For public – contains redacted information

Niraparib for first-line maintenance treatment of advanced ovarian cancer (review of TA673)

Technology appraisal committee A [2nd December 2025]

Chair: Radha Todd

Lead team: Andrew Champion, Zoe Philips, Victoria Houghton

External assessment group: BMJ Technology Assessment Group (BMJ-TAG)

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Company: GlaxoSmithKline

Niraparib for first-line maintenance treatment of advanced ovarian cancer

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on advanced stage III and IV ovarian, fallopian tube and peritoneal cancer (ovarian cancer; OC)

Causes

- Exact causes not fully understood but several risk factors: increasing age, lifestyle and environmental factors (smoking, overweight, exposure to asbestos), hormone replacement therapy and certain medical conditions (e.g. endometriosis, diabetes) and genetic factors have been associated with elevated risk
- Homologous recombination deficiency (HRD) increases genetic instability and risk of OC
- Half of HRD positive cases attributed to BRCA1/2 mutations (BRCAm)

Epidemiology

- 7,078 people were diagnosed with OC in 2022, ~ 60% diagnosed at FIGO stage III-IV with low cure potential
- Epithelial OC accounts for 90% of cases, 70% of which are classified as high-grade serous subtype (marketing authorisation population)

Symptoms and prognosis

- Symptoms are usually non-specific which can delay diagnosis. They include bloating, early satiety, loss of appetite, persistent pain in abdomen or lower abdomen, increased need to urinate, changes in bowel habits, symptoms of irritable bowel syndrome, unexplained fatigue and unexplained weight loss
- In England (2016–2020), 5-year survival rates for stage III and IV ovarian cancer were 31.9% and 16.0%, respectively

BRCAm, Breast cancer gene mutation; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency; OC, ovarian cancer.

Patient perspectives

Additional maintenance treatment options would be beneficial

Submissions from Ovarian Cancer Action, Ovacome Ovarian Cancer Charity, Target Ovarian Cancer

- Ovarian cancer is devastating for patients and their families/ friends, with a poor prognosis for those diagnosed at a late stage
- Patients and their families face a great deal of anxiety over treatment itself, and whether the disease will recur (which it does for most). Maintenance treatments offer patients more time between chemotherapy treatments
- Niraparib is convenient in terms of administration, offering good quality of life for patients, for whom treatment side effects are manageable
- Patients welcome opportunity to be involved in making decisions about care and feel they can take some control at what is a very uncertain time
- Choice is important so that there are alternate options when side effects are not tolerated

"Ovarian cancer not only limits the time a woman has to live, it also limits what a woman is able to do with the time she has left."

"When you have ovarian cancer you are not yourself - life revolves around the disease and in the very worst moments you have no interest in your family, friends and general life outside of the disease and what it is putting your body and mind through"

"…Living with OC now, with me being NED (no evidence of disease) for over 6 years feels different as I take a maintenance drug which is very effective. It's my parachute."

Clinical perspectives

Improved survival outcomes in advanced ovarian cancer with introduction of PARP inhibitors

Submission from clinical expert

- Treatment aim in newly diagnosed advanced ovarian cancer is to provide patients with longer time before subsequent treatment is needed, and to improve duration of overall survival
- Maintenance treatment with niraparib significantly extends progression-free survival in patients with advanced ovarian cancer
- PARP inhibitors (such as niraparib) have improved survival outcomes in people with advanced ovarian cancer
- Niraparib has the greatest effect in patients with BRCA mutations but also provide benefit in HRD positive BRCA wild type ovarian cancer
- Side effects of niraparib are manageable; few patients needing to stop treatment due to adverse effects

The survival results at 5 years in the pivotal PRIMA trial are higher than has been seen in trials in the pre-PARPi era and the inclusion of niraparib maintenance represents a new and highly positive outcome result for patients with advanced ovarian cancer.

BRCA, Breast cancer gene; HRD, homologous recombination deficiency; PARPi, poly-ADP ribose polymerase inhibitor

Equality considerations

Company:

- No known equality issues relating to the use of niraparib

NICE NG241:

- Rate of familial ovarian cancer is higher in Ashkenazi Jewish ethnicity

Patient organisation (Ovacome):

- People may struggle to access treatments if they do not understand treatment options and choices. This includes people with learning disability, people with English as a second language or low levels of literacy

Are there any additional equality issues that need to be considered?

NG, NICE guideline

Niraparib (Zejula, GSK)

Marketing authorisation	• Indicated "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" • Marketing authorisation from MHRA on 6 December 2022
Current NICE recommendation	• Recommended for use within Cancer Drugs Fund (TA673) • In TA673, committee noted that longer follow-up data from PRIMA could help address uncertainty about clinical effectiveness of niraparib • In current evaluation, longer follow-up data from PRIMA and new data from PRIME trial
Mechanism of action	• Poly-ADP-ribose polymerase (PARP) inhibitor • Inhibits PARP proteins involved in DNA repair
Administration	• Oral monotherapy • Recommended starting dose: 200 mg (two 100 mg tablets), taken once daily. For people who weigh ≥77 kg and have a baseline platelet count ≥ 150,000/μL, recommended starting dose is 300 mg (three 100 mg tablets), taken once daily
Price	• £4,500 for 1 pack of 56 x 100 mg tablets • £6,750 for 1 pack of 84 x 100 mg tablets • Patient access scheme applicable

NICE

DNA, deoxyribonucleic acid; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency; MHRA, Medicines and Healthcare products Regulatory Agency; PARP, poly-ADP ribose polymerase

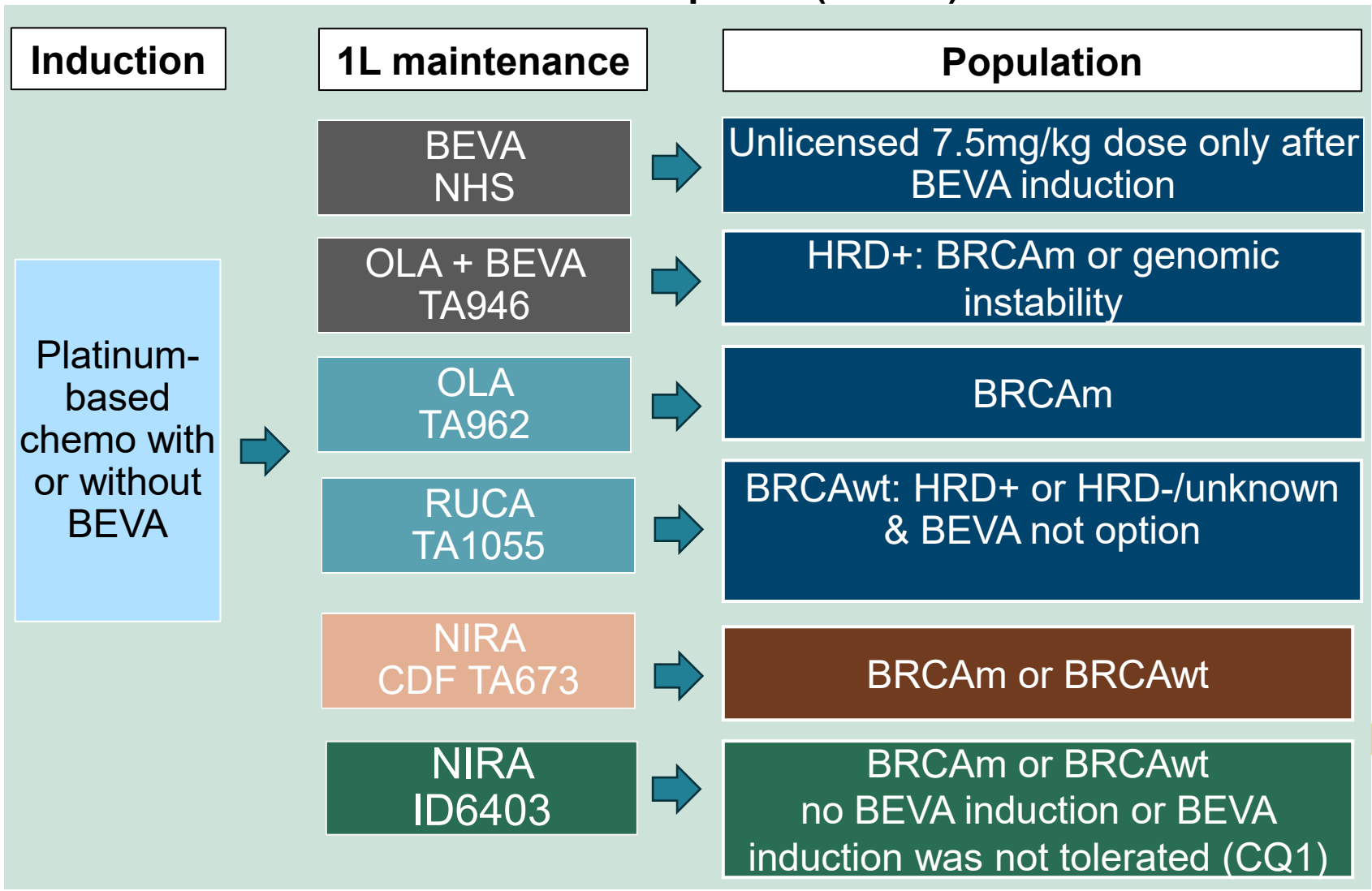
Key issues

Issue	ICER impact
Comparators and positioning of niraparib	Unknown 
Trials used for ITC	Large 
Assumption of clinical equivalence	Large 
Model structure	Unknown 
Consideration of HRD status	Unknown 
Data to inform treatment comparisons in model for BRCAwt population	Large 
Data to inform treatment comparisons in model for BRCAm population	Large 
Time to treatment discontinuation	Large 

BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; HRD, homologous recombination deficiency; ITC indirect treatment comparison

Advanced ovarian cancer (stage III-IV) – treatment pathway

1L maintenance treatment after response (CR/PR) to induction chemotherapy



Comparator in submission?

- Not included
- Included: olaparib for BRCAm; rucaparib for BRCAwt population
- Reviewed in current appraisal
- Current appraisal-proposed positioning

Commissioning

- Cancer drug fund (CDF)
- Routine commissioning

Is the treatment pathway reflective of clinical practice?

See appendix for treatment options by genomic status

BEVA, bevacizumab; BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type chemo, chemotherapy; CDF, Cancer Drugs Fund; CR/PR, complete response/partial response; CQ1, clarification question1; HRD, homologous recombination deficiency; NIRA, niraparib; OLA, olaparib; RUCA, rucaparib.

