NICE National Institute for Health and Care Excellence

Public observer slides – no confidential information included

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy

Lead team presentation

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Company: GSK
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Key terms and abbreviations

Term/abbreviation	Definition
OC	Ovarian cancer (ovarian, fallopian tube or primary peritoneal cancer)
PRIMA	Name of the company's pivotal trial (NCT02655016)
Platinum CT	Platinum chemotherapy (platinum-based compound or platinum-based therapy alone e.g. cisplatin or carboplatin)
RS	Routine surveillance
NVRD	No visible residual disease
PDS	Primary debulking surgery
IDS	Interval debulking surgery
OS	Overall survival
PFS	Progression-free survival
PFS2	Time from randomisation to second progression
BRCA mutation	Mutation in BRCA1 or BRCA2 tumour suppressor gene
CDF	Cancer Drugs Fund

Key clinical issues (1)

- **Generalisability of dosing used in PRIMA to clinical practice**
  - Is the dosing used in the clinical trial reflective of the likely dosing in clinical practice and therefore, are the results from PRIMA generalisable to clinical practice?
- **Generalisability of population in PRIMA to the marketing authorisation population**
  - Would people with stage III ovarian cancer and no visible residual disease (NVRD) after primary debulking surgery (PDS) be considered to have a different prognosis compared with people with NVRD after interval debulking surgery (IDS)?
  - Would niraparib have a different effect on stage III NVRD after PDS compared with after IDS?

Key clinical issues (2)

- **Estimating proportion of people with stage III and NVRD after surgery**
  - What is the most plausible estimate of the proportion of people with stage III and NVRD irrespective of type of surgery?
  - Is the proportion of people with stage III NVRD after IDS in PRIMA representative of the proportion of stage III NVRD irrespective of surgery in clinical practice?
  - What is the most plausible estimate of the proportion of people with stage III NVRD after PDS?
- **Estimating PFS for people with stage III NVRD after PDS**
  - Is using the PRIMA ITT population analyses appropriate for decision making? (ERG ITT approach)
  - Is adjusting the PRIMA stage III NVRD after IDS population to the proportion of people with stage III NVRD irrespective of surgery type in clinical practice appropriate? (ERG reweighted approach)
  - Does the committee consider the company's justification for the MA population analysis to be appropriate?
  - Is the company's method of applying HRs from other sources to PRIMA ITT PFS curves robust?

NVRD: no visible residual disease; PDS: primary debulking surgery; IDS: interval debulking surgery; ITT: intention to treat

Ovarian cancer: disease background

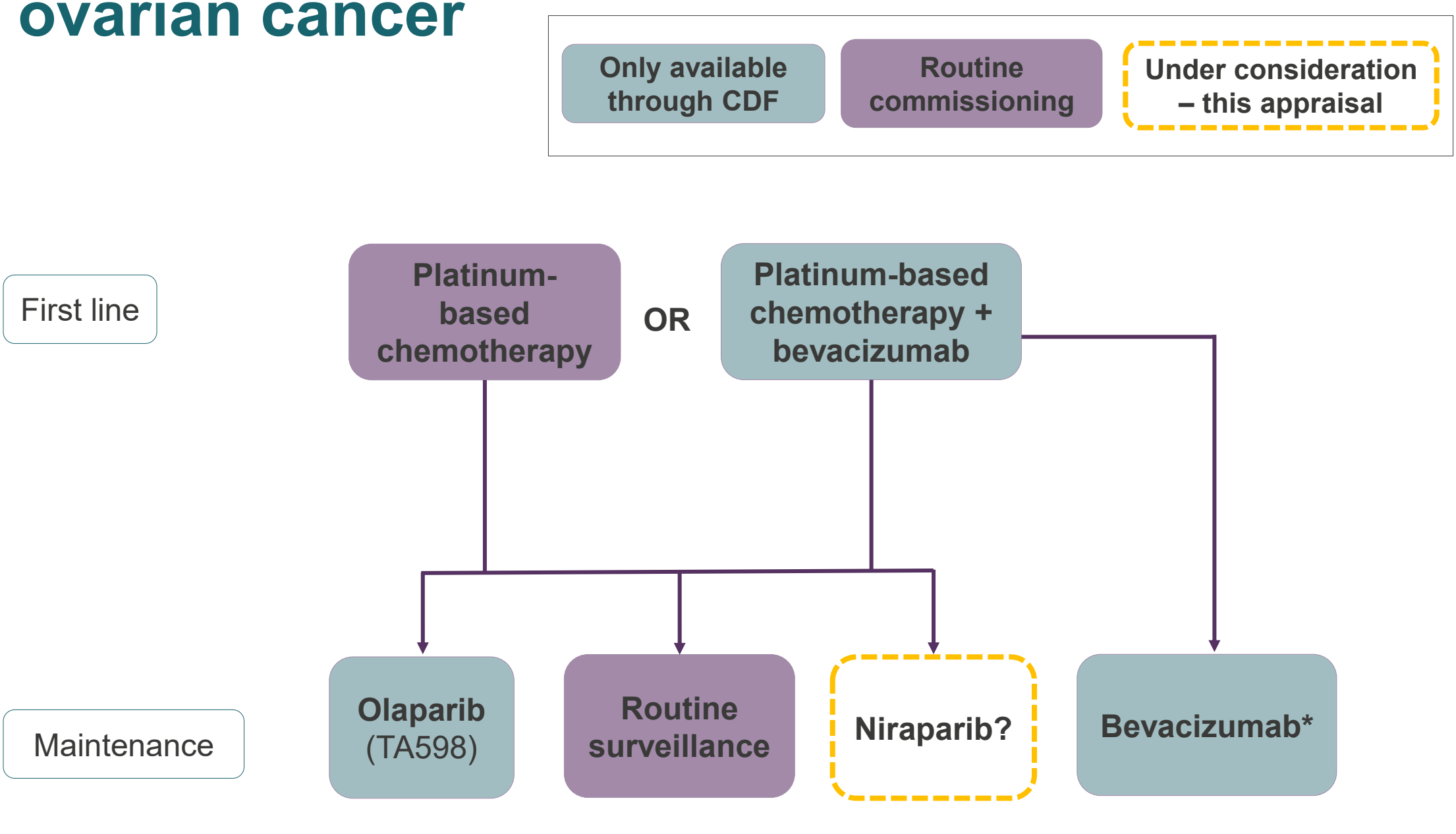
- Ovarian cancer (OC) occurs in different parts of the ovary or fallopian tubes
- Classified from stage I to stage IV; advanced OC from stages II to IV
  - Stage I: disease is only within ovaries
  - Stage II: disease has grown outside ovaries but is still within pelvis
  - Stage III: locally advanced (spread outside pelvis into abdominal cavity)
  - Stage IV: distant metastasis to other body organs
- Average age at diagnosis is 65 years
- In 2017, 6,236 people were diagnosed with OC in England
- 5-year survival in 2013 to 2017 in England was estimated to be 42.9% for all stages, 26.9% for stage III and 13.4% for stage IV disease

Surgical treatment of ovarian cancer

- **Primary debulking surgery (PDS):** surgery aiming to remove the bulk of the tumour conducted before 1st line chemotherapy treatment

- **Interval debulking surgery (IDS):** surgery aiming to remove the bulk of the tumour conducted between cycles of 1st line chemotherapy

First-line treatment options for advanced ovarian cancer



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*available through old CDF; use is off-label due to dosing

Niraparib

Mechanism of action	Poly-ADP-ribose polymerase (PARP) inhibitor Inhibits PARP proteins involved in DNA repair
Marketing authorisation	"as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy"
Administration & dose	Oral monotherapy. Recommended starting dose: 200 mg (two 100 mg capsules), once daily For people who weigh ≥ 77 kg and have baseline platelet count ≥ 150,000/µL, recommended starting dose: 300 mg (three 100-mg capsules), once daily
List price	• £4,500 per pack (£80.35 per 100 mg unit) • Approved simple discount patient access scheme

Patient group perspectives (1)

- **Ovacome**
- **Ovarian Cancer Action**
- **Target Ovarian Cancer**

- Choice of maintenance therapy to extend progression-free survival and continued input from oncology teams offers significant psychological as well as health benefits
- There is unmet need for more effective maintenance therapies in the first line setting especially for non-BRCA mutated population
- Niraparib has increased treatment options and provided a better quality of life by increasing the period between disease progression with longer periods without chemotherapy
- Ovarian cancer affects every aspect of their life – their relationships, work, family life and social life. In many cases there can be additional challenges due to stigma, cultural insensitivity, a feeling of isolation and in some cases unaddressed psychosexual issues… Family members and carers are also impacted by all of these issues

Patient group perspectives (2)

"Niraparib means I can get on with doing things and feeling healthy while at the same time knowing something is suppressing the tumours which feels more proactive than just waiting"
Patient statement (Ovarian Cancer Action)

"As I've had two recurrences, progression free survival is of utmost importance to me"
Patient statement (Ovarian Cancer Action)

"I'm not BRCA, everything seems targeted at those with a genetic mutation"
Patient statement (Target Ovarian Cancer)

"Despite the side effects, Niraparib has allowed me another window of wellness. It has given me sufficient quality of life to continue to enjoy my "new normal" as a cancer patient.."
Patient statement (Ovarian Cancer Charity)

Adverse event profile

Patient group perspectives:

- Side effects do occur but are more manageable than regular chemotherapy
- Side effects include: anaemia, fatigue, nausea and decreased platelet count
- The type and extent of side effects experienced by an individual are unknown until treatment starts
- “Initially fine no problems, after not having it for a week as out of stock, when I started taking it again I became very breathless, abdominal pain, and bowel problems, but continuing on it for now.”
- “Started on 2 x 100mg a day but could not tolerate 200mg so been on 100mg for over a year. Experienced breathlessness and platelets too low.”

