NICE National Institute for Health and Care Excellence

Olaparib with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer

Lead team presentation

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Key terms and abbreviations

Term/abbreviation	Definition
Olap+beva15	Olaparib with bevacizumab 15mg/kg maintenance treatment (technology under appraisal)
Beva15	Bevacizumab monotherapy delivered at the licensed dose of 15 mg/kg
Beva7.5	Bevacizumab monotherapy delivered at the reduced, non-licensed dose of 7.5 mg/kg
RS	Routine surveillance
PAOLA-1	Name of the company's pivotal trial (NCT02477644)
Platinum CT	Platinum chemotherapy (platinum-based compound or platinum-based therapy alone e.g. cisplatin or carboplatin)
PFS	Progression-free survival
OS	Overall survival
PFS2	Second progression-free survival
HRD-positive/HRD negative	People with and without homologous recombination deficiency respectively
BRCA-positive/BRCA-negative	People with and without BRCA 1/2 mutations respectively

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Other terms and abbreviations are explained in the slide notes

Disease background

- Ovarian cancer (OC) occurs in different parts of the ovary or fallopian tubes
- Classified from stage I to stage IV; advanced ovarian cancer falls within stages II and IV
  - Stage II: disease has grown outside the ovaries but is still within pelvic area
  - Stage III: locally advanced (has spread outside pelvis into abdominal cavity)
  - Stage IV: distant metastasis to other body organs has occurred
- 5-year survival 2013 to 2017 in England was 42.9% for all stages, 26.9% for stage III and 13.4% for stage IV disease
- Mutated inherited genes that increase the risk of ovarian cancer include those that lead to homologous recombination deficiency (HRD) and the cancer is described as HRD positive
- BRCA genes are the most well known of HRD-positive genes. They play a role in repairing DNA via homologous recombination, and mutations in the BRCA 1/2 genes result in HRD, so all patients who are BRCA-positive are HRD-positive. However some people who are BRCA-negative will also be HRD-positive as they have mutations in other genes in this pathway
- NICE recommend platinum CT in the first and second-line settings and platinum-based regimens are also used for 3rd and later lines of treatment
- Targeted therapies aimed at improving or maintaining response to platinum CT are also recommended by NICE throughout the treatment pathway, but most are only available via the CDF; the only targeted treatment currently available in routine commissioning is olaparib for relapsed, BRCA-positive OC after 3 or more courses of platinum CT

Key clinical issues

- What is the reasoning behind using PARPi early in the course of disease?
- Is this treatment more likely to prevent, or merely delay recurrence?
- If people do not progress after surgery and first line chemotherapy with bevacizumab followed by maintenance olaparib and bevacizumab (and do not require further treatment), at what stage might you be reasonably confident that the cancer would not recur?
- After that time, would they have the same lifespan as the general population?
- Immaturity of data/options for further data collection: Would further data collection in PAOLA-1 help resolve current uncertainties in long-term effect estimates?
- How great is the unmet need for new treatments for patients with HRD-positive disease that are in response (complete or partial) to first-line treatment?
- Given HRD-testing is not routinely done in the NHS, could olap+ beva15 be implemented?
- How robust is the PAOLA-1 HRD-positive subgroup data?
- The comparator in the trial does not align with current NHS practice, how is this best handled?

Patient and carer perspectives

"...Olaparib has given me a far better quality of life over the last 3 years, than all the other stages of my treatment. [...]The side effects are minimal compared to chemotherapy."

"after the initial diagnosis and first lot of treatment I thought there is just no way I can do that again. Chemotherapy is so tough."

"Yes there is a huge unmet need [...] We need treatments that stop it coming back. We need more alternatives to chemotherapy which is so gruelling."

"**2010** : Diagnosis...chemotherapy/ surgery; **2011/12** Relapse...chemotherapy; **2013** Relapse...second line surgery (including colostomy) chemotherapy/avastin; **2016** Relapse...chemotherapy; **2017** to present olaparib"

"I continue to work full time, have very few side effects, namely lowered [blood pressure], occasional nausea and sometimes my bowels are affected. All in all, as with Avastin, I continue to be [no evidence of disease], have a great quality of life and continue work full time"

" I couldn't access olaparib until the cancer came back, surely prevention is better"

"I'm not BRCA, everything seems targeted at those with a genetic mutation"

"what difference on a daily basis....apart from the first three months which was tough (side effects such as really bad nausea/fatigue etc.). I live a wonderful, manageable life."

"My Mum has BRCA [mutation] Lynparza [olaparib] makes a huge difference, chemo strips everything, even good cells it makes you feel ill, whereas tablets don't, they give you your life back [...] You don't have to have constant picc line in as that in its self is another fear as can cause problems [...] as her daughter it was wonderful to see my Mum back again as she was"

Olaparib

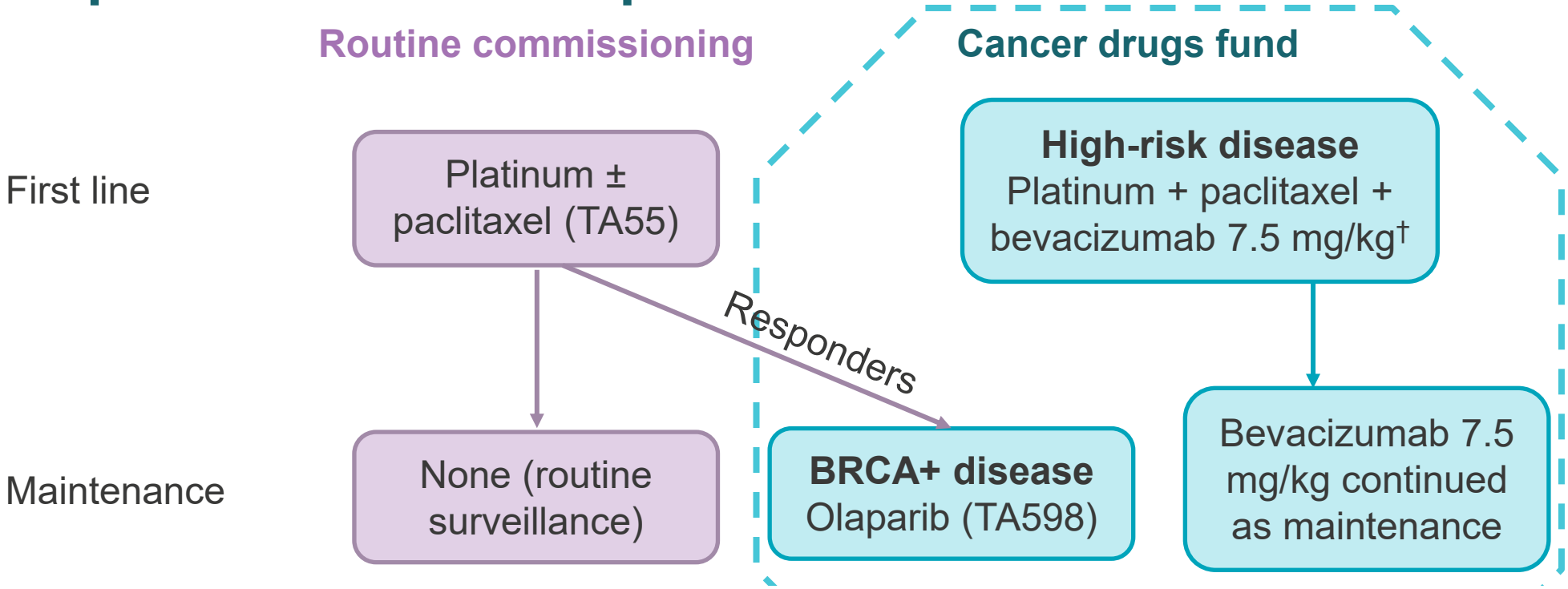
This appraisal considers the following **extension** to the current olaparib licence