Key issues: Comparators and positioning of niraparib

Background

- Bevacizumab monotherapy and olaparib with bevacizumab included in scope but company did not consider these to be relevant comparators

Company

- In line with TA946, olaparib with bevacizumab only recommended in people who have completely or partially responded to first-line platinum-based chemotherapy with bevacizumab
- Use of bevacizumab monotherapy as a maintenance therapy requires completion of first-line induction chemotherapy in combination with bevacizumab (BEV10 commissioning criteria)
- SACT data for niraparib shows that majority of people did not receive bevacizumab during induction treatment and received platinum-based chemotherapy alone

EAG comments

- Accepts rationale for excluding bevacizumab monotherapy and olaparib with bevacizumab as comparators
- Suggests that any NICE recommendation for niraparib clearly stipulates that it applies where bevacizumab is not a treatment option (consistent with the wording for TA1055)

Clinical expert: use of niraparib will be largely confined to people with a BRCA mutation or BRCA-wild type HRD positive who do not require bevacizumab or for whom bevacizumab is not appropriate

Is the company's positioning of niraparib appropriate?
Are bevacizumab monotherapy and olaparib with bevacizumab appropriate comparators ?
Can the committee only make a recommendation where bevacizumab is not a treatment option?

BRCA, Breast cancer gene, External Assessment Group; HRD, homologous recombination deficiency; SACT, systemic anti-cancer therapy; TA, technology appraisal

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Key clinical trials: PRIMA

	PRIMA
Design	Randomised, double-blind, phase III trial
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	Oral niraparib 300 mg once daily or, individualised starting dose of 200 mg for people with baseline body weight <77 kg or platelet count <150,000 per cubic millimetre or both* (N=487)
Comparator(s)	Placebo oral once daily (N=246)
Max treatment duration	36 months. People benefitting from treatment per investigator assessment were eligible to continue receiving treatment beyond 3 years
Follow up	73.9 months for niraparib; 73.8 months for placebo
Key outcomes	PFS (primary outcome) OS; TFST; PFS2; HRQoL; adverse effects of treatment
Locations	181 centres in 20 countries (Europe, North America)
Used in model?	Yes

* PRIMA trial was amended on 27 November 2017 to incorporate an individualised starting dose

ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival; PFS2, second progression-free survival; TFST, time to first subsequent treatment

See appendix for comparator trial summaries

Key clinical trials: PRIME

	PRIME
Design	Randomised, double-blind, phase III trial
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 included irrespective of postoperative residual disease status
Intervention	Oral niraparib 300 mg once daily or, starting dose of 200 mg for people with baseline body weight <77 kg or platelet count <150,000 per cubic millimetre or both (N=255)
Comparator(s)	Placebo oral once daily (N=129)
Max treatment duration	Up to 36 months
Median follow up	27.5 months for niraparib; 27.6 months for placebo
Key outcomes	PFS (primary outcome) OS; TFST; adverse effects of treatment
Locations	29 centres in China
Used in model?	Yes

Company: PRIME study complements PRIMA - provides information on niraparib's efficacy regardless of risk of relapse. Notably, PRIME included people with stage III OC with no residual disease after primary debulking surgery and used individualised starting doses from beginning of trial, consistent with UK clinical practice

ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival; TFST, time to first subsequent treatment

PRIMA and PRIME results: progression free survival

See appendix for PRIMA PFS results at primary analysis cut-off

For all subgroups from PRIMA, hazard ratios indicated a statistically significant improvement in investigator-assessed PFS for niraparib compared with placebo

Hazard ratios reported for investigator-assessed progression-free survival from the PRIMA and PRIME trials

Population	PRIMA hazard ratio (95% CI)	PRIME hazard ratio (95% CI)
ITT	0.66 (0.55 to 0.78)	0.47 (0.36 to 0.62)
HRd	0.51 (0.40 to 0.66)	Not reported
BRCAm	0.43 (0.31 to 0.59)	Not reported
HRd/BRCAwt	[redacted]	Not reported
BRCAwt	[redacted]	Not reported
HRp/BRCAwt	[redacted]	Not reported

PRIMA results based on final data cut-off at 8th April 2024
PRIME result based on data cut-off at 30th September 2021
Investigator assessed PFS used in company model (rather than blinded independent central review PFS)

BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat; PFS, progression-free survival

PRIMA and PRIME results: overall survival

See appendix for second PFS and TFST results

For all populations, hazard ratio favoured niraparib versus placebo, except ITT and BRCAwt populations in PRIMA, results not statistically significant

Hazard ratios reported for overall survival from the PRIMA and PRIME trials

Population	PRIMA hazard ratio (95% CI)	PRIME hazard ratio (95% CI)
ITT	1.01 (0.84 to 1.23)	0.63 (0.38 to 1.03)
HRd	0.95 (0.705 to 1.290)	0.88 (0.43 to 1.78)
BRCAm	0.94 (0.627 to 1.412)	Not reported
HRd/BRCAwt	[redacted]	Not reported
BRCAwt	[redacted]	Not reported
HRp/BRCAwt	[redacted]	Not reported

PRIMA results based on final data cut-off at 8th April 2024
PRIME results based on data cut-off at 30th September 2021

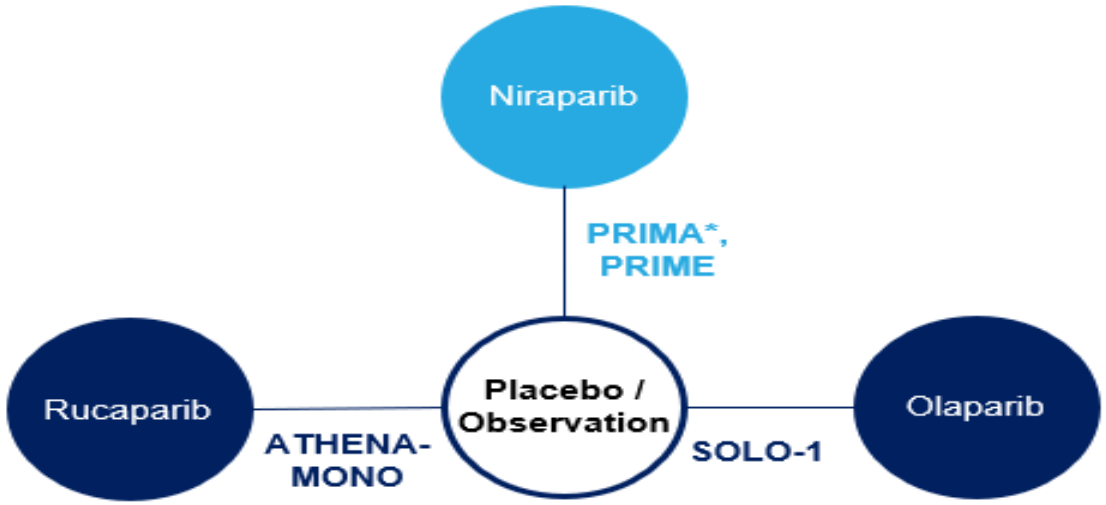
See appendix for PRIMA survival curves

BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat; PFS, progression-free survival

Overview of company indirect treatment comparisons

- Primary objective: estimate relative effects for i) olaparib vs niraparib in BRCAm population and ii) rucaparib vs niraparib in BRCAwt population
- Four trials included in ITC feasibility assessment: SOLO-1, ATHENA-MONO, PRIME, and PRIMA
- Significant limitations identified in feasibility assessment and any analyses fundamentally flawed→ **ITCs conducted as exploratory analysis**

Network of evidence for ITC feasibility assessment



*Patient-level data available for PRIMA, aggregate-level data available for all other studies

† high risk population refers to stage III patients with visible residual disease following primary debulking surgery and stage IV patients

Niraparib vs Olaparib

- Comparisons of PFS conducted on subgroup of BRCAm and high-risk† population of SOLO-1 → fairer comparison with respect to visible residual disease status for PRIMA population
- No OS subgroup data for high-risk subgroup in SOLO-1 → OS comparison not conducted – see appendix

Niraparib vs Rucaparib

- Subgroup analyses for ATHENA-MONO not published in PRIMA-like population (i.e high risk population) → ITC based on PRIME data rather than PRIMA comprising mix of low- and high-risk patients
- No overall BRCAwt subgroup data in ATHENA-MONO → comparison specifically within overall BRCAwt population not conducted – see appendix

BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; ITC, indirect treatment comparison; OS, overall survival

Key issues: Trials used for ITC

Background

For comparisons of niraparib with rucaparib, company performed ITCs using data from PRIME

Company

- PRIMA only comprised high-risk population; restricting ITCs to a high-risk population is essential for valid statistical inference but absence of high-risk subgroup data from ATHENA-MONO
- In contrast to PRIMA, PRIME included both high and low-risk subgroups, allowing comparisons between niraparib and rucaparib in a mixed population→ fairer comparison
- Acknowledges proportions of low- and high-risk patients in both ATHENA- MONO and PRIME are unknown
- Substantial differences in key prognostic factors/effect modifiers between PRIME and ATHENA-MONO; differences generally favoured ATHENA-MONO

EAG comments

- Considerable differences in baseline characteristics of PRIME and ATHENA-MONO (see appendix)
- PRIME trial solely comprised Chinese population, and HRD status was assessed using an unvalidated assay → concerns with relevance to UK clinical practice; notes PRIME excluded from TA1055 ITCs
- For comparisons of niraparib with rucaparib, considers that comparison of ATHENA-MONO with PRIMA most reflective of clinical practice → **conducted updated ITCs using PRIMA data**
- EAG's clinical experts: high-risk population likely to experience a greater relative treatment benefit from PARP inhibitors compared with low-risk population; supported by data from ATHENA-MONO and SOLO-1 trials

For indirect comparisons of niraparib with rucaparib, is it more appropriate to use data from the PRIME trial (company approach) or from the PRIMA trial (EAG approach)?