Drug safety update – October 2020

- Reports of severe hypertension (including rare cases of hypertensive crisis) and rare cases of posterior reversible encephalopathy syndrome
- Blood pressure to be taken at least weekly for first 2 months and monitored monthly for first year, then periodically

Decision problem

	Scope	Company submission
Population	People with advanced high grade ovarian, fallopian tube, or primary peritoneal cancer that has responded (complete or partial) to first-line platinum-based chemotherapy	Cost-effectiveness analysis presented as per NICE scope. This includes PRIMA ITT population plus people with stage III NVRD after PDS (not included in PRIMA)
Intervention	Niraparib (Zejula)	As per NICE scope
Comparators	Routine surveillance	As per NICE scope
Sub-groups	BRCA mutation status	Clinical evidence presented by BRCA mutation status Cost-effectiveness analyses are not presented by BRCA-mutation status

ITT: intention to treat; NVRD: no visible residual disease; PDS: primary debulking surgery

Clinical effectiveness

Pivotal trial: PRIMA

Trial design	Randomised, double-blind, multi-centre phase III trial of maintenance niraparib vs placebo	
	10 UK sites	
Population	• Advanced (stage III / IV) ovarian cancer who were in complete or partial response to PBC with ECOG performance status of 0 or 1 • People with stage III disease with no visible residual disease after primary debulking surgery were excluded	
Intervention/ comparator	**Intervention arm** (n=487)	**Comparator arm** (n=246)
	Niraparib fixed dose (300mg) once daily (n=317)	Matching placebo (n=158)
	Niraparib individualised dose (300mg **or,** 200mg if baseline body weight of <77kg, a platelet count of <150,000/μL or both) once daily (n=170)	Matching placebo (n=88)
Outcomes	PFS (BICR; primary endpoint); OS; TFST; PFS2; HRQoL; adverse effects of treatment	
Stratification factors	Administration of neoadjuvant chemotherapy, complete or partial response to PBC, HRD gene mutation status	

PBC: platinum-based chemotherapy; NVRD: no visible residual disease; PFS: progression-free survival; BICR: blinded independent central review; OS: overall survival; TFST: time to first subsequent treatment; HRQoL: health-related quality of life; HRD: homologous recombination deficiency

PRIMA results: ITT progression-free survival

PFS based on BICR (months)		
	Niraparib (n=487)	**Placebo (n=246)**
Median (95% CI)	13.8 (11.5,14.9)	8.2 (7.3,8.5)
Censored observations, n (%)	255 (52.4)	91 (37.0)
Event rate, n (%)	232 (47.6)	155 (63.0)
p-value	<0.0001	
Hazard ratio (95% CI)	0.62 (0.502, 0.755)	
PFS based on IA (months)		
Median (95% CI)	13.8 (11.3, 14.2)	8.2 (7.6, 9.8)
Hazard ratio (95% CI)	0.63 (0.514, 0.763)	

Data maturity: 47.6% and 63.0% (niraparib and placebo, respectively)

ITT: intention to treat PFS: progression-free survival; BICR: blinded independent central review; CI: confidence interval; IA: investigator assessment

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PRIMA results: ITT overall survival

OS (months)		
	Niraparib (n=487)	Placebo (n=246)
Median (95% CI)	[redacted]	[redacted]
Censored observations, n (%)	[redacted]	[redacted]
Event rate, n (%)	[redacted]	[redacted]
p-value	[redacted]	
Hazard ratio (95% CI)	0.70 (0.442, 1.106)	

Data maturity: 9.9% and 12.6% (niraparib and placebo, respectively)

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ITT: intention to treat; OS: overall survival;
CI: confidence interval

PRIMA results: ITT time to second progression (PFS2)

PFS2 (months)		
	Niraparib (n=487)	Placebo (n=246)
Median (95% CI)	[redacted]	[redacted]
Censored observations, n (%)	[redacted]	[redacted]
Event rate, n (%)	[redacted]	[redacted]
p-value	[redacted]	
Hazard ratio (95% CI)	0.81 (0.577, 1.139)	

Data maturity: [redacted]% and [redacted]% (niraparib and placebo, respectively)

[redacted]

PFS2 defined as time from date of randomisation to date of disease progression on next anti-cancer therapy

ITT: intention to treat; CI: confidence interval

Generalisability of dosing used in PRIMA to clinical practice – (issue 1) (1)

Background

- Marketing authorisation includes individualised dosing
- In PRIMA, 65% of people started on fixed dosing (300 mg) and 35% on individualised dosing
- Of those on individualised dosing, [redacted]% started on 300mg [redacted]% started on 200mg
- Shorter follow up of the individualised dosing group - more uncertainty
- By month 5 in PRIMA: [redacted]% on 300mg, [redacted]% on 200mg and [redacted]% on 100mg of niraparib

Company's subgroup analysis – fixed vs individualised dosing

PFS based on BICR	Fixed		Individualised	
	Niraparib (n=317)	Placebo (n=158)	Niraparib (n=170)	Placebo (n=88)
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Event rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	0.59 (0.457, 0.757)		0.69 (0.481, 0.982)	

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MA: marketing authorisation; BICR: blinded independent central review; PFS: progression-free survival; HR: hazard ratio; CI: confidence interval

Generalisability of dosing used in PRIMA to clinical practice – (issue 1) (2)

ERG comments

- Sub-group analysis should be considered exploratory
- PRIMA not powered to detect a difference between subgroups
- Lack of evidence on efficacy of 100 mg dose

Stakeholder comments

- NOVA trial (niraparib in relapsed setting) shows similar PFS in those who were dose-reduced to 200mg and those having 300mg, indicating no loss of effectiveness

Clinical expert comments

- Individualised dosing is beneficial for managing adverse effects of treatment and decreases dose reductions which are common in early months of treatment

Is the dosing used in PRIMA reflective of the likely dosing in clinical practice?

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PFS: progression-free survival

Approach for adjusting PRIMA to the marketing authorisation population (1) (TR issues 2, 3 & 4)

Background

- PRIMA included people with stage III NVRD after IDS and people with stage IV NVRD after PDS or IDS
- PRIMA excluded people with stage III disease with NVRD after PDS
- License includes all people with stage III NVRD, irrespective of surgery

Excluded in PRIMA	Included in PRIMA	
Stage III NVRD after PDS	Stage III NVRD after IDS	Stage IV NVRD after IDS or PDS
Included in marketing authorisation		

- Company and ERG propose different approaches to account for the population excluded from PRIMA
- Answers to the following questions will help determine which approach is most appropriate:
  - Would people with stage III NVRD after PDS be considered to have a different prognosis compared with after IDS?
  - Would niraparib have a different effect on stage III NVRD after PDS compared with after IDS?