Anticipated marketing authorisation	"Lynparza in combination with bevacizumab is indicated for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability"
Administration & dose	300 mg (2 x 150-mg tablets) **taken orally twice daily** (600 mg per day)
Mechanism of action	Poly-ADP-ribose polymerase (PARP) inhibitor which inhibits PARP proteins involved in DNA repair
Commercial arrangements	Patient access scheme (PAS) in place: simple discount that applies to all indications

Bevacizumab: current usage and proposal

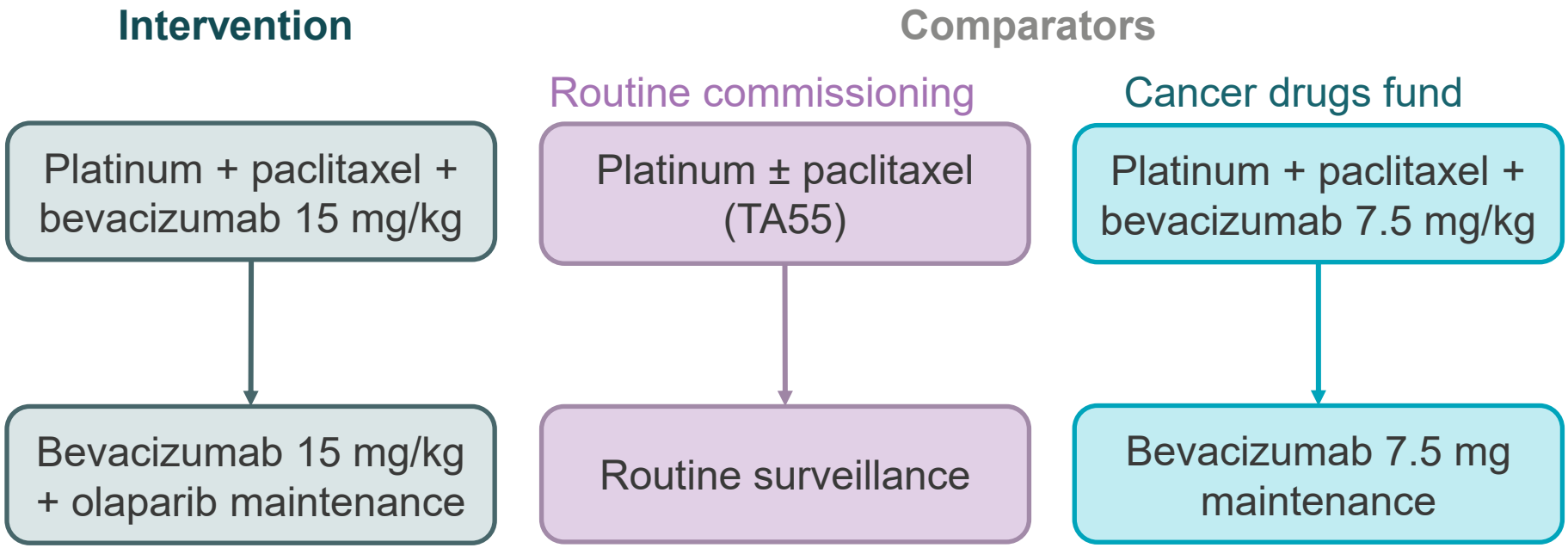
- Bevacizumab 15 mg/kg has a licence for first line treatment with platinum and paclitaxel for ovarian cancer for stages IIIB-IV. However, NICE TA284 (2013) issued negative guidance
- But first-line bevacizumab (combined with platinum), and maintenance treatment with bevacizumab at the lower, unlicensed dose 7.5 mg/kg is available via the 'old CDF' [pre-2016] only for: (1) FIGO stage III debulked but residual disease more than 1 cm, OR (2) Stage IV disease, OR (3) Stage III at presentation and requiring neo-adjuvant chemotherapy
- Those not eligible for bevacizumab via the CDF are treated with platinum combination chemotherapy alone, followed by routine surveillance, unless they are BRCA positive when they can receive olaparib maintenance after the platinum, via the CDF
- **Olaparib in combination with bevacizumab is suggested by the company for HRD positive disease only, which includes BRCA but also some other patients. A specific test is required for HRD, not currently used in the NHS.**
- **It includes only those patients who have responded to first line platinum *with* bevacizumab which is not routine for most people, and when given, is at a lower than the licensed dose in the NHS**

Current options for first line treatment and maintenance for patients with HRD-positive disease



- Current practice illustrated in figure above
  - Routine first line treatment for patients with HRD-positive disease is platinum CT alone
  - Some patients with high-risk disease (i.e FIGO stage III debulked but residual disease more than 1 cm, OR Stage IV disease, OR Stage III at presentation and requiring neo-adjuvant chemotherapy) are eligible for platinum CT with beva7.5 first line via CDF
- Olap+beva15 maintenance treatment (technology under appraisal) can only be offered to those who have responded to platinum CT+beva
- So for olap+beva15 to be implemented, a change to routine first-line treatment pathway is required – all HRD-positive patients would have to be offered platinum CT+beva first line, in order to select the responders that would go onto get olap+beva15 as maintenance

Scope intervention and comparators



- Figure illustrates intervention and comparators as defined in NICE scope
- Scope takes account of changes to first line treatment pathway that would occur if olap+beva15 is recommended
- Company assumption is that all of the first line therapy options are equally effective
- It argues that because of this, only the maintenance phase is relevant to decision making – company base case ICERs are therefore derived from its maintenance-only model
- However, company has also provided an alternative analysis called the 'Extended regimen analysis', which addresses the interventions and comparators as defined in the scope

Decision problem

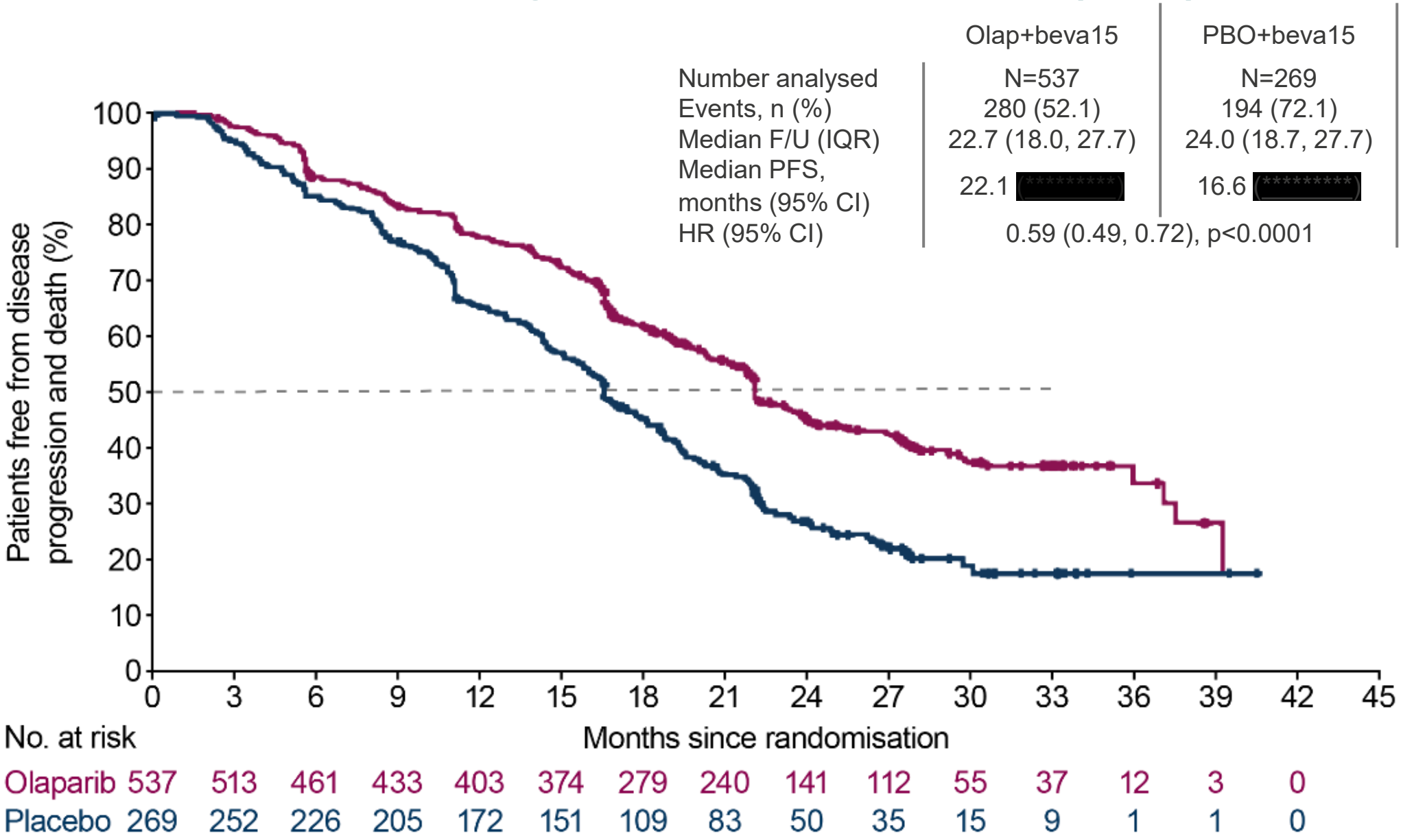
Company's definition of the decision problem reflected NICE scope with following exceptions

