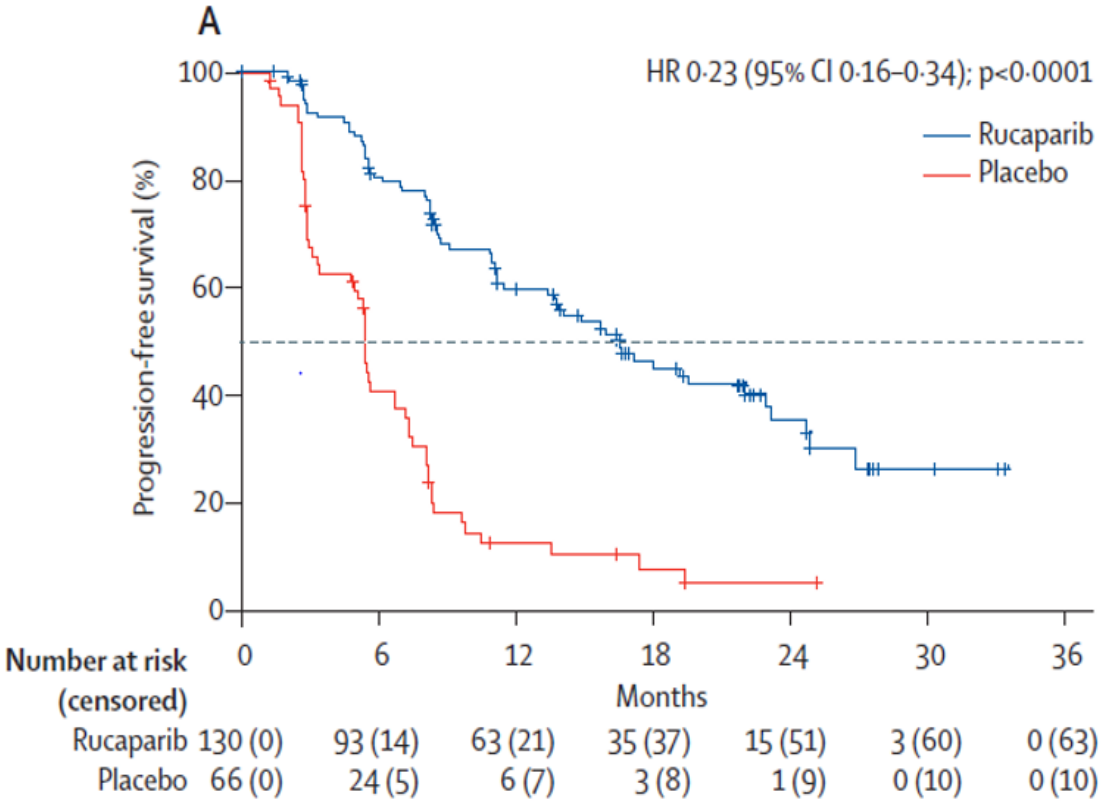
[redacted]

ARIEL3 Progression-free survival Kaplan-Meier curves: ITT and BRCA cohort

ITT



BRCA cohort



Source: Figure 4 of company submission

[redacted]

ARIEL3 Interim overall survival Kaplan-Meier curves: ITT and BRCA cohort

ITT

BRCA cohort

Source: Figure 23 and Figure 21 of appendix L of company submission

Issue 2: Clinical trial evidence ARIEL3 – Generalisability to UK clinical practice

Background

- BRCA group of ARIEL3 includes **germline** and **somatic BRCA mutations**→ Slightly different from clinical practice which would not include **somatic** mutations as **testing not routinely available**
- ERG: Patients were slightly younger (mean age:61) and had better performance status. More patients had prior bevacizumab (22%) than expected in clinical practice

Stakeholder comments

- ARIEL3 is **generalisable to UK practice** according to clinical experts
- Importantly, ARIEL3 did not restrict extent of residual disease at study entry
- **Magnitude of benefits** of PARPi is **similar in germline and somatic mutations**
- Around **20%** have germline or somatic **BRCA mutations in UK** - proportion with somatic mutations is small (6-7%)
- Efficacy in ARIEL3 non-BRCA group is probably **conservative** compared to clinical practice as it is a 'pure' group and doesn't include somatic BRCA mutations
- **ERG**: ARIEL3 differs from clinical practice in terms of proportion with BRCA mutation (20% in clinical practice vs 35% in trial) – rucaparib efficacy may be overestimated in ITT population compared to its expected efficacy in clinical practice