NVRD: no visible residual disease; IDS: interval debulking surgery; PDS: primary debulking surgery

Generalisability of population in PRIMA to marketing authorisation population (issue 2) (1)

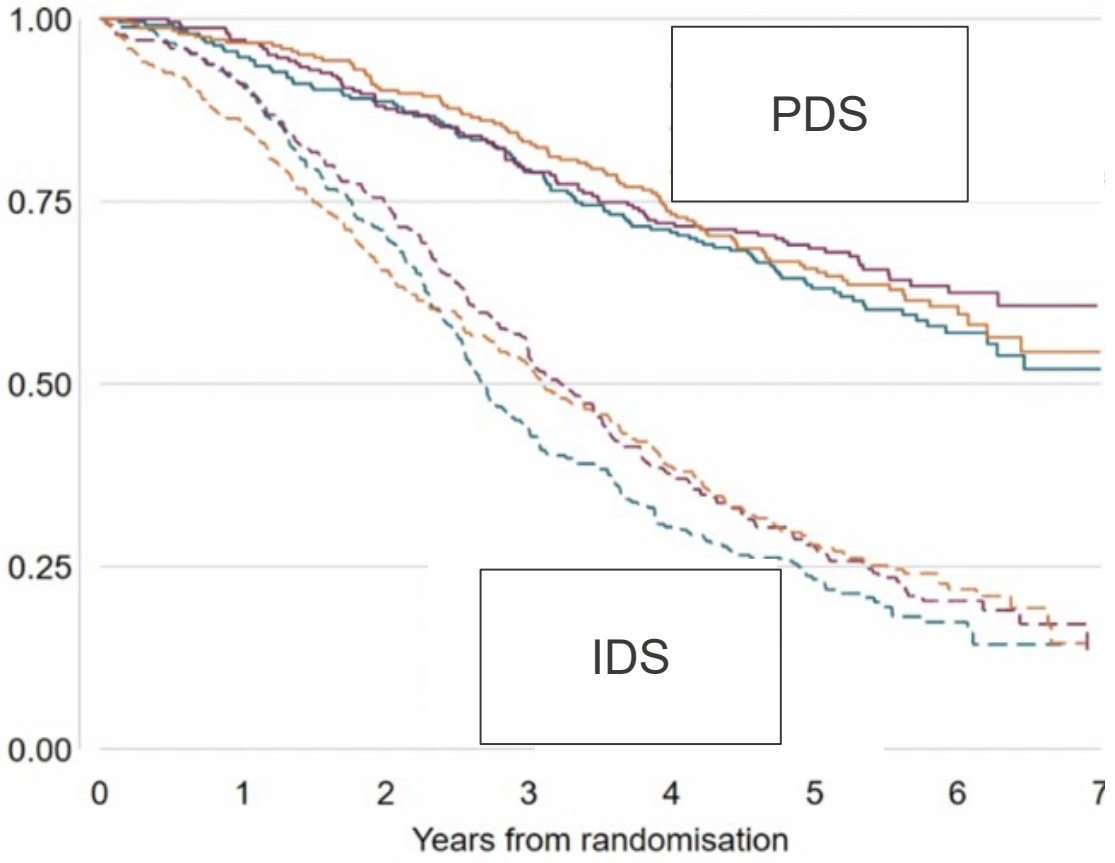
Background

- Company believe prognosis of stage III NVRD after PDS and IDS is different – adjustment with external data needed to account for this
- ERG believe prognosis of stage III NVRD after PDS and IDS can be considered similar – PRIMA data can be used

Company comments

- Selection for PDS is biased towards those with better prognosis (lower staging, reduced disease burden, better fitness, less co-morbidities; ICON-8 trial shows large difference in survival between IDS and PDS)
- Clinical experts expect better prognosis with PDS than IDS – also shown by studies by Vergote et al. (2010) and Kehoe et al. (2015)
- PAOLA-1 shows longer median PFS in 'lower risk' population (stage III NVRD after PDS) compared with a 'higher risk' population (including large proportion of IDS patients with NVRD)

ICON-8: OS in OC patients on chemotherapy – PDS vs IDS



NVRD: no visible residual disease; IDS: interval debulking surgery; PDS: primary debulking surgery; PFS: progression-free survival

Generalisability of population in PRIMA to marketing authorisation population (issue 2) (2)

ERG comments:

- Lack of evidence for difference between stage III NVRD after PDS and IDS:
  - ICON8 shows difference in OS between PDS and IDS and differences in disease characteristics between these patients is likely. Outcomes may differ between groups and NVRD might be a stronger prognostic factor for people who have PDS than IDS
  - But, ICON8, Vergote et al. and Kehoe et al. do not provide quantifiable data to compare PDS and IDS subgroups
  - PAOLA-1 results not generalisable to PRIMA due to confounding

Clinical expert comments

- No clinical distinction in people achieving NVRD via PDS or IDS
- Prognosis in these groups is expected to be similar

Stakeholder comments

- CHORUS trial showed IDS was not inferior to PDS
- NVRD after IDS and PDS should be equivalent and benefit from maintenance PARPi should be similar

NVRD: no visible residual disease; IDS: interval debulking surgery; PDS: primary debulking surgery; OS: overall survival; PARPi: Poly-ADP-ribose polymerase inhibitor

Approach for adjusting PRIMA to the marketing authorisation population (2) (TR issues 2, 3 & 4)

Would people with stage III NVRD after PDS be considered to have a different prognosis compared with after IDS?

Would niraparib have a different effect on stage III NVRD after PDS compared with after IDS?

No

Is proportion of stage III NVRD after IDS in PRIMA ([redacted]) representative of proportion of stage III NVRD irrespective of surgery in clinical practice? If no, what is?

Yes

Is using the PRIMA ITT population analyses appropriate for decision making? (ERG ITT approach)

No

Is adjusting the PRIMA stage III NVRD after IDS population to the proportion of people with stage III NVRD irrespective of surgery type in clinical practice appropriate? (ERG's reweighting approach)

Yes

Use ERG's reweighting approach

No

What would committee like to see?

Yes

What is the most plausible estimate of the proportion of people with stage III NVRD after PDS?

Is the company's approach using 'NVRD effect' and 'treatment effect' adjustment appropriate?

NVRD: no visible residual disease; IDS: interval debulking surgery; PDS: primary debulking surgery; ITT: intention to treat

If answer is ‘no’ - see following slides

Skip this slide if answer 'yes' on slide 23

Estimating proportion of people with stage III NVRD after surgery

Background

- Company estimated [redacted] of MA population have stage III NVRD after PDS using observational data from the University of Edinburgh Ovarian Cancer Database
- [redacted] of PRIMA population have stage III NVRD after IDS

Clinical expert comments

- ERG and company's clinical experts estimate 25 to 40% of MA population is stage III NVRD after PDS; 50 to 60% is stage III NVRD irrespective of type of surgery
- Likely NVRD rates have improved in recent years, but no data to reliably estimate proportion

ERG comments

- Proportion with NVRD after surgery varies across UK practice
- 1 region in the UK unlikely to represent outcomes across the country

- **What is the most plausible estimate of the proportion of people with stage III NVRD irrespective of type of surgery?**
- **Is proportion of stage III NVRD after IDS in PRIMA representative of proportion of stage III NVRD irrespective of surgery in clinical practice?**

Generalisability of population in PRIMA to marketing authorisation population (issue 2) (3)

If people with stage III NVRD after PDS and after IDS are considered to have the **same prognosis** and **same expected treatment effect** with niraparib, consider **ERG approaches**

ERG’s suggested approaches:

- Assume no difference in prognosis between stage III NVRD after PDS and after IDS
- Remove uncertainty from using external sources

If proportion of stage III NVRD in PRIMA is reflective of UK practice:

Consider ERG ITT approach: use PRIMA ITT analysis – no adjustment needed

If proportion of stage III NVRD in PRIMA is different to UK practice:

Consider ERG reweighting approach: reweight PRIMA stage III NVRD after IDS data to estimate stage III NVRD following PDS treatment effect
(requires valid estimate of proportion of stage III NVRD following PDS)

NVRD: no visible residual disease; IDS: interval debulking surgery; PDS: primary debulking surgery; ITT; intention to treat

Proportional hazards (issue 4)

Background

- Company concluded relative hazards for the PFS ITT data are likely to vary over time - the assumption of proportional hazards is unlikely to hold for PFS for the ITT population

Company comments

- Company’s model does not assume PHs between niraparib and RS for PFS
- Assuming PHs between niraparib and RS OS may be appropriate as PH assumption cannot be rejected

ERG comments

- As proportional hazards unlikely to hold, PFS HR and 95% CI is difficult to interpret and potentially misleading

PFS: progression-free survival; ITT: intention to treat; HR: hazard ratio; CI: confidence interval; RS: routine surveillance; PH: proportional hazards

Generalisability of population in PRIMA to marketing authorisation population (issue 2) (4)

- **Is using the PRIMA ITT population analyses appropriate for decision making? (ERG ITT approach)**
- **Is adjusting the PRIMA stage III NVRD after IDS population to the proportion of people with stage III NVRD irrespective of surgery type in clinical practice appropriate? (ERG’s reweighted approach)**

NVRD: no visible residual disease; IDS: interval debulking surgery; ITT; intention to treat

If answer is ‘yes’ - see following slides

Skip this slide if answer 'no' on slide 23

Estimating proportion of people with stage III NVRD after surgery

Company

- Estimated [redacted] of MA population have stage III NVRD after PDS using observational data from the University of Edinburgh Ovarian Cancer Database