ECOG, Eastern Cooperative Oncology Group; ITC, indirect treatment comparison; ITT, intention to treat; PARP, poly-ADP ribose polymerase

Indirect treatment comparisons results vs olaparib

See appendix for PFS-BICR, second PFS and TFST ITC results

Results of company's Bucher ITCs comparing PFS-INV: niraparib (PRIMA) vs olaparib (SOLO-1)

Population	Hazard ratio	95% CI
BRCAm; high-risk	[redacted]	[redacted]

- Difference not statistically significant; confidence interval very wide
- OS results not reported (see ITC overview)

Results of EAG's Bucher ITCs: niraparib (PRIMA) vs Olaparib (SOLO-1)

Population	Hazard ratio	95% CI
PFS-INV		
BRCAm	[redacted]	[redacted]
BRCAm (high-risk)	[redacted]	[redacted]
OS		
BRCAm	[redacted]	[redacted]
BRCAm (high-risk)	Not performed	

BRCAm, Breast cancer gene mutation; EAG, External Assessment Group; ITC, indirect treatment comparison; ITT, intention to treat; OS, overall survival; PFS-INV, investigator-assessed progression-free survival

Indirect treatment comparison results vs rucaparib

See appendix for second PFS and TFST ITC results

Results of company's Bucher ITCs: niraparib (PRIME) vs rucaparib (ATHENA-MONO)

Population	Hazard ratio	95% CI
PFS-INV		
ITT	[redacted]	[redacted]
PFS-BICR		
ITT	[redacted]	[redacted]
HRd/BRCAwt	[redacted]	[redacted]
HRp/BRCAwt	[redacted]	[redacted]
OS		
ITT	[redacted]	[redacted]

- No statistically significant differences across all populations
- ITCs for BRCAwt subgroups not performed for PFS-INV
- Results within overall BRCAwt population (relevant to decision problem) not reported for PFS or OS (see ITC overview)

Results of EAG's Bucher ITCs: niraparib (PRIMA) vs rucaparib (ATHENA-MONO)

Population	Hazard ratio	95% CI
PFS-INV		
ITT	[redacted]	[redacted]
HRd/BRCAwt	[redacted]	[redacted]
BRCAwt	[redacted]	[redacted]
HRp/BRCAwt	[redacted]	[redacted]
OS		
ITT	[redacted]	[redacted]
HRd/BRCAwt	[redacted]	[redacted]
BRCAwt	Not performed	-
HRp/BRCAwt	[redacted]	[redacted]

*analyses for the BRCAwt population performed using a hazard ratio reported for PRIMA trial in the company's submission and a hazard ratio calculated using pseudo-IPD from a combination of the HRp/BRCAwt and HRd/BRCAwt populations

CI, confidence interval; EAG, External Assessment Group; HRd, homologous recombination deficient; HRp, homologous recombination proficient; OS, overall survival; PFS-BICR, blinded independent central review-assessed progression-free survival; PFS-INV, investigator-assessed progression-free survival; PFS2, second progression-free survival; TFST, time to first subsequent treatment

Key issues: Assumption of clinical equivalence (1)

Background

- No direct comparisons between niraparib and relevant comparators in a clinical trial setting for first-line maintenance treatment of advanced ovarian cancer→ company conducted exploratory ITCs (see ITC overview slide)

Company

- Differences in trial populations and paucity of necessary published information in comparator trials precluded undertaking of a robust ITC → ITCs fundamentally flawed
- Assumed clinical equivalence between niraparib and olaparib in model (HR=1 for PFS and OS), based on:
  - ITC showing no statistically significant differences between niraparib (PRIMA) and olaparib (SOLO-1) in PFS
  - comparison of SACT data for niraparib and olaparib showing overlapping OS up to 27 months before divergence, which is due to small patient numbers in tail of KM
  - RWE for a South Korean study comparing olaparib and niraparib in BRCAm patients showing no statistically significant differences in PFS or OS
  - expert opinion that based on above data, reasonable to assume class effect for PARPi monotherapies
- Clinical equivalence between niraparib and rucaparib also assumed in model based on:
  - ITCs (PRIME vs ATHENA-MONO) showing no statistically significant difference in PFS or OS
  - class effect for PARPi monotherapies

BRCAm, Breast cancer gene mutation; HR, hazard ratio; ITC, indirect treatment comparison; KM, Kaplan-meier; RWE, real-world evidence; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PFS, progression-free survival; SACT, systemic anti-cancer therapy

Key issues: Assumption of clinical equivalence (2)

Company

- Performed fixed margin analysis (see appendix) to assess non-inferiority, in line with methods in Kaul and Diamond (2007)
  - non-inferiority was demonstrated for 2 of the 8 ITCs (25%) performed (see appendix)
  - not possible to perform fixed margin analyses for ITCs of OS due to data from ATHENA-MONO not demonstrating the superiority of rucaparib over placebo in either the ITT or HRd populations
- Performed a Monte-Carlo simulation to estimate probability that hazard ratio for niraparib compared with placebo was lower than hazard ratio for comparator compared with placebo
  - See appendix for results and categorisation of results

EAG comments

- Concerned that equivalence, or non-inferiority, between niraparib and comparator treatments has not been demonstrated in a statistically robust, or clinically meaningful, manner
- Several concerns with fixed margin analysis:
  - for analyses of PFS-BICR, different non-inferiority margins based on subgroup used for assessments → disparity of margins indicates non-inferiority margins not necessarily clinically meaningful (clinically meaningful margins expected to be consistent)
  - no evidence that non-inferiority analysis would translate into niraparib being non-inferior to olaparib and rucaparib from a clinical perspective
  - same trials used to derive non-inferiority margin also used to assess non-inferiority for ITC → 'dual use' of data from the ATHENA-MONO and SOLO-1 trials may unintentionally bias assessments of non-inferiority

EAG, External Assessment Group; HRd, homologous recombination deficient; ITC, indirect treatment comparison; ITT, intention to treat; OS, overall survival; PFS-BICR, blinded independent central review-assessed progression-free survival

Key issues: Assumption of clinical equivalence (3)

EAG comments

- Concerns with Monte-Carlo simulations:
  - values drawn from normal distributions based on hazard ratios. Normal distributions should have been applied to logarithm of hazard ratios rather than hazard ratios themselves
  - categorisation levels provided by company do not provide definitive assessment of non-inferiority (e.g. no indication of what 'close to 50%' entails
- Would have preferred standard non-inferiority analyses using widely implemented approaches using clinically validated non-inferiority margins derived from data sources that do not form a core component of analyses
- Regarding ITCs → lack of statistically significant results does not equal equivalence; non-statistically significant results are often the outcome for ITCs that are reliant on single trials for each comparator
- Limitations with ITCs performed by both company and EAG → these ITCs represent the only available measures of the relative efficacy of niraparib compared to both olaparib and rucaparib
- Prefer using hazard ratios derived from ITCs rather than assuming clinical equivalence

Has non-inferiority or equivalence between niraparib and its comparators been demonstrated?

EAG, External Assessment Group; ITC, indirect treatment comparison

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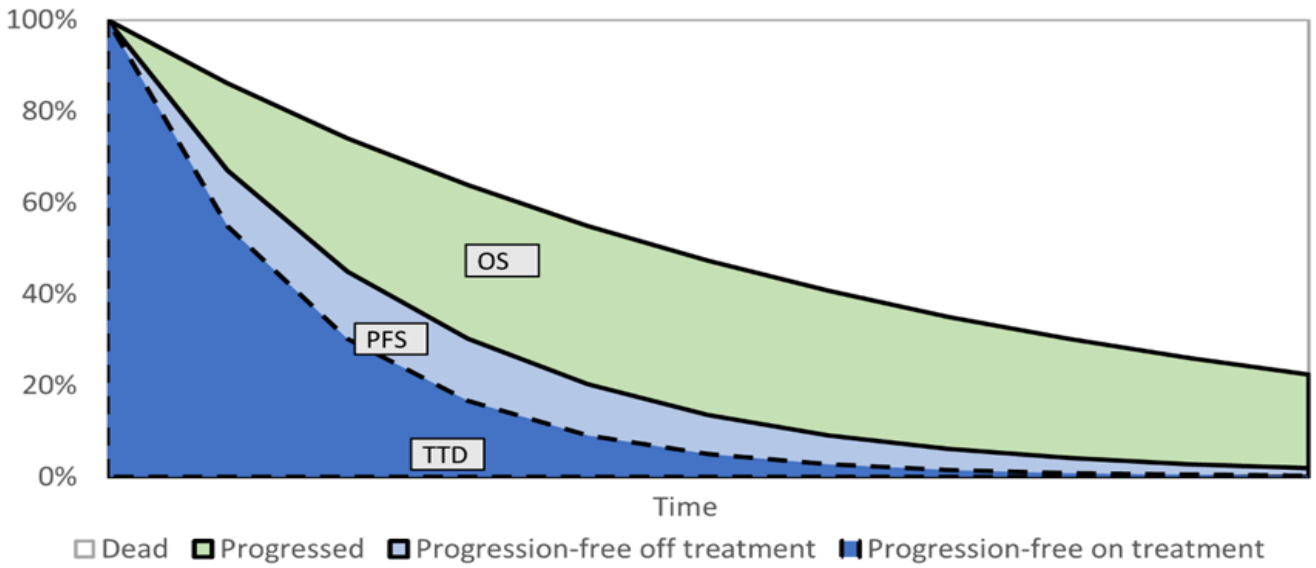
Company's model overview



Company: used 3-health state partitioned survival structure→ 4-state model considered less relevant given that post-progression pathways are similar across first-line PARPi monotherapies. Also, absence of suitable PFS2 data for relevant comparators

EAG: all recent appraisals in same disease area used 4-state partitioned survival model to include PFS2. Due to lack of evidence for specific populations to compare PFS2 against comparators, PFS2 not included in EAG's updated model but noted as a limitation

Probability	Calculated by
PFS	cumulative PFS survivor function applied in model. After 10 years PF, people have the same mortality risk as general population, i.e. 10-year cure assumption applied
PD	difference between OS and PFS cumulative probabilities
Death	cumulative OS survivor function applied in model (1 – OS), constrained to not fall below PFS function

Assumptions with greatest ICER effect:

- Assumed equivalence in PFS and OS between all included PARPi treatments
- Inclusion of a stopping rule for treatment discontinuation of niraparib
- Data source used to inform adverse events

Is the model structure appropriate for decision making?

ICER, incremental cost-effectiveness ratio; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life year

Key issues: Consideration of HRD status

Background

- Key trial for rucaparib, ATHENA-MONO, stratified people by HRD and BRCA status (that is, BRCAm, HRd/BRCAwt, HRp/BRCAwt and HRD unknown/BRCAwt)

Company

- ITCs for niraparib vs rucaparib not performed for relevant BRCAwt subgroups (except PFS-BICR outcome)
- PRIME performed by alternative sponsor → no access to IPD data and limited in ITCs that can be conducted
- ITCs for niraparib vs rucaparib using PRIMA not suitable due to difference in populations between PRIMA and ATHENA-MONO (see slide 17)

EAG comments

- In TA1055, comparisons for BRCAwt population were presented based on HRD classification
- Most appropriate comparison with rucaparib in the current appraisal for the BRCAwt population, would be to separately compare the HRd/BRCAwt and HRp/BRCAwt populations→ most robust use of data from both ATHENA-MONO and PRIMA (see slide 17 outlining EAG preference for PRIMA)
- Conducted ITCs for OS and PFS in HRd/BRCAwt and HRp/BRCAwt populations using data from PRIMA (and ATHENA-MONO)
- Acknowledges PRIMA subgroup analyses of BRCA status result in trial randomisation being broken

For comparisons with rucaparib, is it more appropriate to consider: subgroups stratified by HRD and BRCA status (i.e. HRd/BRCAwt and HRp/BRCAwt) or an overall BRCAwt subgroup for decision making?