[redacted]

Issue 2: Clinical trial evidence – comparability of ARIEL3 and Study 19

Background

Differences between ARIEL3 and Study 19 in terms of **trial design and patients characteristics**:

- Phase III vs Phase II,
- BRCA status was a stratification factor at randomisation in ARIEL3 but confirmed retrospectively in Study 19
- Higher proportion of patients in later treatment lines in Study 19 (patients in 2L: 63% in ARIEL3 vs 46% in Study 19)

Stakeholder comments

- **Experts:** more promising results expected from ARIEL3 because of higher proportion of patients in earlier treatment lines
- **ERG:** more patients had a BRCA mutation in Study 19 (50%) than ARIEL3 (35%). Olaparib efficacy in Study 19 ITT is likely to be overestimated compared to clinical practice
- Also, using Study 19 OS for ITT population of rucaparib will overestimate the rucaparib OS
- Therefore, ERG doesn't consider Study 19 ITT population to be comparable to ARIEL3 or representative of clinical practice – but analyses by BRCA subgroups overcome this issue

[redacted]

Olaparib evidence

Study 19 (n=265)	
Study design	Randomised, double-blind, placebo-controlled, median follow-up 78 months
Population	Adult patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer who have received ≥2 platinum-based chemotherapies and had a response to their most recent platinum-based regimen.
Patients characteristics (vs ARIEL3)	• 55% in partial response and 45% in complete response (66%/34% in ARIEL3) • 46% were in 2L (63% in ARIEL3) • 50% had BRCA mutation (35% in ARIEL3) • 13.5% in placebo arm had subsequent PARPi after progression ([redacted]% in ARIEL3) • BRCA status was confirmed retrospectively (randomisation factor in ARIEL3)
Intervention	Olaparib capsules 800mg/day
Key results	Primary endpoint median PFS: 8.4 months with olaparib vs 4.8 months with placebo (HR 0.35 [95% CI 0.25-0.49] p<0.001) Secondary endpoint median OS: 29.8 months with olaparib vs 27.8 months with placebo (HR 0.73 [95% CI 0.55-0.96]), although did not meet threshold for statistical significance (p<0.0095)

SOLO2 (n=295)
SOLO2 is another randomised controlled trial assessing olaparib tablets vs placebo, in adult patients with BRCA mutations exclusively. Median follow-up 22 months.

[redacted]

Issue 1: Immature overall survival data in ARIEL3

Background

- 88% still alive in the ITT population of **ARIEL3** at data cut-off → OS data are very **immature** and not used in model
- The extent to which PFS benefits will translate into OS benefit is unclear
- Company used **OS data** from **Study 19** which has over **6 years follow-up**
- ERG: Study 19 provides the **most robust data available** but limited evidence to show whether assumption of equivalence between rucaparib and olaparib is conservative or optimistic and what effect the **naïve use of Study 19 OS compared to ARIEL3 PFS** will have in the different populations

Stakeholder comments

- Clinical experts believe that **PARPis** broadly have the **same efficacy**
- Survival in ARIEL3 is expected to be longer than in Study 19, because **rucaparib** in ARIEL3 was used in **earlier treatment lines** than olaparib in Study 19 → a more promising PFS is already observed
- **Crossover in ARIEL 3** will be greater than in previous trials of olaparib and niraparib as availability of PARPi is greater → will reduce magnitude of difference between rucaparib and placebo
- **Greatest benefit** observed with PARPi is in **BRCA mutated patients** (germline/somatic)
- For OS, differences between 2L and 3L are less clear cut. Magnitude of homologous recombination deficiency (HRD) will be responsible for the biggest OS difference and more likely to be tumour- rather than time-dependent

[redacted]

Issue 3: Clinical trial evidence ARIEL3 – most relevant populations?