Clinical expert comments

- ERG and company's clinical experts estimate 25 to 40% of MA population is stage III NVRD after PDS; 50 to 60% is stage III NVRD irrespective of type of surgery
- Likely NVRD rates have improved in recent years, but no data to reliably estimate proportion

ERG comments

- Proportion with NVRD after surgery varies across UK practice
- 1 small region in the UK unlikely to represent outcomes across the country

- **What is the most plausible estimate of the proportion of people with stage III NVRD after PDS?**

Estimating PFS for people with stage III NVRD after PDS (issue 3) (1)

If people with stage III NVRD after PDS and after IDS are considered to have **different prognosis** or **different expected treatment effect** with niraparib, consider **company** approach

Company’s approach:

- Used external data to model PFS in people with stage III disease with NVRD after PDS
- Requires valid estimate of proportion of stage III NVRD following PDS
- Base case: data from PAOLA-1 (olaparib and bevacizumab vs placebo and bevacizumab) applied to PRIMA ITT population data
- Scenario analysis used:
  - SOLO-1 data (olaparib vs placebo in BRCA+ve OC)
  - PAOLA-1 data to adjust the RS PFS curve and PRIMA stage III subgroup data to adjust the niraparib PFS curve

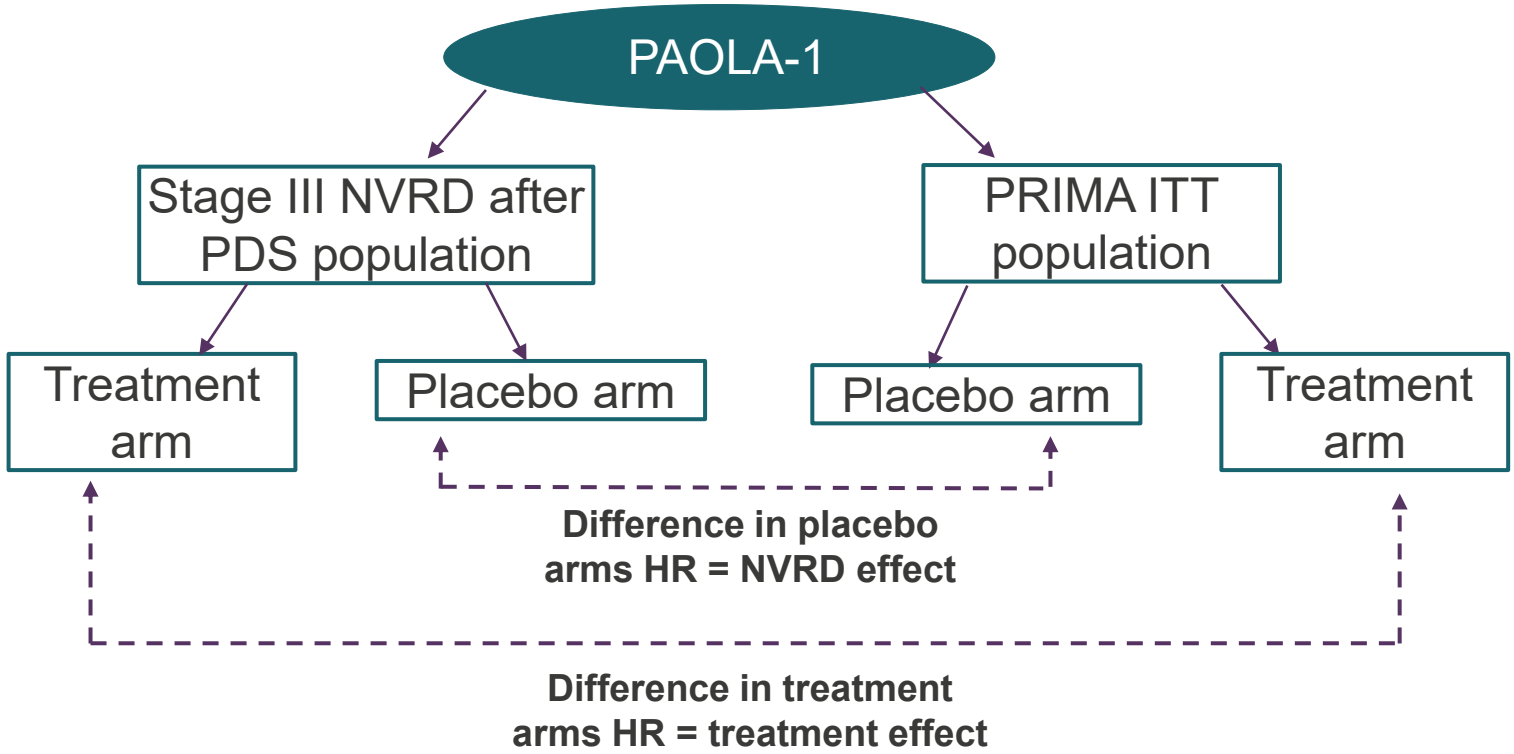
Estimating PFS for people with stage III NVRD after PDS (issue 3) – company's base case approach

- Company used PAOLA-1 to generate 'NVRD effect' and 'treatment effect' HRs
- PAOLA-1 Kaplan-Meier data were digitized to produce pseudo patient level data for 2 groups:
  - Stage III NVRD after PDS
  - Simulated PRIMA ITT population
- NVRD effect was estimated between the two placebo curves
- Treatment effect was estimated between the two treatment curves
- To predict survival curves for stage III NVRD after PDS within the economic model the base case ITT PFS curves were adjusted by applying:
  - the NVRD effect HR to the RS PFS curve
  - the treatment effect HR to the niraparib PFS curve
- Overall MA curves then produced by weighting the ITT and NVRD curves (assuming [redacted]% of patients are NVRD for both niraparib and RS)

This information is shown in a diagram on the following slide

NVRD: no visible residual disease; ITT: intention to treat; HR: hazard ratio; PFS: progression-free survival

Estimating PFS for people with stage III NVRD after PDS (issue 3) – company's base case approach



NVRD effect HR 0.49 (95% CI: 0.329 to 0.723)

Applied to PRIMA ITT routine surveillance PFS curve

Overall MA curves then produced by weighting the ITT and NVRD curves (assuming [redacted]% of the population have NVRD) for both niraparib and RS

Treatment effect HR 0.34 (95% CI: 0.233 to 0.497)

Applied to PRIMA ITT niraparib PFS curve

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NVRD: no visible residual disease; ITT: intention to treat; HR: hazard ratio; PFS: progression-free survival

Estimating PFS for people with stage III NVRD after PDS (issue 3) (2)

ERG's comments on company's approach:

- No reasonable justification given that any adjustment of the PRIMA trial results will provide more reliable results
- PAOLA-1 and SOLO-1 not directly comparable to PRIMA and no adjustments made
- Bevacizumab use in both arms of PAOLA-1 may over estimate 'treatment effect' and under estimate 'NVRD effect'
  - BRCA+ve population in SOLO-1 may over estimate 'treatment effect'
- Company's approach relies on assumption of a class effect

Company comments:

- 'NVRD effect' and 'treatment effect' calculated by comparing patients receiving the same baseline treatment, therefore the impact on confounding minor
- Company's clinical experts agreed they expect a class effect
- PAOLA-1 is most appropriate data source due to distinct subgroups with no overlap between VRD and NVRD groups and includes BRCA mutation +ve and-ve

Stakeholder comments

- PAOLA-1 provides a better prognostic group than SOLO-1 due to differences in the populations included. This aligns with the company's choice of PAOLA-1 in its base case

NVRD: no visible residual disease; PFS: progression-free survival; OS: overall survival

Estimating PFS for people with stage III NVRD after PDS: Proportional hazards (issue 4)

Background

- Company concluded relative hazards for the PFS ITT data are likely to vary over time - the assumption of proportional hazards is unlikely to hold for PFS for the ITT population

Company comments

- PH's assumption holds for the 'NVRD effect' and 'treatment effect' HRs - appropriate to apply HRs to achieve the PFS curves for the NVRD patient group to estimate PFS in the MA population
- Company's model does not assume PHs between niraparib and RS for PFS
- Assuming PHs between niraparib and RS OS may be appropriate as PH assumption cannot be rejected

ERG comments

- As proportional hazards unlikely to hold, PFS HR and 95% CI is difficult to interpret and potentially misleading
- This also impacts the:
  - appropriateness of applying HRs for the NVRD and treatment effect to the PFS curves in PRIMA to estimate the full MA population
  - interpretation of the HR and CIs for fixed and individualised dosing subgroups
- After TE, ERG reiterate that even though PHs assumption holds for 'NVRD' and 'treatment' effect HRs from PAOLA-1, these are being applied to PFS curves in PRIMA where PHs have been demonstrated not to hold

PFS: progression-free survival; ITT: intention to treat; HR: hazard ratio; CI: confidence interval; MA: marketing authorisation

Estimating PFS for people with stage III NVRD after PDS and proportional hazards (issue 3 & 4)

- **Does the committee consider the company’s justification for the MA population analysis to be appropriate?**
- **Is the company’s method of applying HRs from other sources to PRIMA ITT PFS curves robust?**

MA: marketing authorisation; ITT: intention to treat; HR: hazard ratio; PFS: progression-free survival

Key clinical issues (1)

- **Generalisability of dosing used in PRIMA to clinical practice**
  - Is the dosing used in the clinical trial reflective of the likely dosing in clinical practice and therefore, are the results from PRIMA generalisable to clinical practice?
- **Generalisability of population in PRIMA to MA population**
  - Would people with stage III NVRD after PDS be considered to have a different prognosis compared with after IDS?
  - Would niraparib have a different effect on stage III NVRD after PDS compared with after IDS?