Scope population: Women with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer	Company's cost effectiveness results are specific to HRD-positive subgroup	Reflects anticipated marketing authorisation
Scope intervention: Platinum CT with Beva15 followed by Olap+Beva15 only in responding patients	Company presents cost effectiveness results for two different definitions of intervention: • maintenance analysis: Olap+beva15 (in patients in response to 1L Platinum CT with Beva15) • extended regimen analysis: Platinum CT with Beva15 followed by Olap+beva15 only in responding patients	Extended regimen analysis more closely aligned to scope
Scope comparators: (Main) Platinum CT followed by RS (Main); Platinum CT with Beva7.5 followed by Beva7.5 (Scenario)	Comparators in each of company's analyses differed: • maintenance analysis: (1) RS; (2) Beva7.5; (3) Beva15 • extended regimen analysis: (1) Platinum CT followed by RS; (2) Platinum CT with Beva7.5 followed by Beva7.5 maintenance in responding patients; (3) Platinum CT with Beva15 followed by Beva15 only in responding patients	Extended regimen analysis more closely aligned to scope; comparison with Beva15 not relevant to scope

Pivotal trial: PAOLA-1

Trial design	Randomised, maintenance olap+beva15 vs placebo + beva 15	
Population	Advanced (stage III / IV) ovarian cancer **who were in complete or partial response after first-line platinum-taxane chemotherapy with bevacizumab** (0 UK patients) • 22% partial response to first-line treatment in each arm, all other patients had no evidence of disease • 33% had BRCA mutation in each trial arm • 47% and 49% were HRD-positive in two arms	
Intervention/ comparator	Experimental arm	Control arm
	Olaparib 300 mg tablets twice daily for up to 2 years (n=537)	Matching placebo (n=269)
	Both arms	
	Bevacizumab 15 mg/kg every 3 weeks (Q3W) with chemotherapy (and continued after randomisation as maintenance therapy for up to 15 months **Unplanned crossover to other treatments (including PARPi) permitted at the investigators' discretion after treatment discontinuation**	
Outcomes	PFS (investigator-assessed; primary endpoint); PFS2; OS; TFST; TSST; TDT; Adverse effects of treatment; HRQoL	
Stratification factors	First-line treatment outcome at screening; BRCA status **(not HRD status)**	

PAOLA-1 results: progression-free survival (PFS) in ITT



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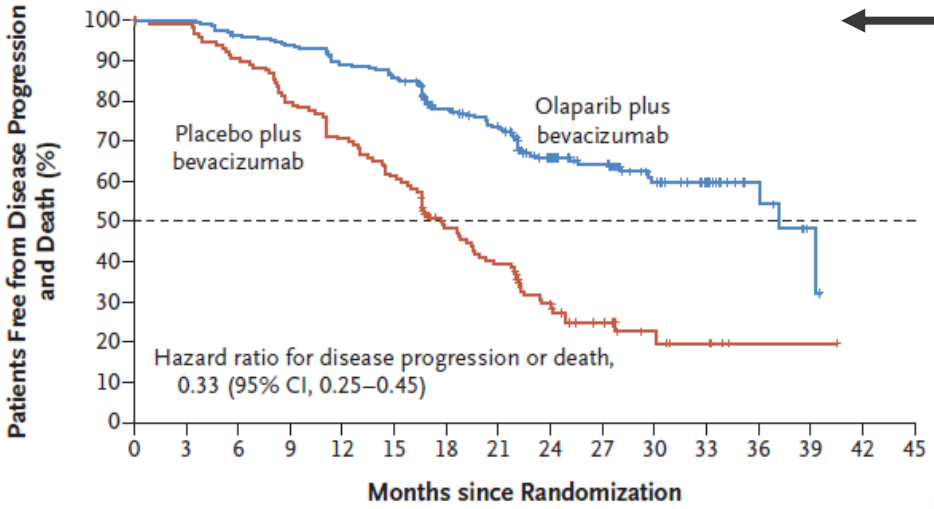
PAOLA-1 HRD-subgroup results: PFS

- HRD-positive subgroup results inform company's economic analyses
- ERG noted HRD subgroup results should be viewed as exploratory and interpreted with caution



No. at Risk

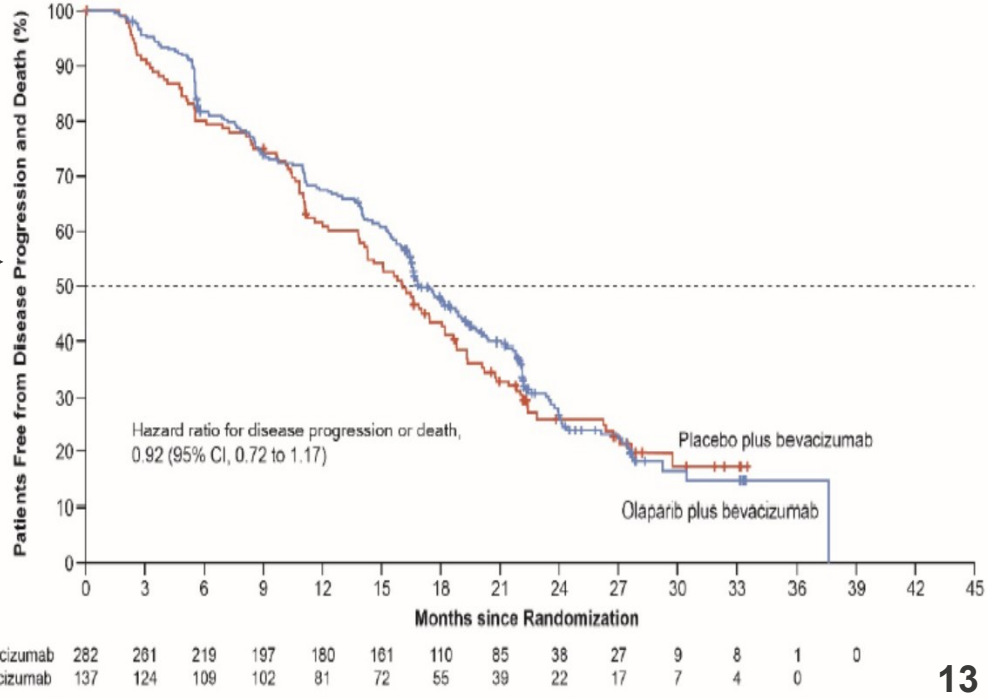
Olaparib plus bevacizumab	255	252	242	236	223	213	169	155	103	85	46	29	11	3	0
Placebo plus bevacizumab	132	128	117	103	91	79	54	44	28	18	8	5	1	1	0