EAG, External Assessment Group; BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; CI, confidence interval; HRD, homologous recombination deficiency; HRd, homologous recombination deficient; HRp, homologous recombination proficient; IPD, individual patient data; ITC indirect treatment comparison; OS, overall survival; PFS, progression-free survival; TA, technology appraisal

Key issues: Data to inform treatment comparisons in model for BRCAwt population

Company

- For the BRCAwt population, a hazard ratio of 1 was applied to both the PFS and OS niraparib survival curves, assuming clinical equivalence (see appendix for survival curves)

EAG comments

- Preference for HRd/BRCAwt and HRp/BRCAwt populations in the economic model (see previous slide)
- Instead, EAG constructed overall BRCAwt population from ATHENA-MONO data using pseudo-IPD from HRp/BRCAwt and HRd/BRCAwt populations to allow ITC against PRIMA for PFS
- Equivalent data not available for OS → EAG applied separate HRs for OS in the HRd/BRCAwt and HRp/BRCAwt population to provide a range of ICERs for combined BRCAwt population
- HRs applied to baseline niraparib curves → EAG notes limitations of applying constant hazard ratio to baseline survival curves that do not support proportional hazards assumption
- Preferred option would have been to conduct ITCs using a fractional polynomial network meta-analysis to capture the underlying complex hazard function
- Alternatively, company could have undertaken a multi-level network meta-regression to inform ITCs

What is the committee's preferred approach to estimate PFS and OS in the BRCAwt population for rucaparib?

- Applying HR of 1 to niraparib survival curves (company base case)
- Applying HRs based on EAG's ITCs
- Alternative method

EAG, External Assessment Group; BRCAwt, Breast cancer gene wild type; HRd, homologous recombination deficient; HRp, homologous recombination proficient; IPD, individual patient data; ITC indirect treatment comparison; OS, overall survival; PFS, progression-free survival

Key issues: Data to inform treatment comparisons in model for BRCAm population

Company

- For the BRCAm population, a hazard ratio of 1 was applied to both the PFS and OS niraparib survival curves, assuming clinical equivalence (see appendix for survival curves)

EAG comments

- Not able to perform ITC for high-risk population of SOLO-1 for OS due to lack of subgroup data → conducted ITC in overall BRCAm population
- As ITC could only be conducted for high-risk population for PFS but not OS, preferred to use BRCAm population hazard ratio in the base-case for both OS and PFS, for consistency between 2 outcomes→ considers these to be best available estimates of relative effectiveness between niraparib and olaparib
- HRs applied to baseline niraparib curves → EAG notes limitations of applying constant hazard ratio to baseline survival curves that do not support proportional hazards assumption
- As for BRCAwt population, preferred option would be to conduct ITCs using a fractional polynomial network meta-analysis to capture the underlying complex hazard function, or a multi-level network meta-regression

What is the committee's preferred approach to estimate PFS and OS in the BRCAm population for olaparib?

- Applying HR of 1 to niraparib survival curves (company base case)
- Applying HRs based on EAG's ITCs in overall BRCAm population (EAG base case)
- Alternative method

EAG, External Assessment Group; BRCm, Breast cancer gene mutation; BRCwt, Breast cancer gene wild type; IPD, individual patient data; ITC indirect treatment comparison; OS, overall survival; PFS, progression-free survival

Key issues: Time to treatment discontinuation (1)

Background

- Rucaparib has an explicit stopping rule of 2 years in SmPC
- No stopping rules in SmPCs for olaparib and niraparib but stopping rules at 2 and 3 years, respectively, in key clinical trials (unless continued treatment considered appropriate)

Company

- TTD for niraparib estimated directly using KM data from PRIMA for first 77-months followed by parametric extrapolation
- Clinical opinion that proportion of people remaining on niraparib after 36 months is estimated to range from 5% to 10%→ assumed that at 36 months, 90% of people discontinue treatment
- TTD KM data not available for olaparib or rucaparib→ TTD estimated based on PFS and adverse events in key trials
- Assumed that 90% of people discontinue treatment with olaparib and rucaparib at 24 months
- Range of scenarios, including use of available SACT data for niraparib and olaparib and use of median time on treatment estimates for olaparib and rucaparib to derive TTD curves

TTD used in company base for niraparib and olaparib, BRCAm population

[redacted]

TTD used in company base for niraparib and rucaparib, BRCAwt population

[redacted]

BRCm, Breast cancer gene mutation; BRCwt, Breast cancer gene wild type; KM, Kaplan meier; PFS, progression-free survival; SACT, systemic anti-cancer therapy; SmPC, summary of product characteristics; TTD, time to treatment discontinuation

Key issues: Time to treatment discontinuation (2)

EAG comments

- Lack of publicly available TTD for olaparib and rucaparib results in uncertainty about the proportion of people estimated to remain on treatment beyond the stopping rules
- Company's approach for niraparib means that only 10% of those who were already remaining on treatment at 36 months continue beyond this time point, rather than it being 10% of all patients
- Clinical expert advised that they expect proportion of people continuing beyond 36 months with niraparib to be lower in clinical practice than PRIMA as these patients are likely fitter and would not expect any patients to continue beyond 5 years
- SACT data for niraparib BRCAm population shows proportion remaining on treatment to be 27.5% and 17% at 3 and 3.5 years, respectively
- For olaparib, SACT data showed 13% of people still on treatment at 3 years
- In company's scenario using SACT data, parametric curves did not provide reasonable fit due to sharp drop at 2 years for olaparib → more flexible curves may have rectified this
- Due to lack of KM data for comparators, and consistency with TA1055 (for rucaparib), EAG preferred analysis:
  - niraparib TTD KM curve applied up to 36 months, upon which all patients discontinue (rather than 90%)
  - rucaparib and olaparib TTD informed by PFS and AE discontinuations up to 24 months, upon which all patients discontinue (rather than 90%)

What is the committee's preferred approach for modelling time to treatment discontinuation for niraparib, olaparib and rucaparib?

AE, adverse event; BRCm, Breast cancer gene mutation; EAG, External Assessment Group; KM, Kaplan meier; PFS, progression-free survival; SACT, systemic anti-cancer therapy; TA, technology appraisal; TTD, time to treatment discontinuation

Other issues

Issue	Overview
Adverse events	**Company:** informed niraparib adverse event rates from a real-world evidence (RWE) study (MONITOR-UK). **EAG:** adverse events should be informed from the same source as treatment effectiveness and discontinuation data for niraparib, which both use PRIMA study. EAG's preferred analysis updated to include niraparib adverse event rates from PRIMA
Niraparib dosing	**Company:** informed starting dose distribution using SACT data→ most accurate reflection of UK clinical practice **EAG:** treatment effectiveness and discontinuation used in model are informed by PRIMA → in EAG base case, dose distribution of niraparib at baseline informed using PRIMA; each cycle informed by observed proportion of patients receiving each of the 3 niraparib doses (100 mg, 200 mg, 300 mg). Same approach accepted by committee in company's original submission
Terminal care costs	**Company:** derived from NICE TA946 and TA962, which used an estimate from Guest et al. 2006 and inflated to 2024 cost year using PSSRU inflation indices **EAG:** prefer using end-of-life costs for cancer from latest PSSRU Unit Costs of Health and Social Care 2024 Manual

EAG, External Assessment Group; HR, hazard ratio; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PFS2, second progression-free survival; PSSRU, Personal Social Services Research Unit; RWE, real world evidence; SACT, systemic anti-cancer therapy; TA, technology appraisal

Summary of company and EAG base case assumptions: BRCAm population

Assumption	Company base case	EAG base case
Olaparib PFS	HR=1 applied to baseline niraparib curve	HR= [redacted] applied to baseline niraparib curve
Olaparib OS	HR=1 applied to baseline niraparib curve	HR= [redacted] applied to baseline niraparib curve
Treatment discontinuation	Niraparib: 90% of people discontinue at 36 months Olaparib: 90% of people discontinue at 24 months	Niraparib: all people discontinue at 36 months Olaparib: all people discontinue at 24 months
Niraparib dosing*	Starting dose distribution informed by SACT data; relative dose intensity informed by PRIMA	Per cycle dosing (including starting dose distribution) informed by PRIMA
Adverse events for niraparib*	Based on RWE study (MONITOR-UK)	Based on PRIMA
Terminal care costs*	Sourced from NICE TA946 and TA962	Sourced from PSSRU

*not included as key issue due to less significant impact on results

BRCAm, Breast cancer gene mutation; EAG, External Assessment Group; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PSSRU, Personal Social Services Research Unit; RWE, real world evidence; SACT, systemic anti-cancer therapy; TA, technology appraisal

Summary of company and EAG base case assumptions: BRCAwt population

Assumption	Company base case	EAG base case
HRD status	Results presented for overall BRCAwt population	Preference for results presented based on HRD classification but unable due to data limitations at time of EAG report
Rucaparib PFS	HR=1 applied to baseline niraparib curve	HR= [redacted] applied to baseline niraparib curve
Rucaparib OS	HR=1 applied to baseline niraparib curve	HR= [redacted] (HRd/BRCAwt population) and HR= [redacted] (HRp/BRCAwt population) applied to baseline niraparib curve
Treatment discontinuation	Niraparib: 90% of people discontinue at 36 months Rucaparib: 90% of people discontinue at 24 months	Niraparib: all people discontinue at 36 months Rucaparib: all people discontinue at 24 months
Niraparib dosing*	Starting dose distribution informed by SACT data; relative dose intensity informed by PRIMA	Per cycle dosing (including starting dose distribution) informed by PRIMA
Adverse events for niraparib*	Based on RWE study (MONITOR-UK)	Based on PRIMA
Terminal care costs*	Sourced from NICE TA946 and TA962	Sourced from PSSRU

*not included as key issue due to less significant impact on results

BRCAwt, Breast cancer gene wild type; EAG, External Assessment Group; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PSSRU, Personal Social Services Research Unit; RWE, real world evidence; SACT, systemic anti-cancer therapy; TA, technology appraisal

Cost-effectiveness results

- All ICERs reported in PART 2 slides because they include confidential discounts
- Company base case reported as NMB due to marginal difference in QALYs. With confidential discounts applied, company base case results in positive NMB for both BRCAm and BRCAwt subgroups (deterministic and probabilistic)
- EAG base case for BRCAm and BRCAwt subgroups result in south-west quadrant ICERs (less effective and less costly). For both subgroups, ICERs were less than £30,000 saved per QALY lost in the southwest quadrant of the cost-effectiveness plane (deterministic and probabilistic)
- Results include company and EAG base cases for BRCAm and BRCAwt subgroups; relevant scenarios applied to both company and EAG base cases