MA: marketing authorisation; NVRD: no visible residual disease; PDS: primary debulking surgery; IDS: interval debulking surgery

Key clinical issues (2)

- **Estimating proportion of people with stage III NVRD after surgery**
  - What is the most plausible estimate of the proportion of people with stage III NVRD irrespective of type of surgery?
  - Is the proportion of stage III NVRD after IDS in PRIMA representative of the proportion of stage III NVRD irrespective of surgery in clinical practice?
  - What is the most plausible estimate of the proportion of people with stage III NVRD after PDS?
- **Estimating PFS for people with stage III NVRD after PDS**
  - Is using the PRIMA ITT population analyses appropriate for decision making? (ERG ITT approach)
  - Is adjusting the PRIMA stage III NVRD after IDS population to the proportion of people with stage III NVRD irrespective of surgery type in clinical practice appropriate? (ERG reweighted approach)
  - Does the committee consider the company's justification for the MA population analysis to be appropriate?
  - Is the company's method of applying HRs from other sources to PRIMA ITT PFS curves robust?

NVRD: no visible residual disease; PDS: primary debulking surgery; IDS: interval debulking surgery; ITT: intention to treat

Cost effectiveness

Key cost effectiveness issues

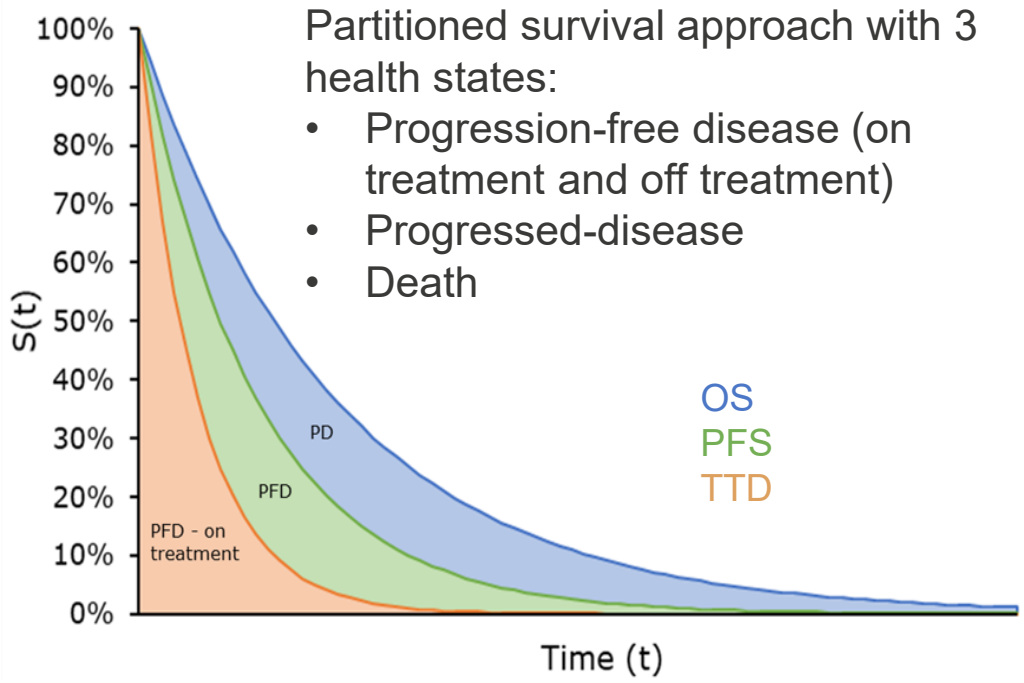
- **Company's model structure**
  - Is it appropriate for decision making?
- **Estimating OS from ΔPFS: ΔOS ratio**
  - Is the company's approach of estimating OS from a ΔPFS: ΔOS ratio instead of using OS KM data from the PRIMA trial appropriate?
  - What ΔPFS: ΔOS ratio is considered clinically plausible and most appropriate for decision making?
- **Time to treatment discontinuation**
  - Is including a 3-year stopping rule in the model appropriate?
  - What proportion of people would continue to receive niraparib beyond 3-years?
  - Would niraparib be given until disease progression?
- **Utility values**
  - Is the company's justification for not including age-related utility decrements in its base case accepted by committee?
- **Subsequent treatments**
  - Are the proportions of people receiving subsequent treatment in PRIMA representative of UK clinical practice?
  - Are the subsequent treatments included in the modelling appropriately?

Company's cost effectiveness model

Model type	3-state partitioned survival model: progression-free, progressed-disease, death	
Time horizon	39 years	
Model cycle	1 month	
Utility values	EQ-5D data from the PRIMA trial with UK valuation set applied Age-related utility decrements not applied	
Discount rates	3.5% for health and cost outcomes	
Perspective	NHS and PSS	
	PRIMA ITT population model	**Marketing authorisation population model**
Population	Adults with **stage III VRD, stage III NVRD after IDS or stage IV** ovarian cancer who are in response to first-line PBC	Adults with **stage III or IV** ovarian cancer who are in response to first-line PBC [redacted]% of population stage III patients with NVRD after PDS
Intervention	Niraparib	
Comparators	Routine surveillance	
Outcomes	OS estimated from 1: 2 ΔPFS:ΔOS	
Treatment discontinuation	[redacted]% who remain on treatment discontinue at 3 years = [redacted]% continuation at 3 years	[redacted]% who remain on treatment discontinue at 3 years = [redacted]% continuation at 3 years

ITT; intention to treat; NVRD: no visible residual disease; IDS: interval debulking surgery; PDS: primary debulking surgery; PBC: platinum-based chemotherapy

Company's model structure (issue 6)



Partitioned survival approach with 3 health states:

- Progression-free disease (on treatment and off treatment)
- Progressed-disease
- Death

Background

- PRIMA collected PFS2 data – could be used to inform a 4-state model
- PFS2 data could capture second progression-related costs and the impact of secondary events on QoL

ERG comments

- Estimating impact of adding PFS2 data not possible
- PFS2 data are 20% mature - more immature data has been included in the company's model

Company comments

- Using 4 states will not alleviate current uncertainty:
  - Subsequent treatments across arms are similar and captured as one-off cost upon progression
  - QoL remains stable during 2nd line treatment so impact on utilities due to relapse negligible
  - PFS-2 data is immature and would add additional uncertainty
  - Adding a PFS-2 health state would not alleviate uncertainty on OS estimates

Is the company's model structure appropriate?