HRD-positive patients

	Olap beva15 N=255	PBO+beva15 N=132
Number analysed		
Events, n (%)	87 (34.1)	92 (69.7)
Median PFS, months (95% CI)	37.2 [redacted]	17.7 [redacted]
HR (95% CI)	0.33 (0.25, 0.45)	
HR (95% CI) (stratified)	[redacted]	

HRD-negative/unknown unknown

	Olap+beva15 N=282	PBO+beva15 N=137
Number analysed		
Events, n (%)	193 (68)	102 (74)
Median PFS, months (95% CI)	16.9 (NR)	16.0 (NR)
HR (95% CI)	0.92 (0.72, 1.17)	
HR (95% CI) (stratified)	NR	



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PAOLA-1 HRD-positive subgroup results: PFS2 (immature)

[redacted]

	Olap+beva15	PBO+beva15
Number analysed	N=255	N=132
Events, n (%)	[redacted]	[redacted]
Median F/U (IQR)	[redacted]	[redacted]
Median PFS2, months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	

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PAOLA-1 HRD-positive subgroup results: OS (immature)

[redacted]

	Olap+beva15	PBO+beva15
Number analysed	N=255	N=132
Events, n (%)	[redacted]	[redacted]
Median F/U (IQR)	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
Restricted mean, months (95% CI)	[redacted]	[redacted]
HR (95% CI) (unstratified)	[redacted]	

HRD-subgroup (1)

Background

- Unmet need for BRCA-negative disease
- ERG concerns:
  - Quality of the subgroup evidence – Missing data (17.6% randomised patients had no available HRD status because no tumour sample or cancelled/failed test
  - HRD testing not routine practice, unlike germline BRCA testing

Company comments

- HRD testing not done because no effective treatments –olap+beva15 would change this
- Olap+beva15 [redacted] outcomes relative to Beva15 alone in HRD-positive, BRCA-negative patients

Clinical expert comments:

- PAOLA-1 data justifies olap+beva15 for HRD-positive disease only
- Just under half of patients with HRD have BRCA mutations (higher in PAOLA-1 HRD-positive subgroup (59% and 49% in Olap+beva15 and Beva15 arms respectively)
- Germline BRCA1/2 only universally available NHS test at present
- HRD testing potentially implementable because pathway would reflect current (non-routine) somatic (tumour) BRCA testing and remove need for separate somatic BRCA testing
  - Tissue access greatest barrier to success - may be significant numbers with insufficient material for testing
  - Test challenging to perform/interpret (18% PAOLA-1 patients classified 'unknown')

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- **Are PAOLA-1 HRD subgroup data robust enough to support decision making?**
- **Is routine HRD testing implementable in the NHS?**

Incomplete PAOLA-1 trial data (1)

Background

- Median PFS has occurred in PAOLA-1 but data for all outcomes is immature
- Long-term PFS2 and OS results of PAOLA-1 potentially confounded by unplanned cross-over and use of subsequent PARPi treatments in both arms

Company comments

- Clinical experts stated 5 years of PAOLA-1 PFS data sufficient to judge OS benefit
- Cited evidence from 3 trials (CHORUS, ICON8, SOLO1) and 1 retrospective study (Bookman, 2019) to show risk of disease progression and death very low in patients who have remained progression-free 5 years after starting first-line therapy
- Usefulness of further data in confirming modelling assumptions demonstrated by latest data-cut from SOLO1 – PFS data based on >5 years of follow-up track extrapolation used to inform CDF entry in TA598
- [redacted]

Clinical expert comments

- One expert agreed with company, other expert noted (1) trial follow up >5 years limited and long-term observational studies (e.g. SEARCH) do not reliably assess progression; (2) after 5 years progression-free, probability of progression in next 5 years is low, (3) very hesitant to use the term 'cure'
- Both agreed use of subsequent targeted treatments in PAOLA-1 is an issue for PFS2 and OS

Stakeholder comments:

- Stage III/IV 5-year survival ~25% but can still relapse after 5-10 years; few considered as cured, especially those with BRCA-positive disease

Would further data collection in PAOLA-1 resolve uncertainties in long-term effectiveness?

Clinical effectiveness estimates

Background

- PAOLA-1 provides no estimates of relative effect for olap+beva15 versus routine surveillance
- In absence of direct trial evidence, company assumes Beva7.5, Beva15 and RS are equally effective and uses PAOLA-1 data for all comparisons
- Company also reported PFS results from an indirect treatment comparison (ITC) but not used in model
- **ERG**: company's ITC-provides robust evidence for comparison with routine surveillance, but data not available to conduct ITC for PFS2 and OS in HRD-positive population

Clinical expert comments

- Both approaches have limitations. On balance, relative effectiveness likely to be most accurately represented by PAOLA-1 results (i.e. not ITC results)
- Data from ICON7 and GOG218 provide some validation for company's assumption of equal effectiveness of comparators in terms of PFS

Data limitations mean PAOLA-1 is the only data source with outcomes for PFS, OS and PFS2 in the HRD-positive population. What impact does using PAOLA-1 data to determine cost effectiveness have on the certainty of the ICERs for the comparison with routine surveillance?

Key clinical issues

- What is the reasoning behind using PARPi early in the course of disease?
- Is this treatment more likely to prevent, or merely delay recurrence?
- If people do not progress after surgery and first line chemotherapy with bevacizumab followed by maintenance olaparib and bevacizumab (and do not require further treatment), at what stage might you be reasonably confident that the cancer would not recur?
- After that time, would they have the same lifespan as the general population?
- Immaturity of data/options for further data collection: Would further data collection in PAOLA-1 help resolve current uncertainties in long-term effect estimates?
- How great is the unmet need for new treatments for patients with HRD-positive disease that are in response (complete or partial) to first-line treatment?
- Given HRD-testing is not routinely done in the NHS, could olap+ beva15 be implemented?
- How robust is the PAOLA-1 HRD-positive subgroup data?
- The comparator in the trial does not align with current NHS practice, how is this best handled?

Key cost-effectiveness issues

- The company and ERG have different approaches to survival modelling, and this is the primary driver of cost effectiveness.
  - The company has assumed that:
    - people who are progression-free at 5 years have the same risk of death as the general population
    - OS is equal to PFS after 5 years
  - ERG's view is that long-term OS would be better based on OS data.

  What is committee view on each approach?
- Should decision making be based on maintenance-only analyses as in the company's base case, or extended regimen analyses which include first line treatment and maintenance options?
- The company and ERG have different approaches to costing treatments. Does the committee agree that the ERG approach is more appropriate given that it reflects the NICE position statement?
- Which utility values used in the model best reflect the health-related quality of life of people with HRD-positive ovarian cancer?
- HRD testing costs should be included in the model but they are not included in the company base case

Company's cost effectiveness model

Model type	4-state partitioned survival model	
Time horizon	50 years	
Model cycle	1 month	
Utility values	EQ-5D data from the PAOLA-1 trial with UK tariff applied	
	Maintenance-only analysis	**Extended regimen analysis**
Population	HRD-positive patients in response to 1L platinum chemotherapy (CT) with Beva15 (trial)	HRD-positive patients - includes evaluation of changed pathway of adding beva15 to platinum CT 1st line
Intervention	Olap+beva15 maintenance	Platinum CT with Beva15 followed by Olap+beva15 only in responding patients
Comparators	1. Routine surveillance (RS) 2. Beva7.5 3. Beva15	1. Platinum CT followed by RS 2. Platinum CT with Beva7.5 followed by Beva7.5 in responding patients 3. Platinum CT with Beva15 followed by Beva15 only in responding patients

None of the company's analyses included first-line treatment outcomes. Some costs of first-line treatment were included in the extended regimen analyses (described in later slide)