BRCAm, Breast cancer gene mutation; BRCwt, Breast cancer gene wild type; EAG, External assessment group; ICER: Incremental cost effectiveness ratio; NMB, net monetary benefit; QALY, quality-adjusted life year

Niraparib for first-line maintenance treatment of advanced ovarian cancer

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Potential uncaptured benefits

Benefits not captured in QALY calculation, as per company submission:

- having more than one treatment option available to delay disease progression→ individuals respond differently to medication due to a number of reasons
- offering a variety of treatments enables healthcare providers to tailor therapies to meet unique needs of each patient
- availability of diverse treatment options encourages innovation and competition

QALY, quality-adjusted life year

Niraparib for first-line maintenance treatment of advanced ovarian cancer

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues

Issue	ICER impact	Slide(s)
Comparators and positioning of niraparib	Unknown 	10
Trials used for ITC	Large 	17
Assumption of clinical equivalence	Large 	20, 21, 22
Model structure	Unknown 	24
Consideration of HRD status	Unknown 	25
Data to inform treatment comparisons in model for BRCAwt population	Large 	26
Data to inform treatment comparisons in model for BRCAm population	Large 	27
Time to treatment discontinuation	Large 	28, 29

BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; HRD, homologous recombination deficiency; ITC indirect treatment comparison

Key committee questions

Key issue/ parameter	Key Committee Questions
Comparators and positioning of niraparib	• Is the company's positioning of niraparib appropriate? • Are bevacizumab monotherapy and olaparib with bevacizumab appropriate comparators ? • Can the committee only make a recommendation where bevacizumab is not a treatment option?
Trials used for ITC	For indirect comparisons of niraparib with rucaparib, is it more appropriate to use data from the PRIME trial (company approach) or from the PRIMA trial (EAG approach)?
Assumption of clinical equivalence	Has non-inferiority or equivalence between niraparib and its comparators been demonstrated?
Model structure	Is the model structure appropriate for decision making?
Consideration of HRD status	For comparisons with rucaparib, is it more appropriate to consider: subgroups stratified by HRD and BRCA status (i.e. HRd/BRCAwt and HRp/BRCAwt) or an overall BRCAwt subgroup for decision making?

BRCAwt, Breast cancer gene wild type; EAG, External Assessment Group; HR, hazard ratio; HRD, homologous recombination deficiency; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival

Key committee questions (2)

Parameter	Key Committee Questions
Data to inform treatment comparisons in model for BRCAwt population	What is the committee's preferred approach to estimate PFS and OS in the BRCAwt population for rucaparib? • Applying HR of 1 to niraparib survival curves (company base case) • Applying HRs based on EAG's ITCs • Alternative method
Data to inform treatment comparisons in model for BRCAm population	What is the committee's preferred approach to estimate PFS and OS in the BRCAm population for olaparib? • Applying HR of 1 to niraparib survival curves (company base case) • Applying HRs based on EAG's ITCs in overall BRCAm population (EAG base case) • Alternative method
Time to treatment discontinuation	What is the committee's preferred approach for modelling time to treatment discontinuation for niraparib, olaparib and rucaparib?
Preferred ICER and threshold	• What is the committee's preferred ICER threshold - and why? • What is the committee's preferred ICER?

BRCAm, Breast cancer gene mutation; EAG, External Assessment Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival

Niraparib for first-line maintenance treatment of advanced ovarian cancer

Supplementary appendix

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Maintenance treatment options by genomic status

Subgroup	Did induction treatment include bevacizumab?	Maintenance treatment
BRCAm	Yes	• Olaparib+bevacizumab (TA946) • Bevacizumab monotherapy • Niraparib (TA673) in CDF
	No	• Olaparib monotherapy (TA962) • Niraparib (TA673) • Niraparib ?
HRd/BRCAwt	Yes	• Olaparib+bevacizumab (TA946) • Bevacizumab monotherapy • Niraparib (TA673) in CDF • Rucaparib
	No	• Niraparib (TA673) in CDF • Rucaparib • Niraparib ?
HRp*/BRCAwt	Yes	• Bevacizumab monotherapy • Niraparib (TA673) in CDF • Rucaparib
	No	• Niraparib (TA673) in CDF • Rucaparib • Niraparib ?

? to be appraised
* Includes HRD status unknown

BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; CDF, cancer drugs fund; HRd, homologous recombination deficient; HRp, homologous recombination proficient; TA, technology appraisal

Comparator trials: ATHENA-MONO and SOLO-1

	ATHENA-MONO	SOLO-1
Design	Randomised, double-blind, phase III trial	Randomised, double-blind, phase III trial
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 included irrespective of postoperative residual disease status	• Advanced (stage III / IV) ovarian cancer who were in complete or partial response to PBC with ECOG performance status of 0 or 1 • People included irrespective of postoperative residual disease status
Intervention	Rucaparib (N=425)	Olaparib (N=250)
Comparator(s)	Placebo (N=111)	Placebo (N=131)
Max treatment duration	Up to 24 months	Up to 24 months
Key outcomes	PFS (primary outcome); OS; TFST; PFS2, HRoL, adverse effects of treatment	PFS (primary outcome); OS; TFST; PFS2, HRoL, adverse effects of treatment
Locations	200 centres in 24 countries (Asia, Australia/New Zealand, Europe, North America)	15 countries (Asia, Australia, Europe, North America, South America)

ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival; PFS2, second progression-free survival; TFST, time to first subsequent treatment

PRIMA results: progression free survival

Maintenance treatment with niraparib led to a statistically significant reduction in the risk of disease progression or death in ITT and HRd populations

Summary of primary and updated PFS analyses in ITT and HRd populations

Analysis (cut-off)	BICR/IA	Median PFS (95% CI), months		HR (95% CI)	p-value
		Niraparib	Placebo		
ITT population (niraparib: 487 patients vs placebo: 246 patients)					
Primary (17 May 2019)	BICR	13.8 [redacted]	8.2 [redacted]	0.62 (0.50, 0.76)	**<0.001**
	IA	13.8 (11.3, 14.2)	8.2 (7.6, 9.8)	0.63 (0.51, 0.76)	**<0.001**
Updated (17 November 2021)	IA	13.8 (NA)	8.2 (NA)	0.66 (0.56, 0.79)	**<0.001**
HRd population (niraparib: 247 patients vs placebo: 126 patients)					
Primary (17 May 2019)	BICR	21.9 [redacted]	10.4 [redacted]	0.43 (0.31, 0.59)	**<0.001**
	IA	21.9 [redacted]	11.2 [redacted]	0.46 (0.34, 0.63)	**<0.001**
Updated (17 November 2021)	IA	24.5 (NA)	11.2 (NA)	0.52 (0.40, 0.68)	**<0.001**

CI, confidence interval; HRd, homologous recombination deficient; ITT, intention to treat; NA, not available; NE, not estimable; OS, overall survival; PFS-BICR, blinded independent central review-assessed progression-free survival; PFS-INV, investigator-assessed progression-free survival

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PRIMA results: Progression free survival on second line of therapy

For all populations hazard ratio favoured niraparib, results not statistically significant

Hazard ratios reported for progression-free survival on the second line of therapy from the PRIMA trial

Population	PRIMA hazard ratio (95% CI)
ITT	[redacted]
HRd	[redacted]
BRCAm	[redacted]
HRd/BRCAwt	[redacted]
BRCAwt	[redacted]
HRp/BRCAwt	[redacted]

PRIMA results based on final data cut-off at 8th April 2024

Progression free survival on second line of therapy not measured in PRIME trial

BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat

PRIMA and PRIME results: time to first subsequent treatment

For all populations, hazard ratios indicated improvement in TFST for niraparib compared with placebo but hazard ratios were only statistically significant for the ITT, HRd, and BRCAm populations

Hazard ratios reported for time to first subsequent treatment from the PRIMA and PRIME trials

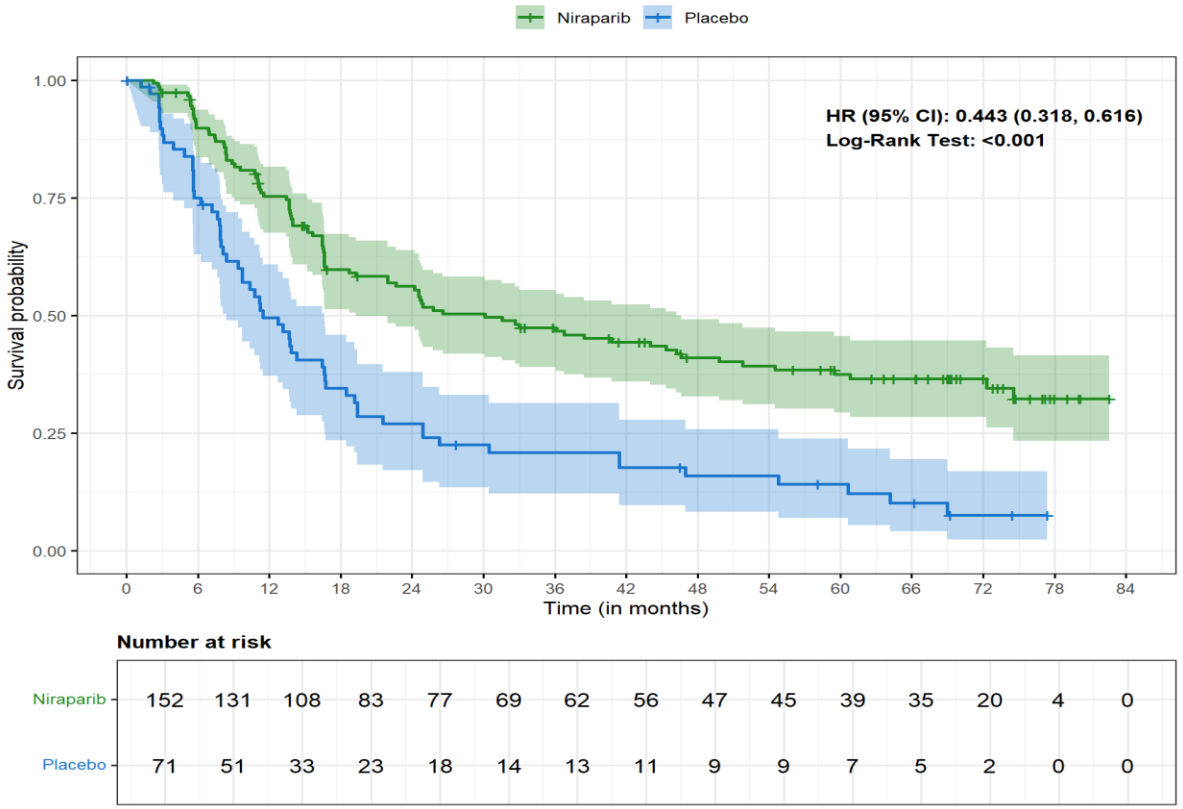
Population	PRIMA hazard ratio (95% CI)	PRIME hazard ratio (95% CI)
ITT	[redacted]	0.45 (0.34 to 0.59)
HRd	[redacted]	Not reported
BRCAm	[redacted]	Not reported
HRd/BRCAwt	[redacted]	Not reported
BRCAwt	[redacted]	Not reported
HRp/BRCAwt	[redacted]	Not reported