NICE

QoL: quality of life; OS: overall survival

Estimating OS from ΔPFS: ΔOS ratio (issue 5) (1)

Background

- OS data are immature
- Median OS was [redacted] months in the niraparib arm and not reached in placebo arm
- Company estimated niraparib OS by applying a HR to PRIMA RS OS curve. HR derived from ΔPFS: ΔOS ratio of 1: 2 from Study 19 (olaparib vs RS for 2nd line treatment)
- Company predict [redacted]% of patients remain alive at age 91 in the MA base case and [redacted]% remain alive at age 91 in ITT base case
- DSU review (Davis et al, 2012) concluded even when robust evidence supporting a correlation between the treatment effect on PFS and OS is available, it remains unclear how that should be converted for cost-effectiveness modelling

Company comments

- Davis et al. 2012 did not include data from OC trials, pre-dated the extended use of PARP inhibitors and was not a full systematic review
- ΔPFS: ΔOS ratio has been used in previous appraisals [TA528, TA598 and TA611]
- Cannot use KM data as niraparib OS curves cannot be validated by real-world data
- Study 19 is best available evidence to inform a ΔPFS: ΔOS ratio
- Applying HR to RS OS arm appropriate – it does not lead to a constant survival advantage
- Based on ONS all-cause risk of death data, an individual aged 91 has a 27% chance of remaining alive

OS: overall survival; PFS: progression-free survival; RS: routine surveillance; ITT: intention to treat; HR: hazard ratio; MA: marketing authorisation; KM: Kaplan-Meier

Estimating OS from ΔPFS: ΔOS ratio (issue 5) (2)

ERG comments

- Evidence not sufficient to suggest using PFS:OS ratio is appropriate
- Sundar et al. (2012) systematic review on PFS and post-progression survival relationship in OC concludes the magnitude of improvement in PFS is the same as magnitude of the improvement in OS
- Systematic review identified in TA598 found the relationship between median times to PFS and OS do not show an equivalent relationship to HRs for these outcomes
- OS HR of [redacted] derived from the ΔPFS: ΔOS ratio of 1:2 (company base case) is not reflective of PRIMA treatment effect (OS HR 0.70, 95% CI: 0.44 to 1.11)
- At[redacted] months, RS and niraparib OS KM curves nearly converge. At same point modelled RS and niraparib OS curves are on a [redacted] trajectory – an implication of applying a HR to the RS arm to estimate OS for niraparib
- Applying a HR to a log-logistic model (used to fit the OS RS curve) is methodologically inappropriate
- Disagrees that applying HR to RS OS arm does not lead to a constant survival benefit
- Study 19 might provide an indication of how OS curves in PRIMA would evolve over time. Also possible that the results observed during PRIMA will not change

- Most plausible PFS: OS ratio in this population not previously agreed by NICE committees
- TA528 concluded that there is no reason to suppose that the OS benefit will be less than the PFS benefit, but it is uncertain if the OS benefit will be equal to or exceed the PFS benefit

OS: overall survival; PFS: progression-free survival; RS: routine surveillance; HR: hazard ratio; OC; ovarian cancer; KM: Kaplan-Meier

Estimating OS from ΔPFS: ΔOS ratio (issue 5) (3)

ERG comments continued

- OS curve derived from PFS:OS ratio should be validated by clinical expert opinion or external data – not a valid argument to use PFS:OS ratio over KM data
- More robust to use data from PRIMA - assumption of a constant relative treatment effect would not be needed
- ERG scenario analyses include using a ΔPFS: ΔOS ratio of:
  - 1:0.66 (as in TA598 CS)
  - 1:1
  - 1:1.13 (corresponding to a HR of 0.70 - treatment effect in PRIMA).

Stakeholder comments

- Appropriate ratio is likely closer to 1:1 than 1:3

Company comments

- Most appropriate ratio is 1:2 and no less than 1:1.13:
  - PRIMA treatment effect HR of 0.70 translates to ΔPFS: ΔOS ratio of 1:1.13
  - Chemotherapy alone increases OS on at least a 1:1 ratio in OC (Sundar et al.)
  - 5 clinical trials in OC show a range between 1:2 and 1:4 (Vergote 2010, Kehoe 2015, Tewari 2019, Bristow 2007 and Armstrong 2006)
  - Clinical experts expect to see at least a 1:1 ratio
  - 1:1 ratio accepted in TA528 (relapsed setting) - outcomes are expected to be better in a 1st line setting
  - Disputes the clinical plausibility of a 1:0.66 ratio
- OS data from PRIMA are very immature. SOLO-2 and Study 19 show as data matures treatment effect on OS improves relative to RS. HR [redacted] lies within the CI of the observed data

NICE

OS: overall survival; PFS: progression-free survival; HR: hazard ratio; CI: confidence interval

Estimating OS from ΔPFS: ΔOS ratio (issue 5) (4)

ERG analysis: PFS to OS ratios and corresponding survival gains in the model		
PFS to OS ratio (α parameter) in the equation: Niraparib mean OS = (RS mean OS + [Mean PFS difference x α])	Resulting hazard ratio applied to the OS RS curve to derive the OS niraparib curve in the model (a HR <1 indicates a survival benefit for niraparib vs RS)	Total undiscounted life years gained with niraparib vs RS
α=0.66	0.84	0.79
α=1	0.74	1.50
α=1.13 (derived from PRIMA data)	0.70	1.83
α=2	[redacted]	[redacted]

- **Is the company's approach of estimating OS from a ΔPFS: ΔOS ratio instead of using OS KM data from the PRIMA trial appropriate?**
- **What ΔPFS: ΔOS ratio is considered clinically plausible and most appropriate for decision making?**

OS: overall survival; PFS: progression-free survival; HR: hazard ratio; RS: routine surveillance

Time to treatment discontinuation (issue 9)

Background

- 3-year stopping rule used by company's - assumed [redacted] of participants who had not discontinued treatment at 3 years continued to receive niraparib
- Summary of product characteristics does not specify a treatment duration of 3 years and recommends that treatment with niraparib should be continued until disease progression or toxicity
- PRIMA clinical evidence will incorporate treatment benefit for people who continued to receive niraparib after 3 years but this proportion is unknown

ERG comments

- The proportion of patients who remained on treatment after follow-up in PRIMA is unknown
- ERG's preferred assumptions include assuming no treatment discontinuation with niraparib

Clinical expert comments

- Likely that:
  - treatment with niraparib would continue at 3-years in people who had controlled residual disease without progression
  - niraparib would be given until disease progression
  - niraparib would be discontinued at 3 years in people who have NVRD
  - [redacted]% is a clinically plausible estimate of proportion of people who would continue treatment at 3 years

- **Is including a 3-year stopping rule in the model appropriate?**
- **What proportion of people would continue to receive niraparib beyond 3-years?**
- **Would niraparib be given until disease progression?**

Utility values (issue 10)

Background

- Company did not include age-related utility decrements in its base-case analysis
- Average age of participants in PRIMA is 62, however the lifetime horizon in the model means patients can live up to 100 years
- Company assume that PFS utility value ([redacted]) is appropriate throughout the full time horizon. This means, by 7 years, patients in the PFS state have a [redacted] utility that the general population (0.78)

Company comments

- Utility values were derived directly from EQ-5D data in PRIMA
- SLR of PARP inhibitor maintenance therapy found utility values ranged from 0.769 to 0.872 (PFD) and 0.649 to 0.828 (PD)
- QoL in PRIMA is consistent across age groups and did not change considerably over 56 weeks
- QoL is not negatively impacted by age which is assumed when using age-adjusted utility values

ERG comments

- Company's approach overestimates the utility of survivors and the cost effectiveness of niraparib
- ERG's preferred assumptions included applying age-related utility decrements in the model

- **Is the company's justification for not including age-related utility decrements in its base case accepted by committee?**

NICE

PFS: progression-free survival; SLR: systematic-literature review; QoL: quality of life

Subsequent treatments (issue 11)

Background

- Small proportion of patients in PRIMA [redacted] (less than [redacted]%). These treatments are recommended in the CDF for second-line use and are therefore not established in routine clinical practice
- In PRIMA 85% and 81% for niraparib and RS arms, respectively, received chemotherapy following progression

Company comments

- Clinical experts suggest that subsequent treatment in PRIMA is representative of UK clinical practice - the exception is PARP inhibitor and immunotherapy use in the niraparib arm ([redacted]% and [redacted]% respectively)
- Recent study (Hall et al. 2020) on real-world treatment patterns in UK patients with advanced ovarian cancer showed results in line with observed information in PRIMA

ERG comments

- Proportion having subsequent treatment in PRIMA lower than expected in clinical practice and in other trials: SOLO-1, 90% and 93% in the olaparib and placebo arms, respectively

Stakeholder comments

- >80% receiving subsequent treatment is reasonable and reflects UK practice

- **Are the proportions of people receiving subsequent treatment in PRIMA representative of UK clinical practice?**
- **Are the subsequent treatments included in the modelling appropriately?**

CDF: Cancer Drugs Fund; RS: routine surveillance

Equality considerations and innovation

Equalities issues

- No issues identified

Innovation

- Company considers niraparib to be an innovative treatment:
  - there is no maintenance treatment approved for routine use in the first-line setting
  - no PARP inhibitors are available for first-line maintenance for BRCA mutation negative patients in the CDF or in routine commissioning
- Technical team considers that all relevant benefits are adequately modelled

- **Are there any equality issues?**
- **Is niraparib a 'step change' in treatment?**
- **Are there benefits not included in the model?**