Survival modelling

Background

- Primary driver of cost effectiveness for both maintenance & extended analyses
- Company: mixture cure model (MCM) to estimate PFS, and sets the OS and PFS2 curves equal to the PFS curve ie PFS represents OS
- ERG: initially preferred standard parametric models for all outcomes but has updated its preferred approach in light of stakeholder comments at TE

Company comments

- Recent data cut from SOLO1 supports the cure assumption and MCM-PFS survival trajectory - no changes made to survival modelling at TE
- Life table data supports [redacted] surviving to age of 90 years
- ERG's pre-engagement modelling clinically implausible

Clinical expert comments

- ERG's pre-engagement modelling is too pessimistic
- No consensus about the cure fractions/5 year cure threshold

ERG comments

- Company's approach to set the OS and PFS2 curves equal to PFS curve is methodologically flawed and has major impact on shape of survival curves and the relative effect of olap+beva15 vs RS
- ERG's updated modelling takes account of clinical expert comments at TE – includes the assumption that a proportion of patients will be statistically 'cured' after 5 years, but survival trajectory is predicted from the OS data

Company mixture cure model for maintenance: PFS

- MCM-generated PFS curves fitted to trial data (as for standard parametric modelling) – considered MCM-Weibull curve provided best-fit to PAOLA-1 data
- Patients predicted to be progression-free (PF) at 5 years considered 'cured' and would have general UK mortality rate
- Percentage PF at 5 years (cure fractions):
  - olap+beva15: [redacted]
  - all comparators (RS, beva 15, & beva 7.5): [redacted]

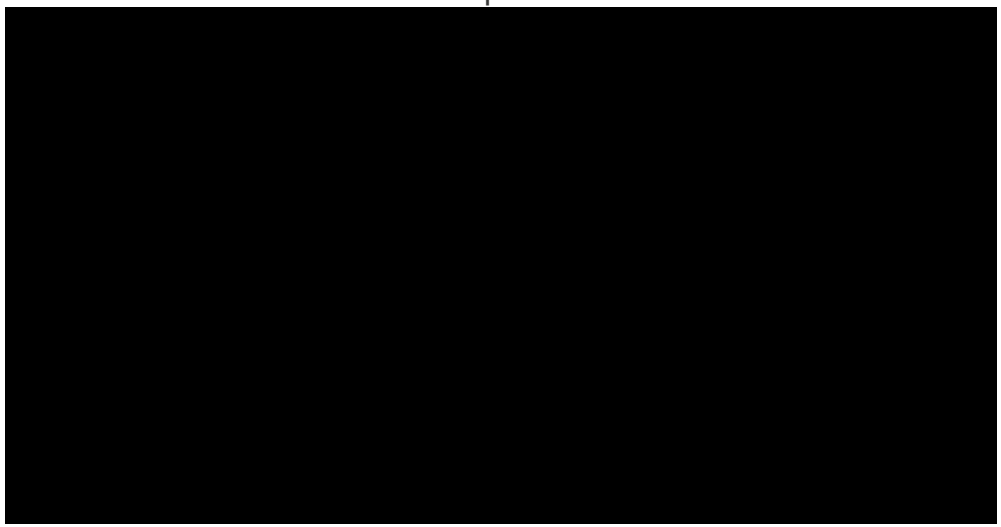
- ERG:
  Wide range of predicted cure fractions reported across the alternative MCMs for PFS: [redacted] for three best-fitting models for olap+bev15 data; [redacted] for the four best-fitting models to the beva15 data
- One clinical expert stated 5 year cure threshold and company's cure fractions were plausible; the other said no evidence for the cure threshold and considered cure fractions of 40% and 20% in olap+Beva15 and Beva15 arms respectively more plausible

Company survival model (OS & PFS2 details)

- Company used standard parametric models to predict long-term PFS2 (lognormal extrapolation) and OS (Weibull extrapolation) up to 5/6 years. But after this the OS curves were set equal to the PFS (& PFS2) curves as OS was predicted to be lower than PFS
- ERG noted:
  - difference in cure rates estimated via PFS MCM model results in a very big and very long predicted OS effect for olap+bev15 versus RS – see figure below
  - setting the OS and PFS2 curves equal to the PFS curves as in company model means that the PFS curves become the OS curves for long-term survivors and therefore the model predictions exclude the long-term outcomes for patients with progressed disease

Comparison of company's modelled OS curves (set equal to PFS curves) with un-adjusted Weibull OS curves: Olap+beva15 arm

Comparison of company's modelled OS curves (set equal to PFS curves) with un-adjusted Weibull OS curves: comparator arm



ERG's updated survival modelling after TE

- Used company's Weibull MCM curves to estimate PFS (as company)
- Capped PFS curves by OS curves instead of setting OS curves equal to PFS. Survival benefit therefore dictated by OS curves, not PFS curves, and patients with progressed disease are not excluded
- Used company's exponential curves fitted to KM OS data. Provides most optimistic OS (and therefore PFS) predictions but poor visual fit

ERG's preferred survival extrapolations (updated post TE)

- Addressed poor visual fit
  - use OS KM data up to month 30 & apply HR 0.75 to exponential curve fitted to comparator arm
  - simplified modelling techniques aims to provide more realistic PFS and OS estimates

- Other limitations: driven by immature OS data; still no evidence for 5-year cure threshold

Source: ERG critique if company's engagement response, figure 6 'ERG's new exploratory analysis'

Comparison of predicted survival estimates using company's (unchanged) and ERG's (updated) extrapolations

PFS	Median (Months)	Years 5	20	30
RS arm				
Company's MCM (unchanged)	***	***	***	***
ERG's updated extrapolation				***
PAOLA-1 Beva15	***	-	-	-
Olap+beva15 arm				
Company's MCM	***	***	***	***
ERG's updated extrapolation	***		***	***
PAOLA-1 Olap+beva15	***	-	-	-

OS	Median Months	Years 5	20	30
RS arm				
Company's MCM (unchanged)	**	***	***	**
ERG's updated extrapolation	**	***		**
PAOLA-1 Beva15	**	-	-	-
Olap+beva15 arm				
Company's MCM (unchanged)	***	***	***	***
ERG's updated extrapolation	***	***	***	***
PAOLA-1 Olap+beva15 arm	***	-	-	-
Survival benefit associated with olap+beva15 in different approaches				
Company's MCM (unchanged)	-	***		***
ERG's updated extrapolation	-	***		***

Summary of differences between company and ERG survival predictions

- **PFS estimates**
  - ERG exploratory estimates [redacted]
- **OS estimates for RS arm**
  - ERG predicts [redacted] median OS for RS than company ([redacted] months), predicts [redacted] percentage alive at 5 years but [redacted] company estimate by 20 and 30 years
- **OS estimates for olap+beva15 arm**
  - ERG also predicts [redacted] median OS for olap+beva15 than the company ([redacted]). Also predicts [redacted] percentage alive than company at 5 years, but [redacted] percentage alive at 20 and 30 years than company
- **End result**
  - Relative survival benefit at 5 years : [redacted] company, [redacted] ERG
  - Relative survival benefit at 30 years: [redacted] company, [redacted] ERG

ERG exploratory analysis demonstrates that (1) OS is the primary driver of cost effectiveness, (2) so uncertainty in OS estimates = uncertainty in ICERs. Are either the company's or the ERG's approaches to survival modelling appropriate for informing decision-making?

Maintenance-only or extended regimen analysis

Background

- Company's maintenance-only analysis produces lower ICERs but excludes costs and benefits of first line treatment
  Company's extended regimen analysis includes first line treatment costs but not benefits
- ERG re-worked the extended regimen analysis with the following treatment benefits included
  - Benefits associated with maintenance treatment received by patients with stable disease (again QALYs from maintenance model were used as proxy)
- Both company and ERG used OSCAR study to inform proportions responding to first line treatment (69% have complete or partial response to first line treatment; 23% have stable disease; 8% progress) – clinical opinion sought re: these proportions at TE

Company comments

- Proportions align to GOG-0218 study but not to the [redacted]
- No changes made to company's maintenance-only or extended regimen analyses at TE

Clinical expert comments

- Proportions are clinically plausible

Technical team comments

- Maintenance analysis does not address decision problem
- ERG's extended regimen analysis preferable because it is more closely aligned to the NICE scope

Does committee consider ERG's extended regimen analysis preferable because it is more closely aligned to the NICE scope?