Background

- Company submitted results for **ITT** and **BRCA subgroup (including BRCA 3L+** for the comparison of rucaparib and olaparib)
- At clarification, ERG requested additional analyses for **non-BRCA** and **BRCA 2L** populations because the effectiveness and comparators differ in these subgroups
- Company highlighted that these were post-hoc analyses, based on small sample sizes → **high uncertainty around the effectiveness** in these subgroups

Stakeholder comments

- **Differences in efficacy** between BRCA and non-BRCA groups according to clinical experts
- But **non-BRCA patients** have capacity to **gain long-term benefit** from PARPis, as shown in Study 19
- **PARPis** will become **available earlier** in treatment pathway so won't be given often in BRCA 3L+ group
- Rucaparib showed effectiveness for any patient responding to platinum-based therapy (ITT population). Isolating BRCA 3L+ is not of value as benefit is seen after 2L therapy
- ERG considers that **analyses by BRCAm status** and **treatment lines are necessary** to make an informed decision
- Comparator in BRCA 3L+ is olaparib capsules, comparing rucaparib to routine surveillance in this subgroup as part of the ITT analysis is inappropriate → will provide **inaccurate cost-effectiveness results**

[redacted]

Issue 4: Rucaparib vs olaparib in BRCA 3L+ cohort

Background

- Network meta-analysis **(NMA)** and matching adjusted indirect comparison **(MAIC) conducted** to assess **comparative effectiveness** of **rucaparib and olaparib** in BRCA 3L+ cohort
- **No statistically significant differences** in PFS between rucaparib and olaparib
- **Direction of effect varied** according to whether Study 19 or SOLO2 was used for olaparib (results favoured olaparib if using Study 19; rucaparib if using SOLO2) → according to experts this is due to differences in populations and formulations (capsules used in study 19, being phased out in favour of tablets and SOLO2 included only BRCA positive patients)
- Company **assumed clinical equivalence in PFS** between **rucaparib and olaparib** for the BRCA 3L+ population
- The analysis is reduced to a **cost-minimisation**

Stakeholder comments

- Clinical experts: assuming PFS equivalence between rucaparib and olaparib **is reasonable**
  - **Study 19** is **closer to rucaparib data** (SOLO2 included BRCA patients only)
- ERG considers that **assuming PFS equivalence** between rucaparib and olaparib is **likely to be optimistic** - lack of statistical significance is not evidence of no difference in treatment effect

[redacted]

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   - is it appropriate to use the olaparib trial Study 19 to predict OS for rucaparib? Is there a class effect for PARP inhibitors?
   - are the populations of ARIEL3 and Study 19 (olaparib) broadly comparable?

3. What are the most relevant populations for the decision problem?

   – is it appropriate to focus on the ITT population or to consider subgroups based on BRCA mutation status and line of therapy, and incorporate different efficacy estimates into the modelling?

4. For the comparison of rucaparib with olaparib in the BRCAm 3L+ population for whom NICE currently recommends olaparib:

   – is the company's assumption of clinical equivalence in PFS between rucaparib and olaparib appropriate?

[redacted]

Key cost-effectiveness issues

1. The company and ERG both used PFS data from ARIEL3 in the model and used olaparib OS data from Study 19 to calculate the rate of death post-progression and OS for rucaparib:

- Company used OS (Study 19) minus PFS for olaparib (Study 19). This implies the same rate of death after progression as olaparib, and therefore the OS benefit of rucaparib includes the PPS benefit of olaparib (Study 19) and the PFS benefit of rucaparib (ARIEL3)
- ERG used OS (Study 19) minus PFS (ARIEL3). This implies a higher rate of death on progression than olaparib, and no additional benefit in OS of rucaparib compared to benefits observed for olaparib
  - is it appropriate to assume the same PPS across PARPi treatments?
  - to model OS, the company's approach uses PFS from 2 studies with different patient populations in the same calculation, and implies a ratio of PFS:OS benefit on rucaparib of [redacted]. Is this reasonable?

2. The company estimated costs for subsequent therapies based on ARIEL3, however given the immaturity of ARIEL3 OS data and that Study 19 OS data are used in the model, the ERG prefers the subsequent treatment distribution from Study 19

  - which study best reflects UK clinical practice in terms of the subsequent therapies used?

3. The base case and key scenario ICERs are above the range normally considered a cost effective use of NHS resources (20-30K/QALY)

4. ICERs in subgroups are in opposite direction to clinical efficacy and HRs from ARIEL3 trial

[redacted]

Cost-effectiveness model

Model type	Partitioned survival model
Population	Maintenance treatment of adults with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy
Intervention	Rucaparib
Comparators	- Routine surveillance (ITT, non-BRCA and BRCA 2L populations) - Olaparib (BRCA 3L+ population)
Time horizon	30 years
Model cycle	1 month
Discount rates	3.5% for both health and cost outcomes
Utility values	EQ-5D data from the ARIEL3 trial with UK tariff applied
Perspective	NHS and PSS