Issues resolved after technical engagement

Summary	Stakeholder responses	Technical team consideration
Generalisability of PRIMA results to UK - proportion of complete and partial response to platinum-based chemotherapy (PBC) in PRIMA	PRIMA population is representative of the UK population	Based on the proportion of complete and partial response to PBC, PRIMA data is generalisable to UK practice
Company updated model to remove long-term remission assumption in terms of survival and assumed progression-free patients stop incurring disease management costs at 7 years	Long-term remission at 7 years is a clinically reasonable assumption	Removing the long-term remission assumption has a minimal effect on the ICER and decreases uncertainty in the model. Clinical expert feedback suggests it is reasonable to assume progression-free patients stop incurring costs at 7 years
Dose likely to be given to people who continued treatment after 3 years is unclear	Doses tolerated at 18 months are likely to continue to be tolerated	It is reasonable to assume that the dose of niraparib tolerated in month 18 will continued to be tolerated throughout the course of treatment

Cost effectiveness results

Please note that there are confidential PAS discounts for comparators. Decision making ICERs will be presented to the committee in Part 2

Cost effectiveness results – company base case

Deterministic analysis

	Costs	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case ITT population					
RS	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	£19,178
Company base case MA population					
RS	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	£14,184

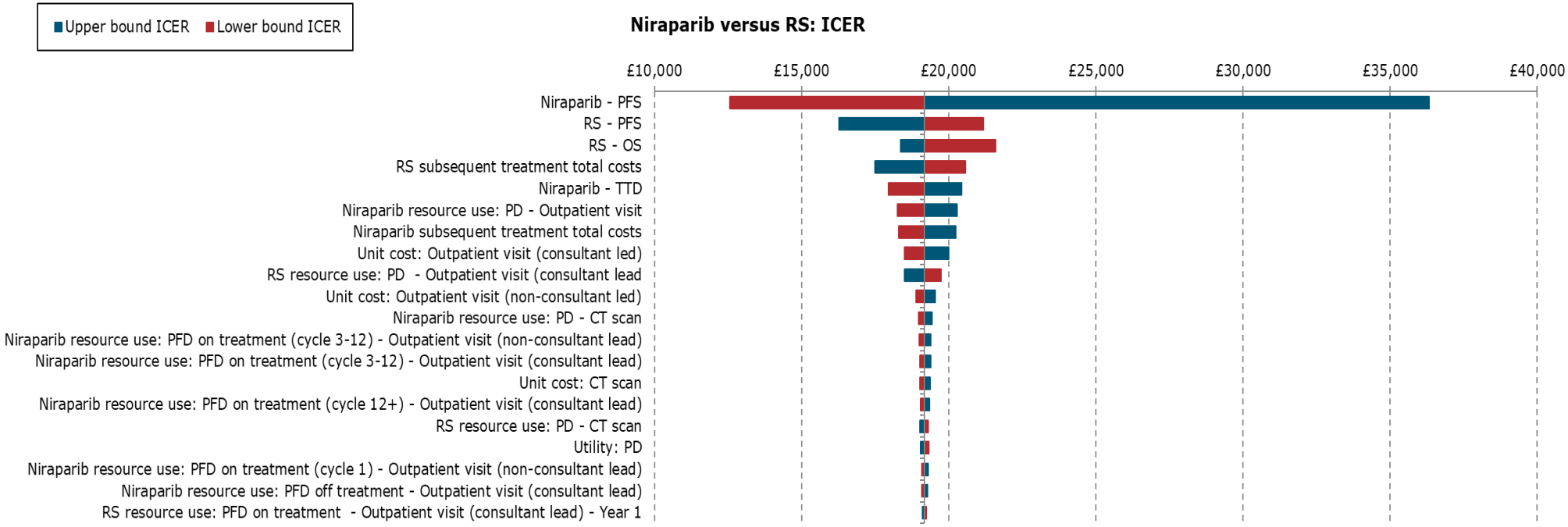
Probabilistic analysis

	Costs	QALYs	Incremental costs (SD)	Incremental QALYs (SD)	ICER (£/QALY)
Company base case ITT population					
RS	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	£18,910
Company base case MA population					
RS	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	£14,383

NICE

ITT: intention to treat; MA: marketing authorisation; SD: standard deviation

Company's deterministic sensitivity analysis – ITT population



Results were most sensitive to:

- the scale and shape of the niraparib PFS distribution
- the routine surveillance PFS distribution
- the routine surveillance OS distribution

Low value determined by:

- Lower bound of 95% CI
- -20% (when CI not available)
- -10% (HRs only)

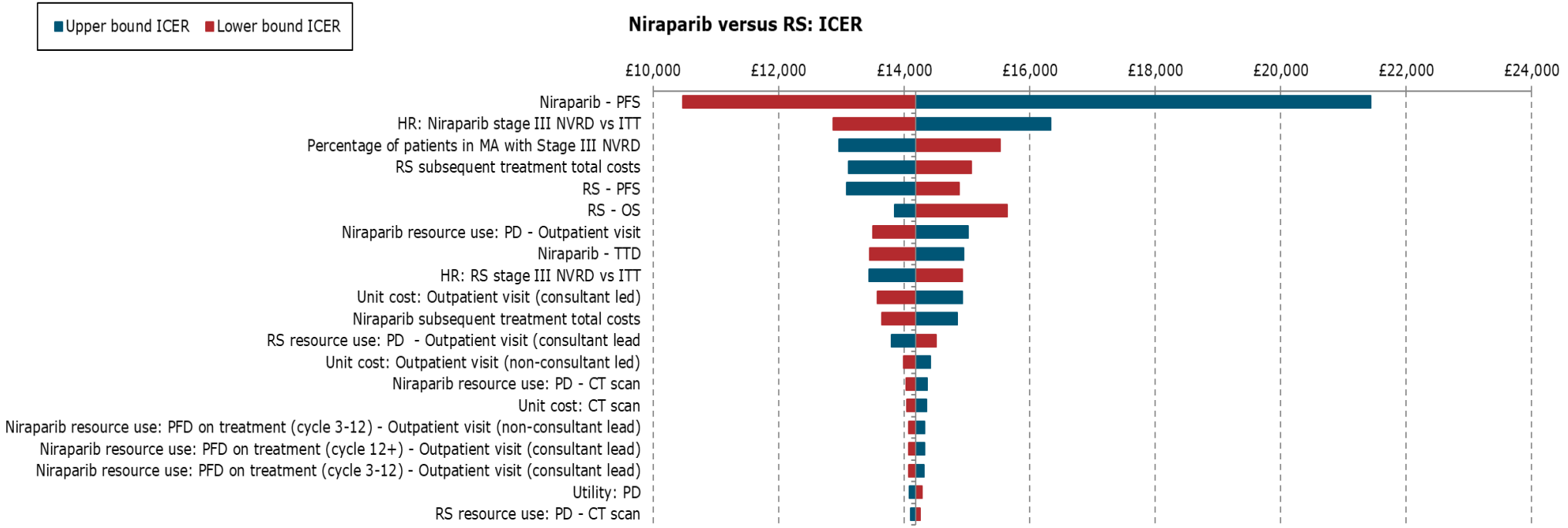
Higher value determined by:

- Higher bound of 95% CI
- +20% (when CI not available)
- +10% (HRs only)

NICE

ITT: intention to treat

Company's deterministic sensitivity analysis - MA population



Results were most sensitive to:

- the scale and shape of the niraparib PFS distribution
- the 'NVRD effect' HR
- the proportion of stage III patients with NVRD after PDS
- routine surveillance subsequent treatment costs

Low value determined by:

- Lower bound of 95% CI
- -20% (when CI not available)
- -10% (HRs only)

Higher value determined by:

- Higher bound of 95% CI
- +20% (when CI not available)
- +10% (HRs only)

NICE

IMA: marketing authorisation

Company's cost effectiveness results – scenario analysis

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ITT scenarios			
Company base case ITT population	[redacted]	[redacted]	19,178
Assume patients who are progression-free at 10 years stop incurring costs	[redacted]	[redacted]	19,266
ΔPFS:ΔOS = 1:1	[redacted]	[redacted]	40,649
ΔPFS:ΔOS = 1:1.13	[redacted]	[redacted]	34,470
ΔPFS:ΔOS = 1:1.5	[redacted]	[redacted]	25,080
MA scenarios			
Company base case MA population	[redacted]	[redacted]	14,184
NVRD effect only	[redacted]	[redacted]	16,241
Assume patients who are progression-free at 10 years stop incurring costs	[redacted]	[redacted]	14,267
ΔPFS:ΔOS = 1:1	[redacted]	[redacted]	34,696
ΔPFS:ΔOS = 1:1.13	[redacted]	[redacted]	27,669
ΔPFS:ΔOS = 1:1.5	[redacted]	[redacted]	18,634
ΔPFS:ΔOS = 1:2.5	[redacted]	[redacted]	11,728

ITT: intention to treat; PFS: progression-free survival; OS: overall survival; NVRD: no visible residual disease

ERG's approach to modelling

ERG preferred assumptions:

- Use of ITT population
- No LTR and assuming PFS patients stop incurring costs at 10 years (vs 7 in company model)
- Use of age-related utility decrements
- No treatment discontinuation with niraparib
- Including cost of heart rate and blood pressure monitoring
- Alternative resource use estimates for PFS

The ERG considered 3 different sets of scenarios to investigate changes in OS modelling:

- PFS to OS ratio of 1:0.66 (as in TA598 company submission)
- PFS to OS ratio of 1:1
- HR between RS OS and niraparib OS of 0.70 (as observed in PRIMA) - PFS to OS ratio of 1:1.13

Each of the ERG's preferred assumptions has limited impact on the ICER when run in isolation

ERG do not agree with use of ΔPFS: ΔOS to estimate OS – more appropriate to use PRIMA data

The ERG was restricted to conducting additional analysis through use of PFS to OS ratios and HRs to estimate the niraparib OS curve. Use of HRs assumes that niraparib has a constant survival advantage over RS for the entire time horizon of the analysis. This is unlikely to represent clinical reality.