Preferred utility values (limited impact on ICER)

Background

- Company used utilities from PAOLA-1 EQ-5D data (5L mapped to 3L) for PFS and first disease progression (PD1) states
- Second disease progression (PD2) value taken from mapped EQ-5D-3L utility derived from SOLO-1 and used in TA598
- **ERG** questioned different utilities for PFS on/off treatment, methods used to estimate these, and ambiguity of method used to estimate PD1 value

Company comments

- No changes made to company's base-case utilities in light of engagement

Clinical experts no comments on this issue

ERG comments

- Continues to lack confidence that utilities are reliable enough to inform the modelling
- Uses the mapped EQ-5D-3L values from TA598 in its own analyses
- Small impact on ICER (<£500)

Health state	Company (PAOLA-1)	ERG (SOLO-1 used in TA598)
PFS on treatment	[redacted]	0.819
PFS off treatment	[redacted]	
PD1	[redacted]	0.771
PD2	0.680	0.68

Source: ERG report, section 4.2.8, table 23

Which utilities does committee consider most appropriate?

Treatment costs

Background

- Also a driver of cost effectiveness; differences remain between company's and ERG's costing
- Technical team view: treatment costs (including subsequent treatment costs) should reflect routine NHS practice as outlined in NICE position statement on consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product – therefore ERG approach is preferred

Summary of differences in company and ERG model costs post-engagement

Cost input	Company (unchanged)	ERG (updated)
Beva15/beva7.5 price	Hypothetical 50% discount applied to Avastin list price to reflect loss of exclusivity in 2020	List price with confidential PAS price used in CPAS appendix
Subsequent PARPi treatment prices	Olaparib: PAS price; Niraparib/Rucaparib: List prices	Olap (PAS) (other treatments are not included in ERG analysis)
Time on treatment	Aligned to time on treatment in PAOLA-1	Determined by drug SmPCs
Approach to modelling subsequent treatments	Olap+beva15 arm: Subsequent platinum CT use aligned to olap+beva15 arm of PAOLA-1; no re-treatment with PARPis permitted All comparator arms: Subsequent treatment use fully aligned to placebo+bev15 arm of PAOLA-1 i.e. 11% received subsequent olaparib; 45% received rucaparib; 45% received niraparib	Both arms: Costs fully matched to NHS routine practice i.e. treatments that are currently available routinely were included (proportions determined by POALA-1) but PARPi treatments only available via CDF were excluded

Does the committee consider that the ERG's treatment costs are more appropriate?

HRD-testing costs

Background

- In response to engagement, company stated that [redacted]
- ERG's updated modelling includes scenarios with and without HRD testing costs included for all patients
- ICER increased by ~£5000 in both the comparison with RS and Beva7.5 when HRD-testing costs were included (results based on extended regimen analysis and reflect ERG's preferred assumptions)

Technical team

- Committee's decision needs to be based on cost effectiveness in routine commissioning – as HRD testing is not current practice, the introduction of it to the NHS would require an uplift in resources that, at present, relates solely to the use of this technology
- Therefore HRD testing costs should be included in the model

Does the committee agree that HRD testing costs should be included in the model?

Company base case results

Maintenance-only results — **Deterministic** | **Probabilistic**

Comparison: Olap+beva15 versus RS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Olap+beva15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£21,606**
Beva15	[redacted]	[redacted]	[redacted]				
Olap+beva15	[redacted]	NR	[redacted]	[redacted]	NR	[redacted]	£21,564
Beva15	[redacted]	NR	[redacted]				

Comparison: Olap+beva15 versus beva7.5

Olap+beva15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,375
Beva7.5	[redacted]	[redacted]	[redacted]				
Olap+beva15	[redacted]	NR	[redacted]	[redacted]	NR	[redacted]	£18,404
Beva7.5	[redacted]	NR	[redacted]				

Company results for the comparison with beva15 are not presented because they are outside of the scope.

Extended regimen results (probabilistic results were not reported)

Comparison: Olap+beva15 versus RS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Olap+beva15	NR	NR	NR	NR	NR	NR	**£26,286**
Beva15	NR	NR	NR				

Comparison: Olap+beva15 versus beva7.5

Olap+beva15	NR	NR	NR	NR	NR	NR	£19,925
Beva7.5	NR	NR	NR				

Company results for the comparison with beva15 are not presented because they are outside of the scope

ERG exploratory analyses results (updated)

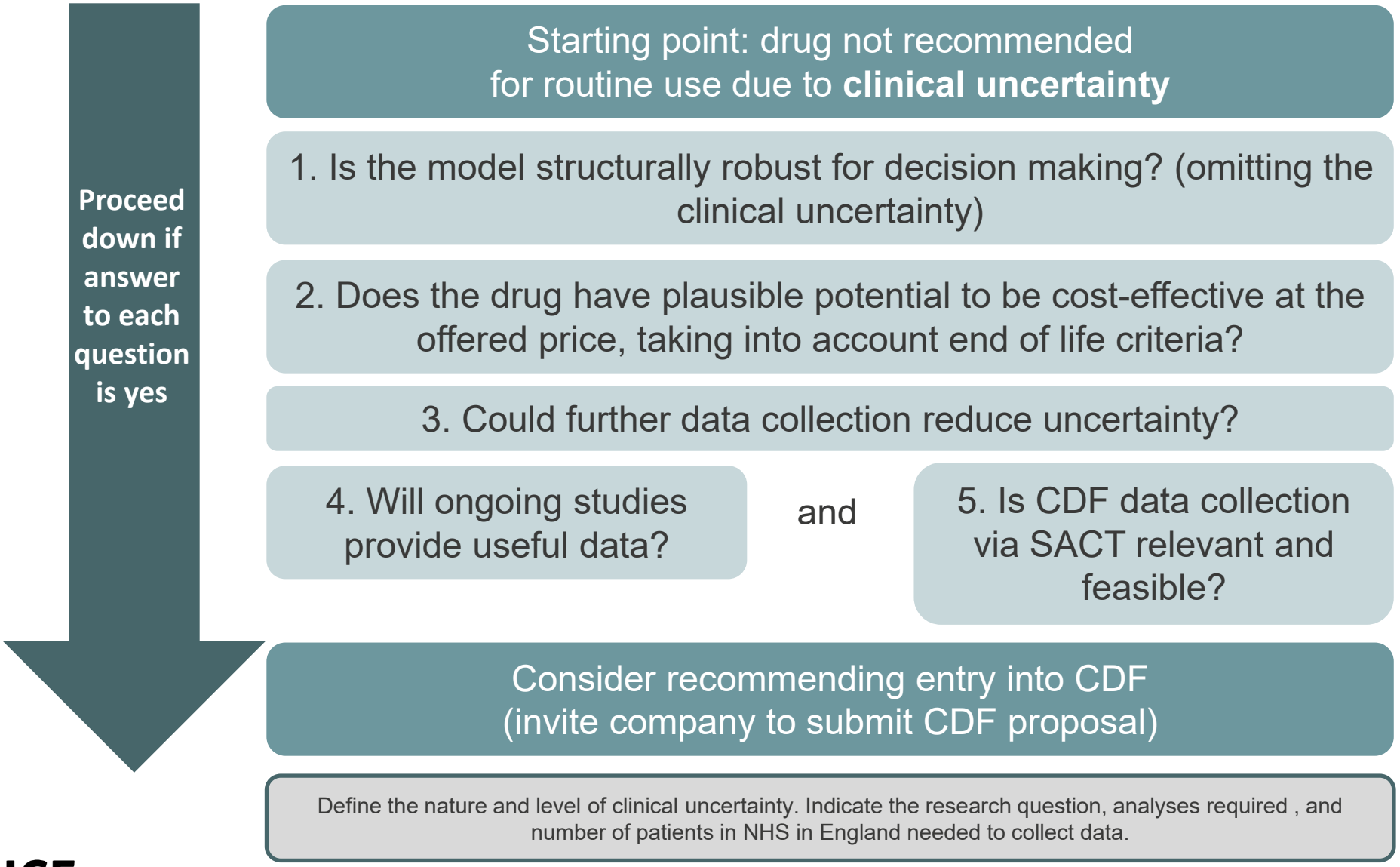
Results per patient	Olap+beva15	Comparator	Incremental value
Extended regimen analysis with ERG corrections			
Comparison: Olap+beva15 versus RS			
Total costs	[redacted]	[redacted]	£62,813
Total QALYs	[redacted]	[redacted]	1.84
ICER	-	-	**£34,165**
Comparison: Olap+beva15 versus beva7.5			
Total costs	[redacted]	[redacted]	£45,900
Total QALYs	[redacted]	[redacted]	1.86
ICER	-	-	£24,726
Results using all ERG preferred assumptions			
Comparison: Olap+beva15 versus RS			
Total costs	[redacted]	[redacted]	£84,113
Total QALYs	[redacted]	[redacted]	0.95
ICER	-	-	£88,438
ICER with HRD testing costs included			**£93,350**
Comparison: Olap+beva15 versus beva7.5			
Total costs	[redacted]	[redacted]	£67,200
Total QALYs	[redacted]	[redacted]	0.95
ICER	-	-	£70,570
ICER with HRD testing costs included			£75,476