PRIMA results based on final data cut-off at 8th April 2024
PRIME result based on data cut-off at 30th September 2021

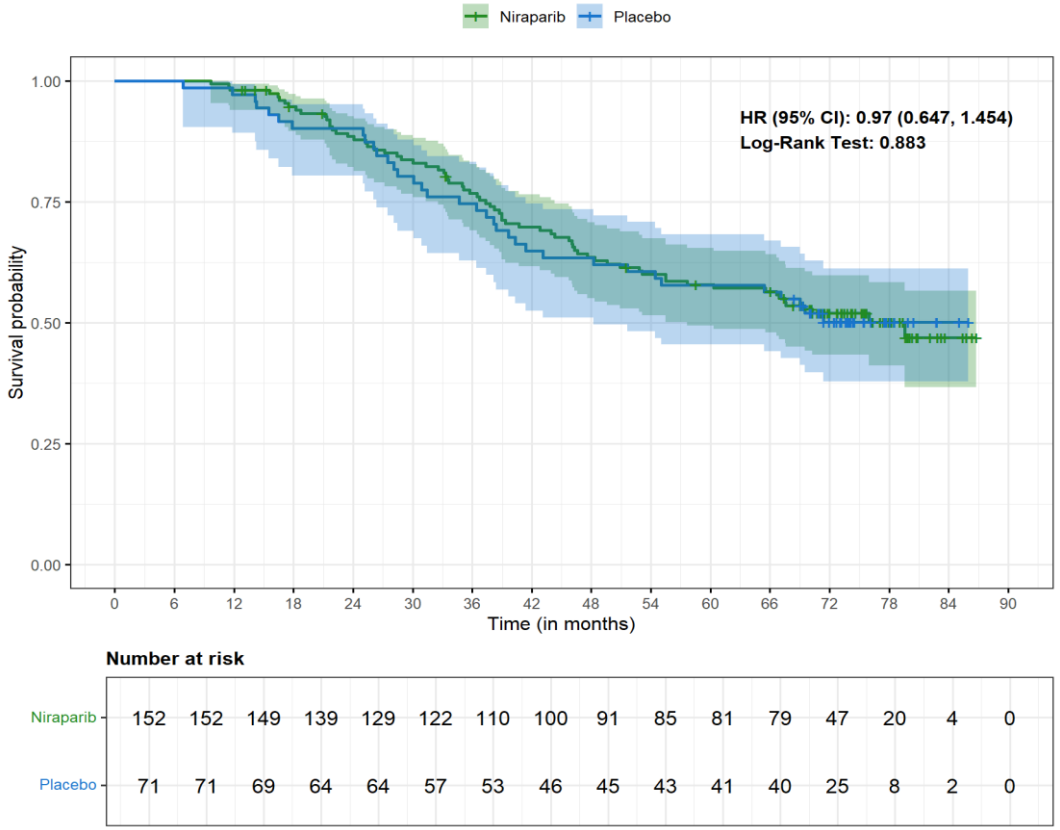
BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat; TFST, time to first subsequent treatment

KM survival curves: BRCAm

KM plots for PFS (INV) for the BRCAm population in PRIMA



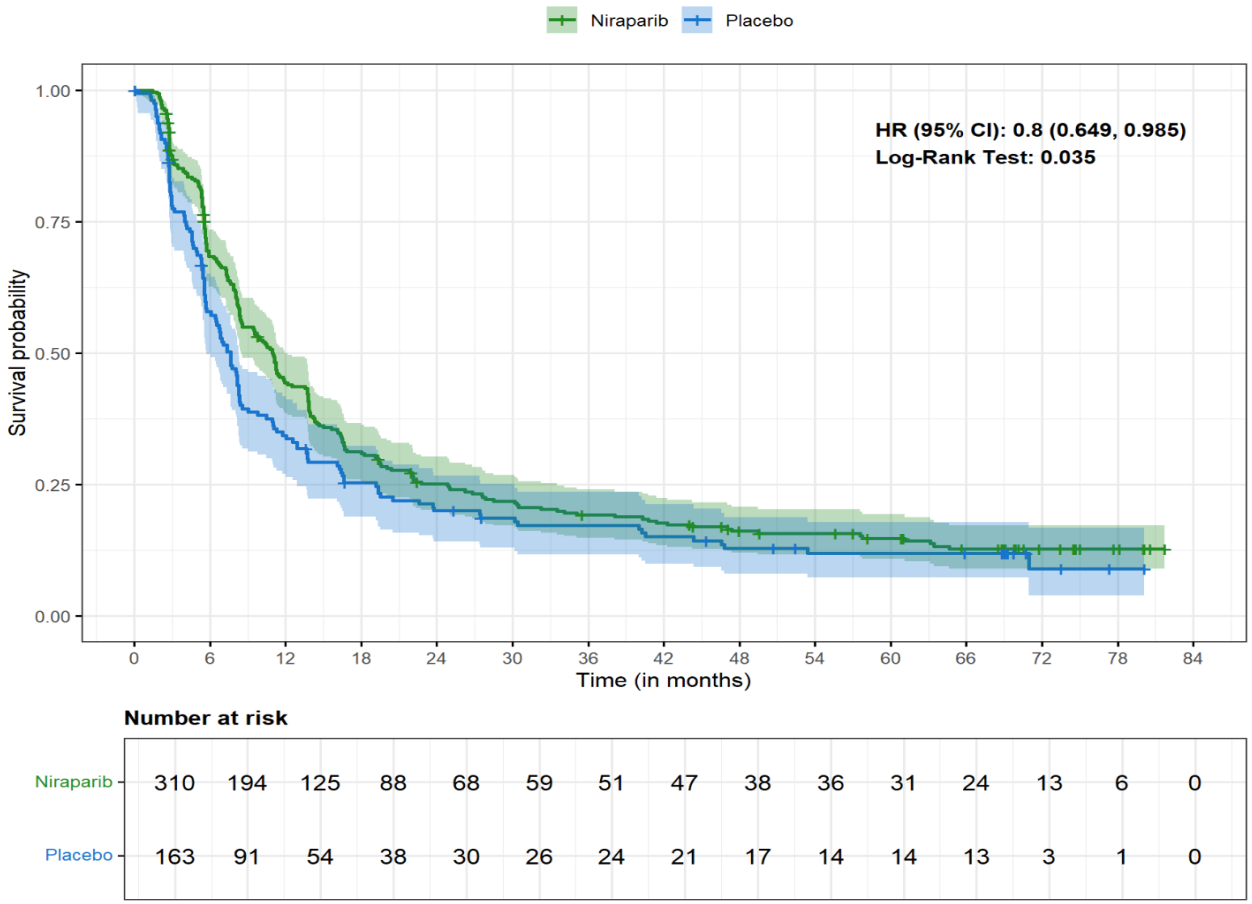
KM plots for OS for the BRCAm population in PRIMA



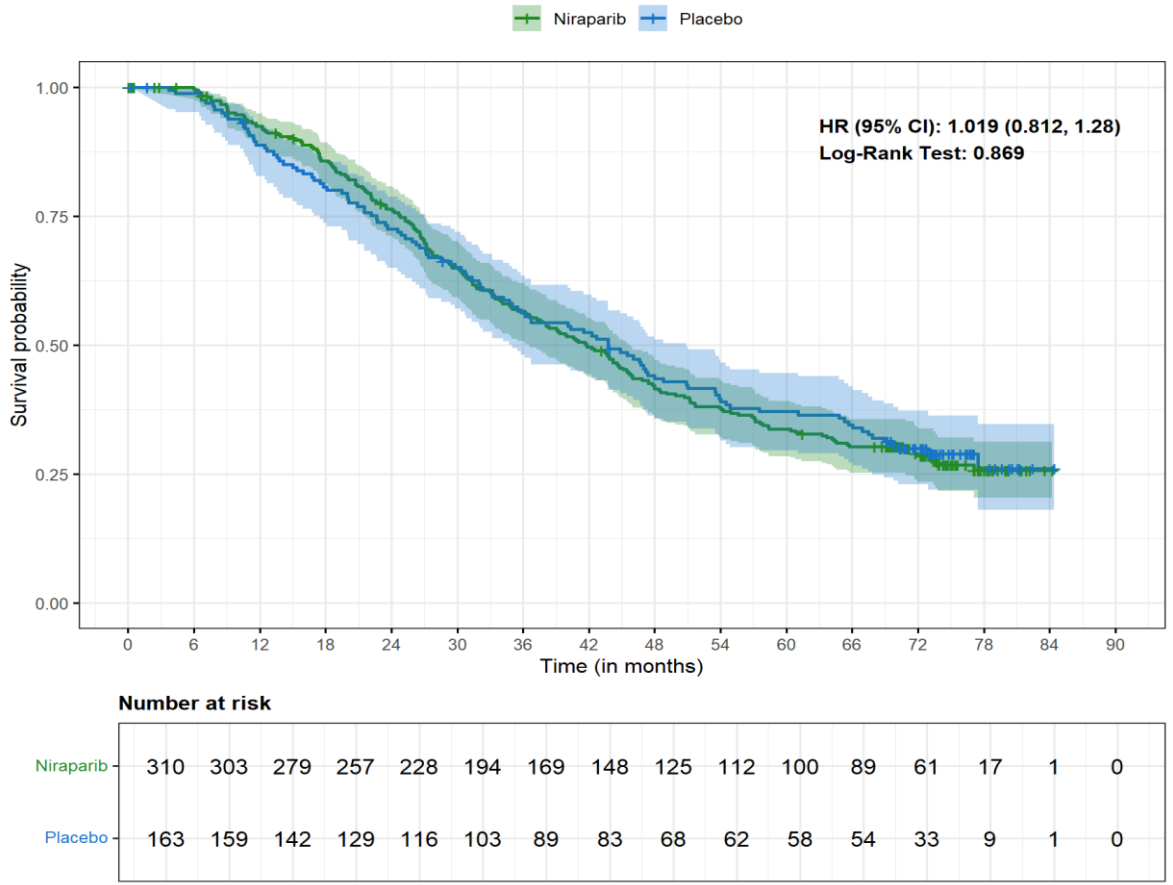
BRCAm, Breast cancer gene mutation; CI, confidence interval; HR, hazard ratio; KM, Kaplan meier; OS, overall survival; PFS, progression-free survival