Issue 5: Approach to calculating post-progression survival

Background

- In the model, PFS is from ARIEL3; OS from Study 19
- **Company** calculated PPS as the **difference between Study 19 OS and Study 19 PFS**, and then used Study 19 PPS outcomes in the model, assuming **PPS outcomes** for rucaparib are **equivalent to olaparib** in Study 19
- **ERG:** company method unconventional as the calculation of PPS is disconnected from the PFS informing the analyses. ERG prefers to calculate PPS as the **difference between Study 19 OS and ARIEL3 PFS**
- **Company**: ERG's approach inappropriate as it produces shorter PPS outcomes for rucaparib, as PFS in ARIEL3 is longer than in Study 19
- Company's approach results in an **"implied" PFS:OS ratio of** [redacted] which ERG considers is very **optimistic**, as the ratio of 1:2 was considered optimistic by committee in appraisals of niraparib (TA528) and olaparib (GID1296)

Stakeholder comments

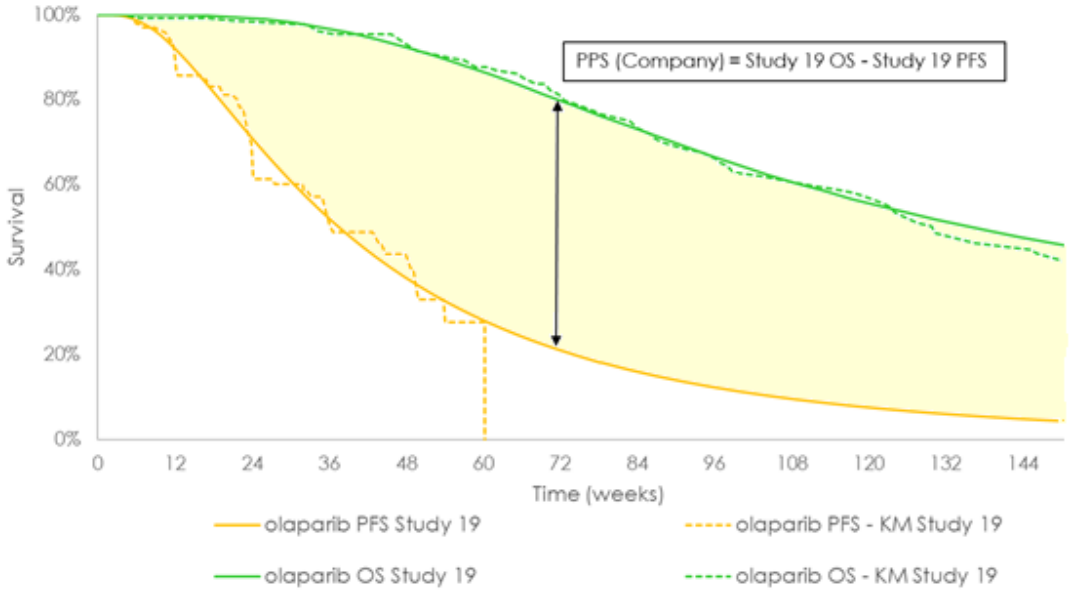
- **Company** tried to **avoid PFS:OS** ratio and underlines that large ratio is due to long tail of OS splines distribution
- **Clinical experts** commented that PFS in ARIEL3 may appear longer than in Study 19 → might be due to higher proportion of patients in later treatment lines in Study 19
- Clinical experts highlighted that proportion of patients having **PARPi post progression** in placebo arm **will increase**
- **OS curve** tail in Study 19 **flattens after 3 years**, and 11% of patients (BRCA and non-BCRA) are **long-term responders**. Rucaparib is expected to behave similarly
- Clinical experts believe that using an **OS:PFS ratio may not reflect** the long-term survival observed
- **ERG doesn't endorse** use of **PFS:OS ratio** but considers it **informative** to understand what the company's approach results in

[redacted]