Key cost-effectiveness issues

- The company and ERG have different approaches to survival modelling, and this is the primary driver of cost effectiveness.
  - The company has assumed that:
    - people who are progression-free at 5 years have the same risk of death as the general population
    - OS is equal to PFS after 5 years
  - ERG's view is that long-term OS would be better based on OS data.

  What is committee view on each approach?
- Should decision making be based on maintenance-only analyses as in the company's base case, or extended regimen analyses which include first line treatment and maintenance options?
- The company and ERG have different approaches to costing treatments. Does the committee agree that the ERG approach is more appropriate given that it reflects the NICE position statement?
- Which utility values used in the model best reflect the health-related quality of life of people with HRD-positive ovarian cancer?
- HRD testing costs should be included in the model but they are not included in the company base case

Committee decision making: CDF recommendation criteria



NICE

Ongoing data collection in PAOLA-1

Outcome	Data maturity at time of primary PFS analyses		Next planned data cut date
	ITT	HRD-positive	
PFS	59%	46%	Final: [redacted]
PFS2	39%	28%	Final: when PFS2 data are ~53% mature or after a maximum duration of one year after primary PFS analysis, whichever occurs first
OS	NR	16%	Interim: Same time as final PFS2 analysis Final: when OS data are ~60% mature, or three years after the main PFS analyses, whichever occurs first (will only be performed if final PFS2 data are not statistically significant)

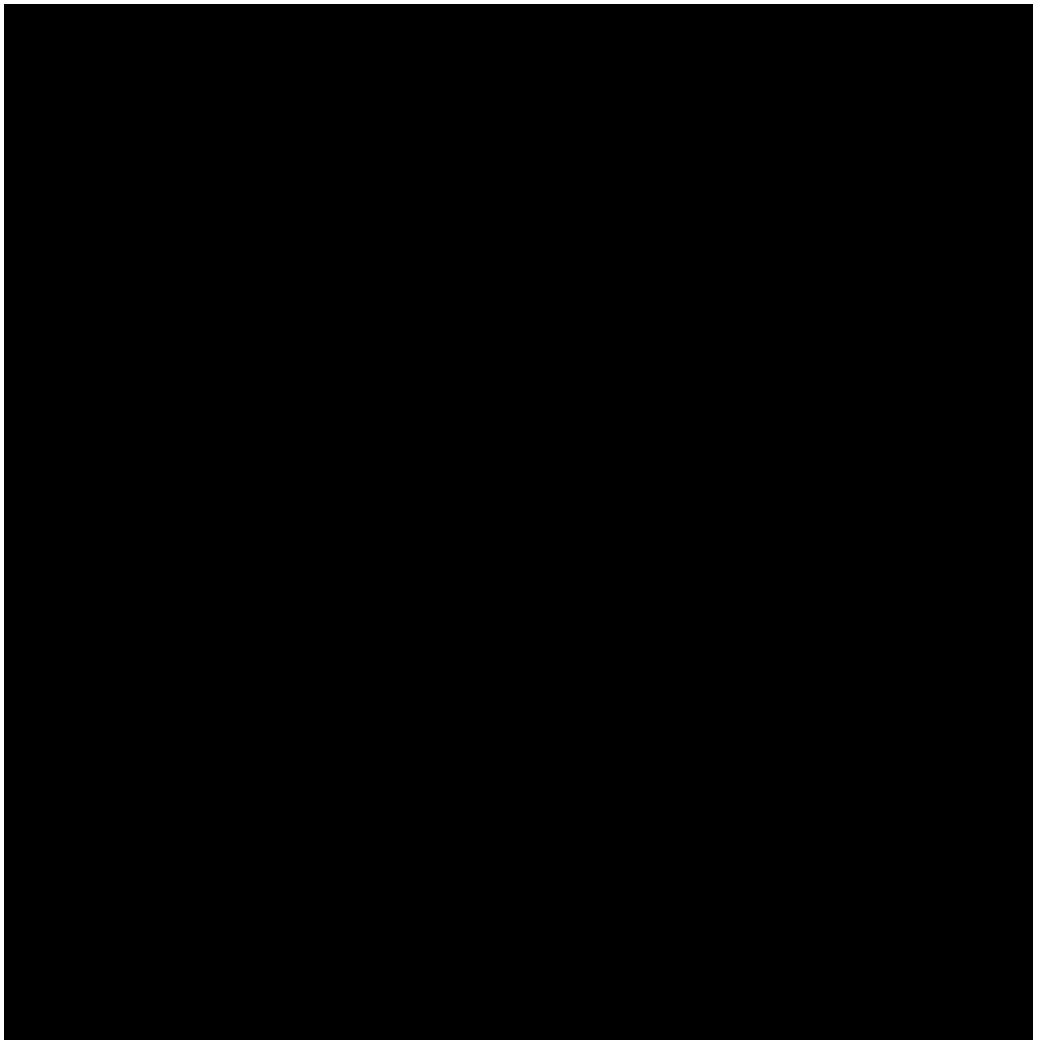
Equalities issues

Does committee need to make any reasonable adjustments to the guidance to ensure equality of access for people who cannot undergo gene testing for equalities reasons?