ERG concludes: without having more mature OS data from PRIMA it is not possible to make inferences on the survival benefits of niraparib without a paramount level of uncertainty

ITT: intention to treat; LTR: long-term remission; PFS: progression-free survival; OS: overall survival; RS: routine surveillance; HR: hazard ratio

Cost effectiveness results – ERG analysis

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Use of a PFS to OS ratio of 1: 0.66 (HR between RS OS and niraparib OS of 0.84)					
RS	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	£79,146
Use of a PFS to OS ratio of 1: 1 (HR between RS OS and niraparib OS of 0.74)					
RS	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	£45,265
Use of a HR between RS OS and niraparib OS of 0.70 (PFS to OS ratio of 1: 1.13)					
RS	[redacted]	[redacted]	-	-	-
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	£38,284

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PFS: progression-free survival; OS: overall survival; HR: hazard ratio

Consideration for the Cancer Drugs Fund (CDF)

Company comments:

- PRIMA trial is ongoing and will continue to collect data on OS (next data cut [redacted] expected [redacted] data maturity)
- CDF would allow PRIMA trial data to mature and provide insight around uncertainty of OS
- Systemic anti-cancer therapy (SACT) data would decrease uncertainty around the outcomes for the full marketing authorisation population

Stakeholder comments:

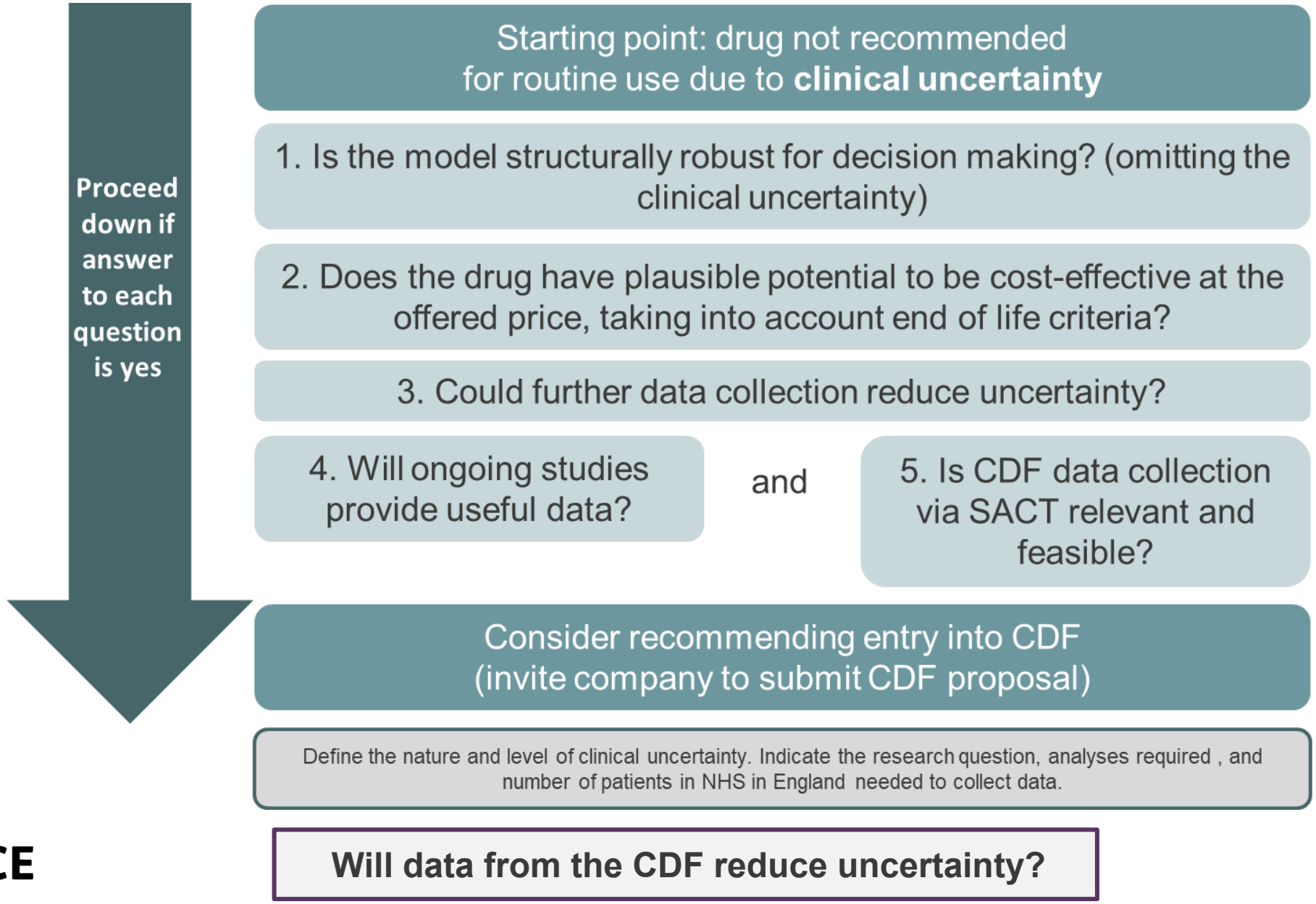
- Suitable candidate for CDF

NICE comments

- Availability of SACT data for stage III NVRD after PDS would depend on this population accessing niraparib during the data collection agreement

PFS: progression-free survival; CDF: cancer drugs fund; SACT: systemic anti-cancer therapy; NVRD: no visible residual disease; PDS: primary debulking surgery

Committee decision making: CDF recommendation criteria



Will data from the CDF reduce uncertainty?

NICE

Key cost-effectiveness issues

- **Company's model structure**
  - Is it appropriate for decision making?
- **Estimating OS from ΔPFS: ΔOS ratio**
  - Is the company's approach of estimating OS from a ΔPFS: ΔOS ratio instead of using OS KM data from the PRIMA trial appropriate?
  - What ΔPFS: ΔOS ratio is considered clinically plausible and most appropriate for decision making?
- **Time to treatment discontinuation**
  - Is including a 3-year stopping rule in the model appropriate?
  - What proportion of people would continue to receive niraparib beyond 3-years?
  - Would niraparib be given until disease progression?
- **Utility values**
  - Is the company's justification for not including age-related utility decrements in its base case accepted by committee?
- **Subsequent treatments**
  - Are the proportions of people receiving subsequent treatment in PRIMA representative of UK clinical practice?
  - Are the subsequent treatments included in the modelling appropriately?

Back-up slides

Estimating long-term remission

Background

- At technical engagement, the company updated its model to remove the long-term remission assumption in terms of survival and assumed that progression-free patients stop incurring disease management costs at 7 years

ERG comments

- For the company's estimate of long-term remission, using external sources of evidence is methodologically weak
- Agrees that PRIMA does not provide robust evidence to substantiate a cure threshold for niraparib
- The ERGs preferred assumptions in its model included removing the long-term remission approach
- ERG presented scenario analysis in which patients who are progression-free at 7 or 10 years stop incurring disease management costs

Company comments

- Information from clinical experts and published long-term evidence indicates LTR at 7 years is a clinically reasonable assumption

NICE

When can long-term remission be reasonably assumed?

Company's cost effectiveness results – scenario analysis

Stage III NVRD after PDS %	ICER (£/QALY)
Company analysis before technical engagement (model includes assumption of long-term remission)	
[redacted]% (scenario analysis)	12,105
[redacted]% (scenario analysis)	13,183
[redacted]% (base case)	13,870
Company analysis after technical engagement (long-term remission assumption removed from model)	
[redacted]% (company base case)	14,184

ITT: intention to treat; PFS: progression-free survival; OS: overall survival; NVRD: no visible residual disease