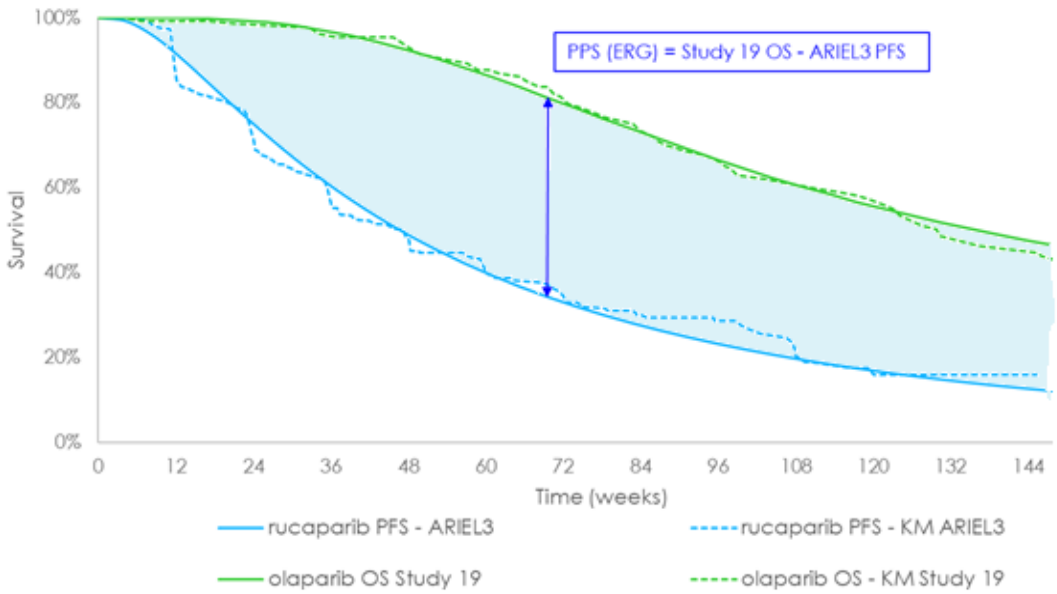
Issue 5: Approach to calculating post-progression survival

- Graphs based on ITT population (same approach used for non-BRCA and BRCA 2L)
- For BRCA 3L+, PFS and OS equivalence between rucaparib and olaparib was assumed - PPS was calculated as difference between Study 19 OS and ARIEL3 PFS

Company's approach



ERG's approach



- Company's approach: the rate of disease progression for rucaparib is the same as for olaparib, PPS is calculated as the difference between Study 19 OS and Study 19 PFS
- ERG's approach: PPS should not be disconnected from PFS informing the analyses. PPS is calculated at the difference between Study 19 OS and ARIEL3 PFS

- **Using the ERG's approach increases the ICER, e.g. by about £6,000 for the ITT population**

[redacted]

Issue 7: Subsequent therapy cost calculation

Background

- **Company** used subsequent therapy data from **ARIEL3** to calculate subsequent therapy costs
- OS is from **Study 19** → **ERG** considers it would be more appropriate to use the subsequent therapies from Study 19

Stakeholder comments

- **Availability of treatments** for progressed patients **can be different** between the UK and other parts of the world
- Subsequent therapy data used in the model reflects **only treatments available on the NHS**
- Using Study 19 distribution instead of ARIEL3 distribution **increases** the ICER for the **non-BRCA population**

[redacted]

Issues resolved after technical engagement

Issue number	Summary	Stakeholder responses	Technical team consideration
6	Plausibility of the company's extrapolation of survival for non-BRCA and BRCA 2L groups	**Non-BRCA:** company's approach using generalised gamma distribution generates a large difference between mean PFS and mean TTD, which is not plausible as clinical experts advised that most patients discontinue treatment on progression of disease. ERG's preference to use lognormal distribution results in a modelled PFS better aligned with modelled TTD **BRCA 2L:** company's choice of lognormal distribution results in some patients being progression-free at 10 years. Based on data from Study 19, the experts considered this was more plausible than the ERG's use of the Weibull distribution which results in all patients having progressed at 10 years	**Non-BRCA:** ERG's approach (lognormal) is most appropriate because it is more aligned with TTD. **BRCA 2L:** Company's approach (lognormal) is most appropriate because it is more aligned with what was observed in Study 19 at 6 years.