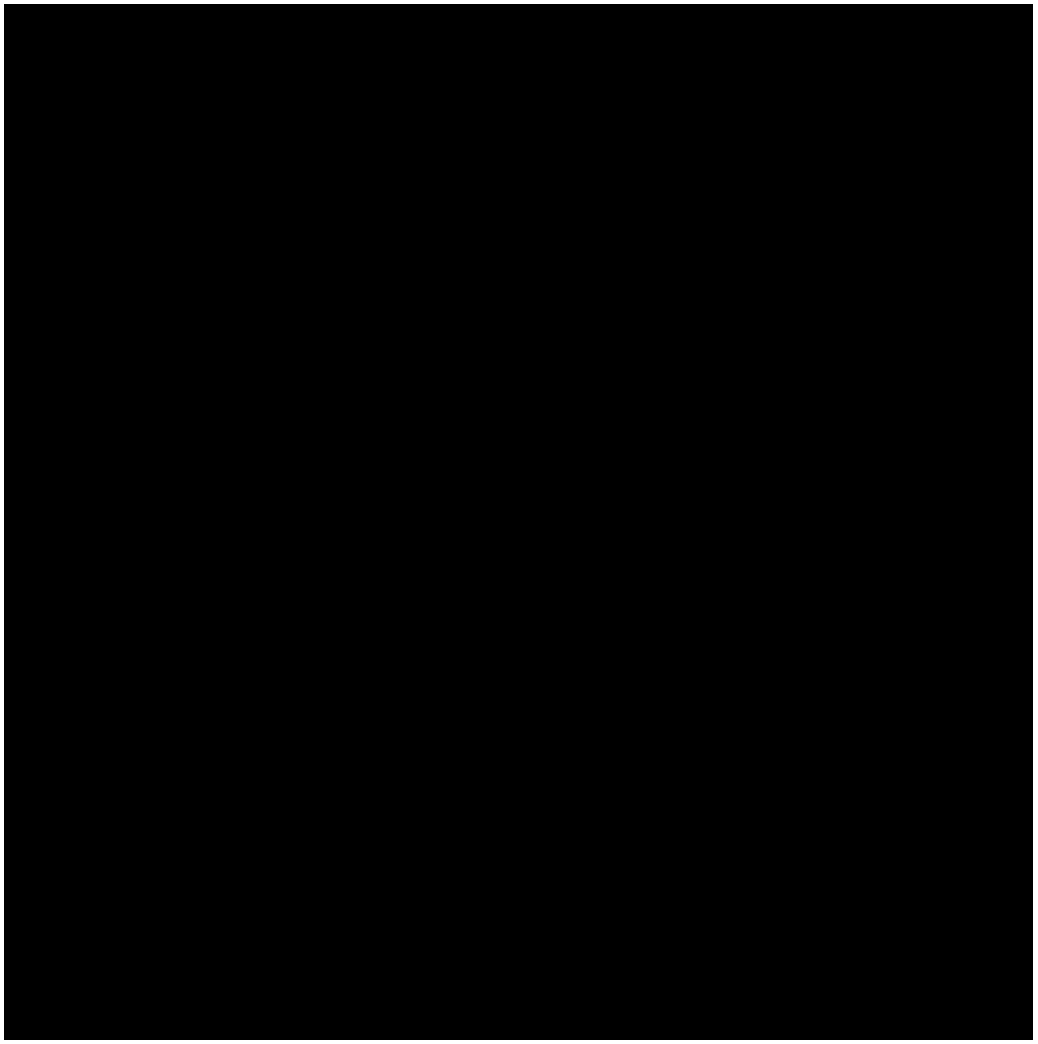
Back up slides

Company's standard parametric models

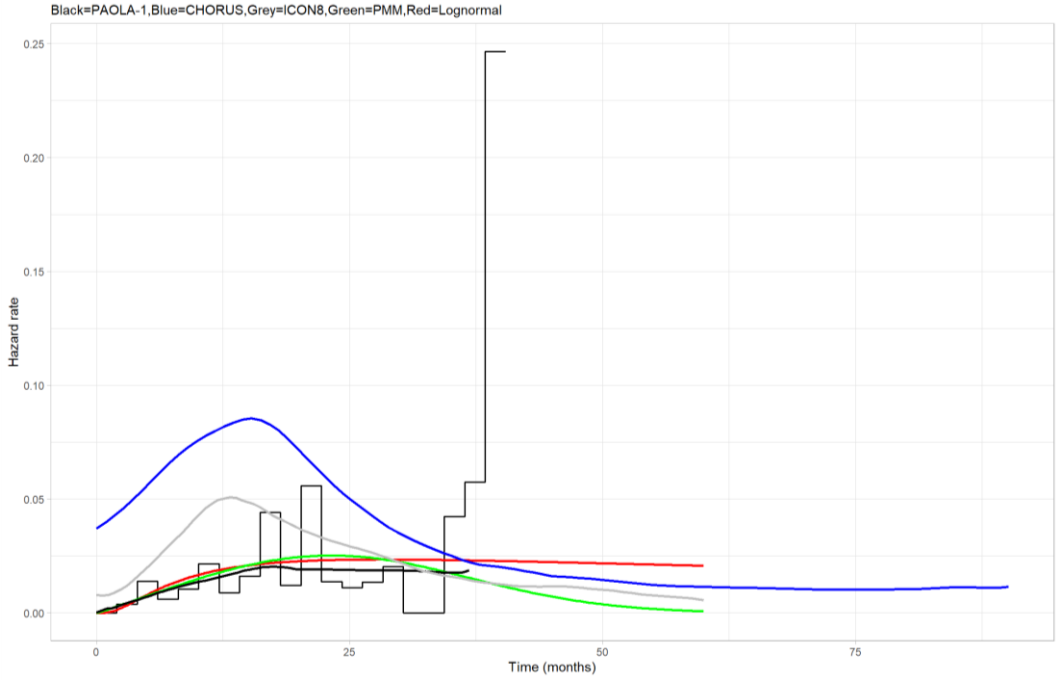
PFS: Visual representation of fitted parametric models to entire HRD-positive data set



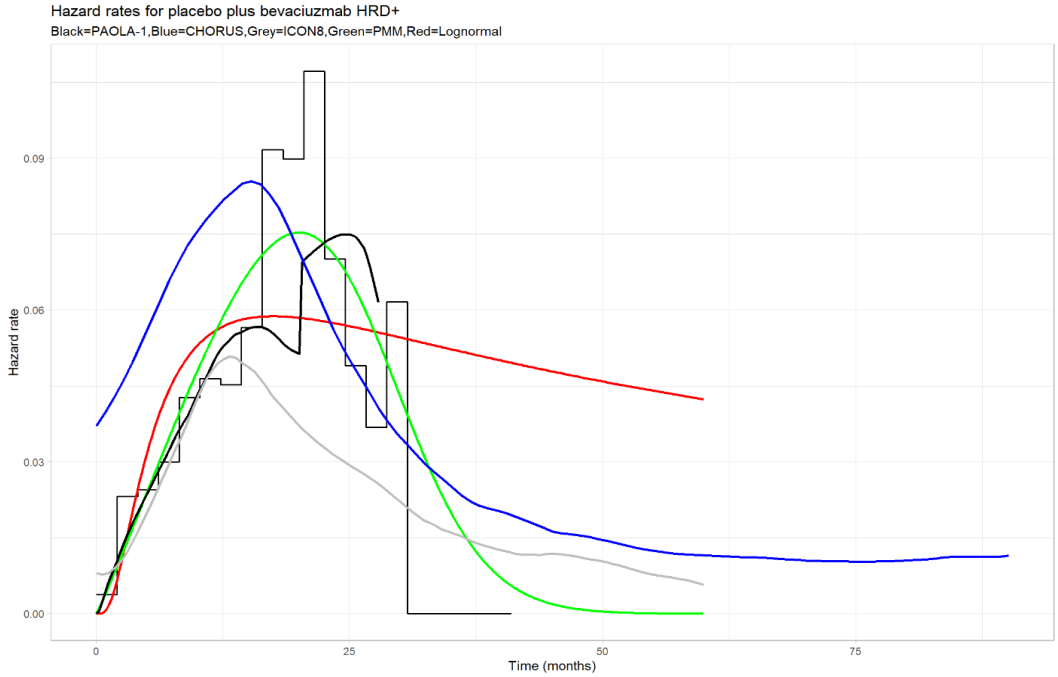
OS: Visual representation of fitted parametric models to entire HRD-positive data set



Company survival model: hazard function plots



Hazard functions for **olaparib + bevacizumab** 15mg/kg KM curve (black), compared to the hazard functions for the ERG's preferred lognormal extrapolations (red), company base-case extrapolations (green), data from CHORUS (blue) and data from ICON8 (grey) (source: company response to technical engagement, figure 14)



Hazard functions for **placebo + bevacizumab** KM curve (black), compared to the hazard functions for the ERG's preferred lognormal extrapolations (red), company base-case extrapolations (green), data from CHORUS (blue) and data from ICON8 (grey) (source: company response to technical engagement, figure 13)