[redacted]

Cost effectiveness results - ITT

Scenario	Incremental costs (£)	Incremental QALYs	Cumulative ICER vs Routine surveillance
Company's base case	[redacted]	[redacted]	£36,319/QALY
ERG's preferred assumptions			
ERG correction of minor errors	[redacted]	[redacted]	£37,832/QALY
PPS modelled as difference between Study 19 OS and ARIEL3 PFS	[redacted]	[redacted]	£43,898/QALY
Subsequent therapies from Study 19	[redacted]	[redacted]	*£43,669/QALY*
PFS off maintenance costs for routine surveillance	[redacted]	[redacted]	*£44,787/QALY*
Remove administration costs for oral therapies	[redacted]	[redacted]	£43,292/QALY
Extension of time horizon to 50 years	[redacted]	[redacted]	*£41,103/QALY*
Technical team's preferred assumptions*	[redacted]	[redacted]	£42,175/QALY

*Assumptions in italic were not included in the technical team's preferred assumptions because of modest impact on ICER

[redacted]

Cost effectiveness results – Non-BRCA

Scenario	Incremental costs (£)	Incremental QALYs	Cumulative ICER vs Routine surveillance
Company's base case	[redacted]	[redacted]	£24,037/QALY
ERG's preferred assumptions			
ERG correction of minor errors	[redacted]	[redacted]	£25,157/QALY
Use of the lognormal distribution for PFS extrapolation	[redacted]	[redacted]	£30,276/QALY
PPS modelled as difference between Study 19 OS and ARIEL3 PFS	[redacted]	[redacted]	£33,861/QALY
Subsequent therapies from Study 19	[redacted]	[redacted]	£42,708/QALY
PFS off maintenance costs for routine surveillance	[redacted]	[redacted]	*£43,792/QALY*
Remove administration costs for oral therapies	[redacted]	[redacted]	*£42,373/QALY*
Extension of time horizon to 50 years	[redacted]	[redacted]	*£38,035/QALY*
Technical team's preferred assumptions*	[redacted]	[redacted]	£41,288/QALY

*Assumptions in italic were not included in the technical team's preferred assumptions because of modest impact on ICER

[redacted]

Cost effectiveness results – BRCA 2L

Scenario	Incremental costs (£)	Incremental QALYs	Cumulative ICER vs Routine surveillance
Company's base case	[redacted]	[redacted]	£42,372/QALY
ERG's preferred assumptions			
ERG correction of minor errors	[redacted]	[redacted]	£42,957/QALY
Use of the Weibull distribution for PFS extrapolation**	[redacted]	[redacted]	*£38,836/QALY*
PPS modelled as difference between Study 19 OS and ARIEL3 PFS	[redacted]	[redacted]	£44,479/QALY
Subsequent therapies from Study 19	[redacted]	[redacted]	£45,494/QALY
PFS off maintenance costs for routine surveillance	[redacted]	[redacted]	*£46,444/QALY*
Remove administration costs for oral therapies	[redacted]	[redacted]	*£44,926/QALY*
Extension of time horizon to 50 years	[redacted]	[redacted]	*£41,831/QALY*
Technical team's preferred assumptions*	[redacted]	[redacted]	£56,994/QALY

[redacted]

*Assumptions in italic were not included in the technical team's preferred assumptions because of modest impact on ICER ** lognormal distribution is technical team's preferred assumption as this was considered more clinically plausible than Weibull at technical engagement (see slide 23)

Cost effectiveness results – BRCA 3L+

Scenario	Incremental costs (£)	Incremental QALYs	ICER vs olaparib (£/QALY)
Company's base case	[redacted]	[redacted]	Rucaparib dominated by olaparib
ERG's preferred assumptions			
	Total costs rucaparib	**Total costs olaparib**	**Incremental costs**
ERG correction of minor errors	[redacted]	[redacted]	[redacted]
Remove administration costs for oral therapies	[redacted]	[redacted]	[redacted]

[redacted]

Key cost-effectiveness issues

1. The company and ERG both used PFS data from ARIEL3 in the model and used olaparib OS data from Study 19 to calculate the rate of death post-progression and OS for rucaparib:

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- ERG used OS (Study 19) minus PFS (ARIEL3). This implies a higher rate of death on progression than olaparib, and no additional benefit in OS of rucaparib compared to benefits observed for olaparib
  - is it appropriate to assume the same PPS across PARPi treatments?
  - to model OS, the company's approach uses PFS from 2 studies with different patient populations in the same calculation, and implies a ratio of PFS:OS benefit on rucaparib of [redacted]. Is this reasonable?

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  - which study best reflects UK clinical practice in terms of the subsequent therapies used?

3. The base case and key scenario ICERs are above the range normally considered a cost effective use of NHS resources (20-30K/QALY)

4. ICERs in subgroups are in opposite direction to clinical efficacy and HRs from ARIEL3 trial

[redacted]

Committee decision making: CDF recommendation criteria