KM survival curves: BRCAwt

KM plots for PFS (INV) for the BRCAwt population in PRIMA



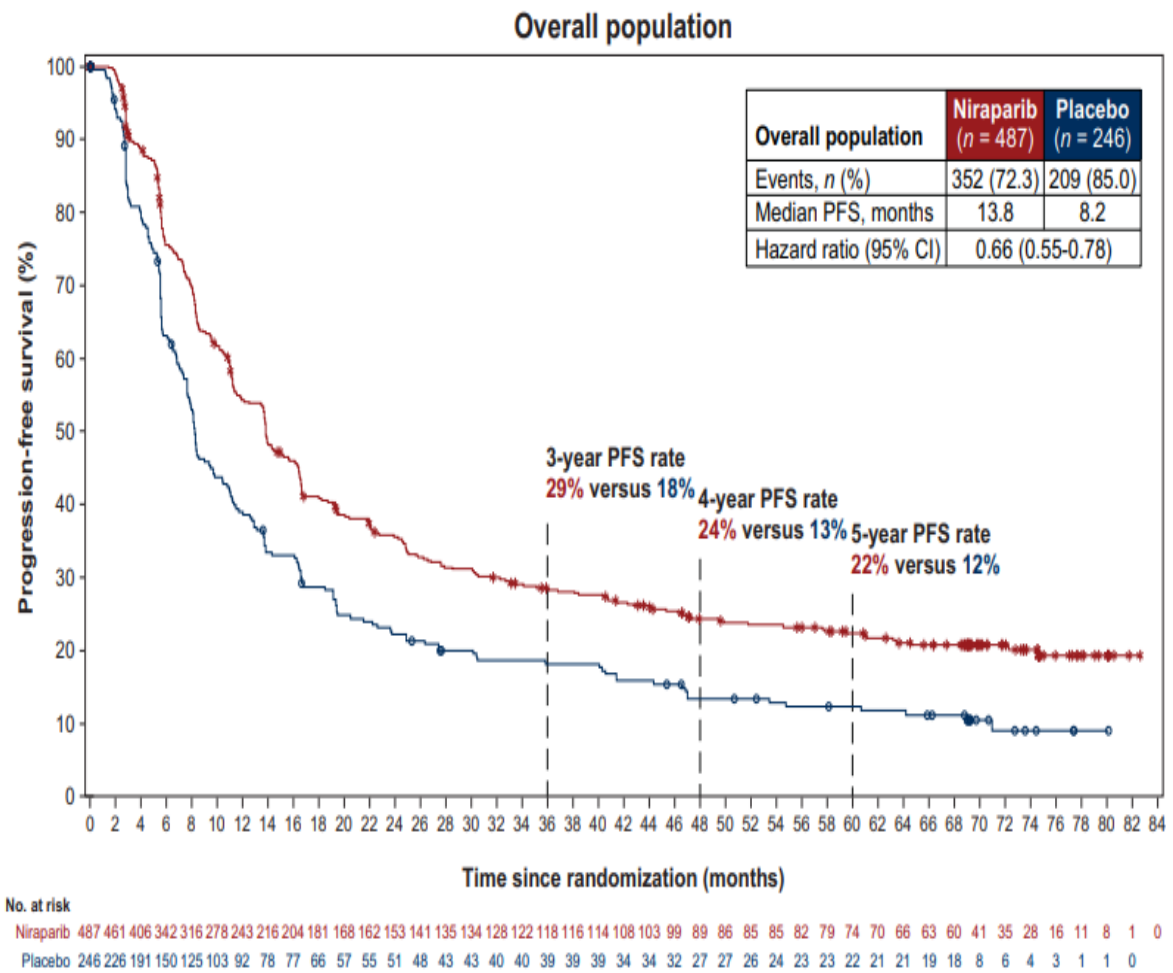
KM plots for OS for the BRCAwt population in PRIMA



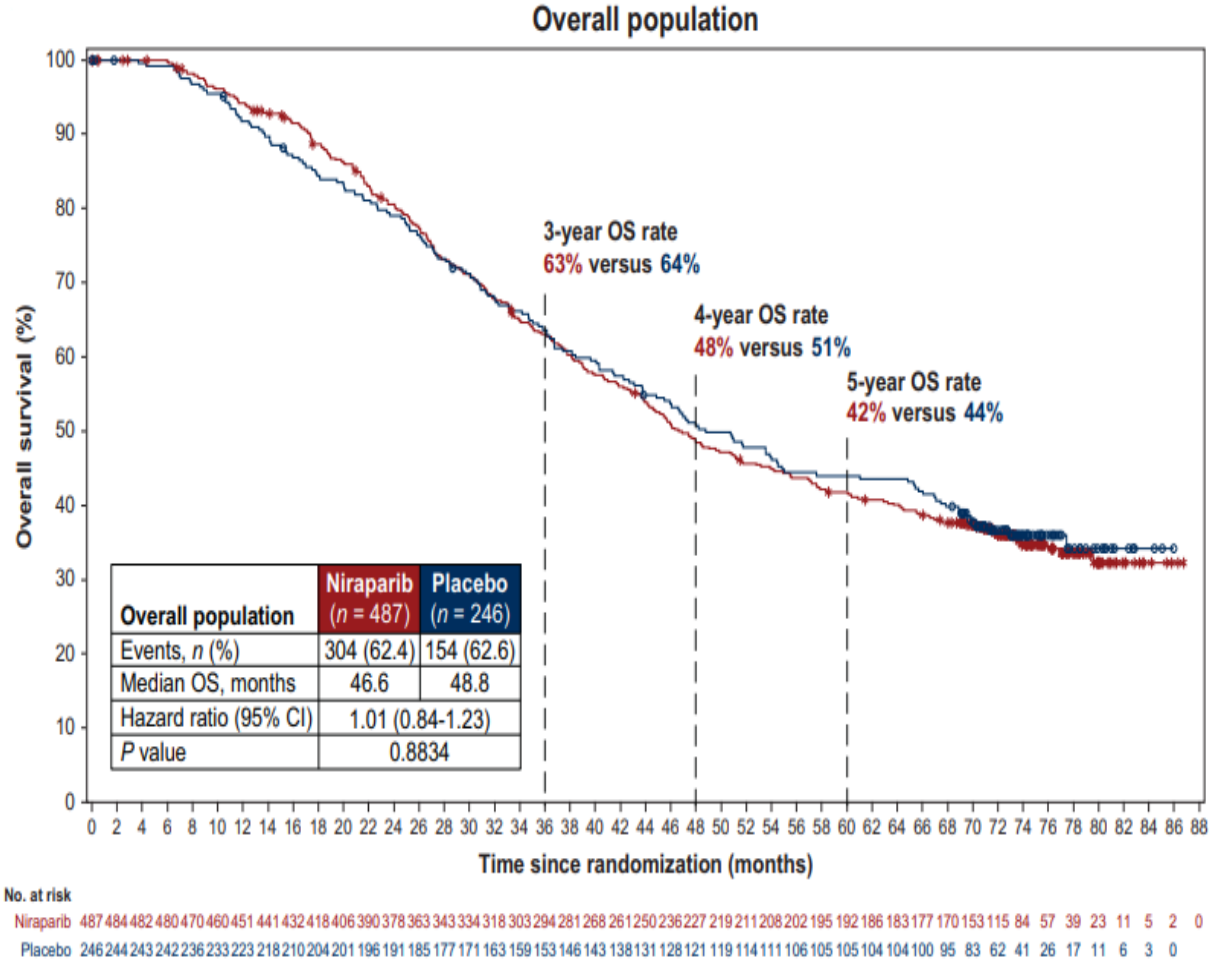
BRCAwt, Breast cancer gene wild type; CI, confidence interval; HR, hazard ratio; KM, Kaplan meier; OS, overall survival; PFS, progression-free survival

KM survival curves: ITT

KM plots for PFS (INV) for the ITT population in PRIMA



KM plots for OS for the ITT population in PRIMA



ITT, intention to treat; KM, Kaplan meier; OS, overall survival; PFS, progression-free survival

Baseline characteristics: PRIME/PRIMA vs ATHENA-MONO

PRIME vs ATHENA-MONO

EAG: considerable differences in baseline characteristics of ITT populations of PRIME and ATHENA-MONO. Noted differences in: median age, ethnicities, proportion with an ECOG PS of 0, proportion with ovaries as primary tumour location, proportion with fallopian tubes as primary tumour location, proportion with a primary peritoneal primary tumour location, proportion with serous histology, proportion of BRCAm patients, proportion who achieved a complete response to first line chemotherapy, definitions of complete response at baseline, proportion with no evidence of disease or complete response, proportion with a CA-125 level that was ≤ULN, the prevalence of HRd patients and HRp patients

PRIMA vs ATHENA-MONO

EAG: some differences in the baseline characteristics of ITT populations of PRIMA and ATHENA-MONO. Noted differences in: ethnicities, prevalence of FIGO stage III patients, proportion of BRCAm patients, proportion who achieved a complete response to first line chemotherapy, proportion who achieved a partial response to first line chemotherapy, prevalence of HRd and HRp patients ,proportion of patients receiving neoadjuvant chemotherapy

BRCAm, Breast cancer gene mutation; CA-125, cancer antigen 125; EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat; ULN, upper limit of normal

Bucher analyses performed by the EAG and company comparing niraparib with olaparib

Comparator (trial)	Population	Outcomes analysed, by company, using PRIMA	Outcomes analysed, by EAG, using PRIMA
(SOLO-1)	ITT	No Bucher analyses performed	No Bucher analyses performed
(SOLO-1)	HRd	No Bucher analyses performed	No Bucher analyses performed
(SOLO-1)	**BRCAm**	**No Bucher analyses performed**	**OS; PFS-INV; PFS2; and TFST**
(SOLO-1)	**BRCAm (high-risk)**	**PFS-INV and PFS-BICR**	**PFS-INV**
(SOLO-1)	HRd/BRCAwt	No Bucher analyses performed	No Bucher analyses performed
(SOLO-1)	BRCAwt	No Bucher analyses performed	No Bucher analyses performed
(SOLO-1)	HRp/BRCAwt	No Bucher analyses performed	No Bucher analyses performed
(SOLO-1)	HRnd	No Bucher analyses performed	No Bucher analyses performed

BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; ITC, indirect treatment comparison; ITT, intention to treat; OS, overall survival; PFS-BICR, blinded independent central review-assessed progression-free survival; PFS-INV, investigator-assessed progression-free survival; PFS2, second progression-free survival on; TFST, time to first subsequent treatment

Bucher analyses performed by the EAG and company comparing niraparib with rucaparib

Comparator (trial)	Population	Outcomes analysed, by company, using PRIME	Outcomes analysed, by EAG, using PRIMA
(ATHENA-MONO)	ITT	OS; PFS-INV;PFS-BICR; and TSFT	OS;PFS-INV;PFS2; and TFST
(ATHENA-MONO)	HRd	OS; and PFS-BICR	OS; PFS-INV; PFS2; TFST
(ATHENA-MONO)	BRCAm	PFS-BICR	PFS-INV
(ATHENA-MONO)	BRCAm (high-risk)	No Bucher analyses performed	No Bucher analyses performed
(ATHENA-MONO)	HRd/BRCAwt	PFS-BICR	OS;PFS-INV;PFS2; and TFST
(ATHENA-MONO)	BRCAwt	No Bucher analyses performed	PFS-INV
(ATHENA-MONO)	HRp/BRCAwt	PFS-BICR	OS; PFS-INV; PFS2; and TFST
(ATHENA-MONO)	HRnd	No Bucher analyses performed	No Bucher analyses performed

BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; ITC, indirect treatment comparison; ITT, intention to treat; OS, overall survival; PFS-BICR, blinded independent central review-assessed progression-free survival; PFS-INV, investigator-assessed progression-free survival; PFS2, second progression-free survival; TFST, time to first subsequent treatment

Company and EAG Bucher analysis results: niraparib vs olaparib

Population	Hazard ratio (95% CI) Company's PRIMA analysis	Hazard ratio (95% CI) EAG's PRIMA analysis
PFS-BICR		
BRCAm	Not performed	Not performed
BRCAm (high-risk)	[redacted]	Not performed
Second progression-free survival		
BRCAm	Not performed	[redacted]
BRCAm (high-risk)	Not performed	Not performed
Time to first subsequent treatment		
BRCAm	Not performed	[redacted]
BRCAm (high-risk)	Not performed	Not performed

BRCAm, Breast cancer gene mutation; CI, confidence interval; EAG, External Assessment Group; PFS-BICR, blinded independent central review-assessed progression-free survival; PFS2, second progression-free survival; TFST, time to first subsequent treatment

Company and EAG Bucher analysis results: niraparib vs rucaparib

Population	Hazard ratio (95% CI) Company's PRIME analysis	Hazard ratio (95% CI) EAG's PRIMA analysis
Second progression-free survival		
ITT	Not performed	[redacted]
HRd/BRCAwt	Not performed	[redacted]
BRCAwt	Not performed	Not performed
HRp/BRCAwt	Not performed	[redacted]
Time to first subsequent treatment		
ITT	[redacted]	[redacted]
HRd/BRCAwt	Not performed	[redacted]
BRCAwt	Not performed	Not performed
HRp/BRCAwt	Not performed	[redacted]

BRCAwt, Breast cancer gene wild type; CI, confidence interval; EAG, External Assessment Group; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat

Fixed margin analysis

In company's fixed margin analysis, maximum non-inferiority margin was derived as lower 95% confidence interval for hazard ratio of comparison of placebo versus comparator treatment. For example: when investigating non-inferiority of niraparib vs rucaparib in ITT population, reported HR and 95%CI for rucaparib vs placebo in ATHENA-MONO ($HR_{RUCA\ vs\ PBO}$=0.47 [95% CI: 0.36 – 0.63]) are inverted to obtain a HR and 95% CI for placebo vs rucaparib ($HR_{PBO\ vs\ RUCA}$ = 2.128 [95% CI: 1.587 – 2.778]). In this example, $d_{max} = 1.587$ and because the 95% CI for effect of niraparib vs rucaparib from Bucher ITC $HR_{NIRA\ vs\ RUCA}$ $HR_{NIRA\ vs\ RUCA}$=[redacted] [redacted] is entirely below d_{max} , non-inferiority is established

Results of non-inferiority analyses using fixed margin analysis for ITCs performed by company

Population	Outcome	Niraparib trial	Comparator trial	Non-inferiority
ITT	PFS-BICR	PRIME	ATHENA-MONO	Established
ITT	OS	PRIME	ATHENA-MONO	Not performed
HRd	PFS-BICR	PRIME	ATHENA-MONO	Not established
HRd	OS	PRIME	ATHENA-MONO	Not performed
HRd/BRCAwt	PFS-BICR	PRIME	ATHENA-MONO	Not established
BRCAm	PFS-BICR	PRIME	ATHENA-MONO	Not established
BRCAm (high risk)	PFS-INV	PRIMA	SOLO-1	Established
HRp/BRCAwt	PFS-BICR	PRIME	ATHENA-MONO	Not established

BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; HR, hazard ratio; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat; OS, overall survival; PBO, placebo; PFS-BICR, blinded independent central review-assessed progression-free survival; PFS-INV, investigator-assessed progression-free survival

Monte-Carlo simulations

Monte-carlo simulation performed by drawing 1,000,000 values from 2 independent normal distributions that were parameterised to align with reported hazard ratios used within each of the ITCs performed by company

Results of non-inferiority analyses using the Monte-Carlo simulations for ITCs performed by company

Population	Outcome	Niraparib trial	Comparator trial	Non-inferiority probability
ITT	PFS-BICR	PRIME	ATHENA-MONO	58.41%
ITT	OS	PRIME	ATHENA-MONO	81.15%
HRd	PFS-BICR	PRIME	ATHENA-MONO	38.34%
HRd	OS	PRIME	ATHENA-MONO	46.18%
HRd/BRCAwt	PFS-BICR	PRIME	ATHENA-MONO	26.97%
BRCAm	PFS-BICR	PRIME	ATHENA-MONO	65.18%
BRCAm (high risk)	PFS-INV	PRIMA	SOLO-1	16.87%
HRp/BRCAwt	PFS-BICR	PRIME	ATHENA-MONO	84.54%

BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITC, indirect treatment comparison; ITT, intention to treat; OS, overall survival; PFS-BICR, blinded independent central review-assessed progression-free survival; PFS-INV, investigator-assessed progression-free survival

PFS survival curves: BRCAm

Progression-free survival in company's base case for BRCAm population (generalised gamma, long-term remission assumption)

[redacted]

Progression-free survival using EAG preferred analysis for BRCAm population (generalised gamma, long-term remission assumption applied)

[redacted]

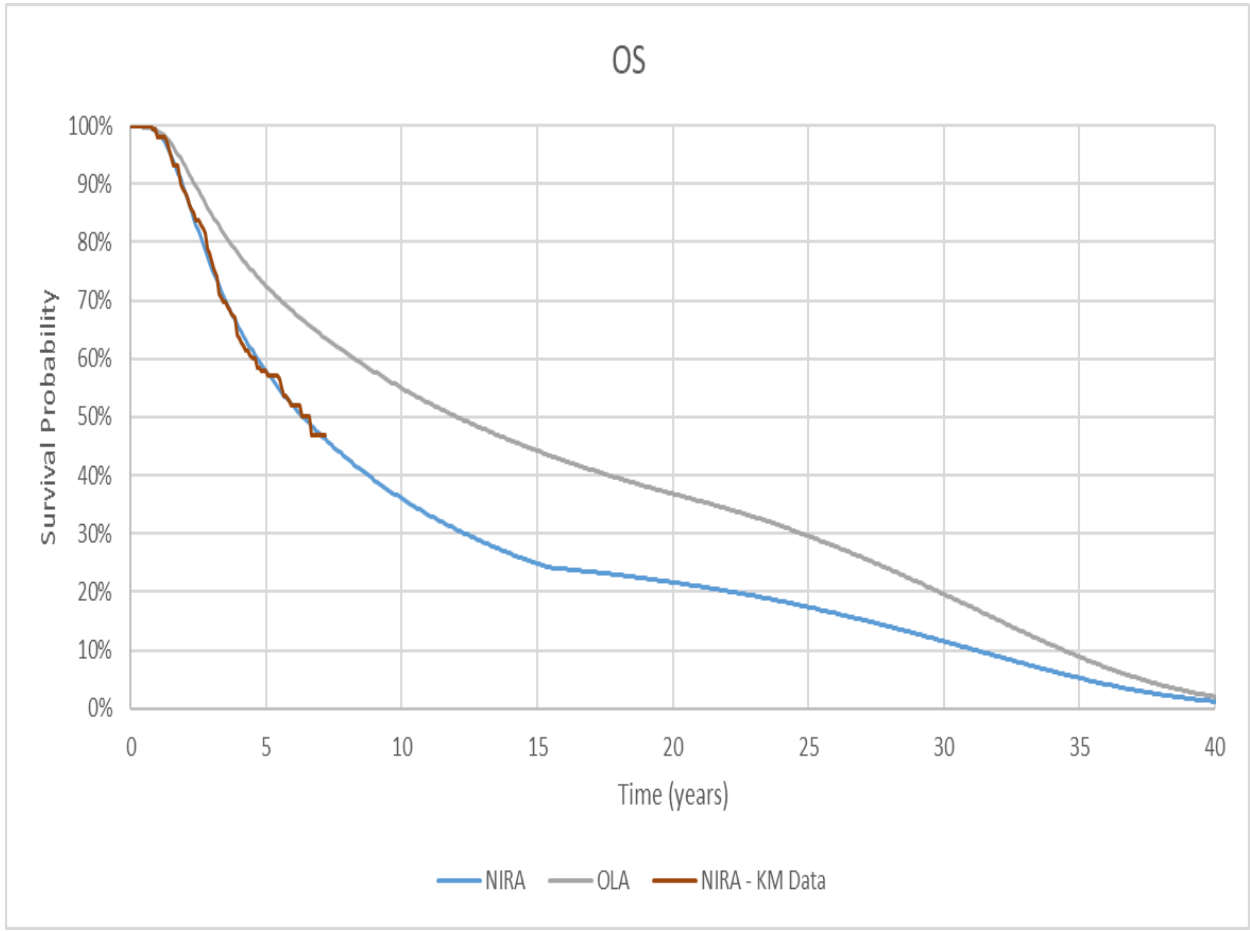
BRCAm, Breast cancer gene mutation; EAG, External Assessment Group; KM, Kaplan meier; HR, hazard ratio; PFS, progression-free survival

OS survival curves: BRCAm

Overall survival in company's base case for the BRCAm population (one-knot normal spline)

[redacted]

Overall survival using EAG preferred analysis for the BRCAm population (HRs applied to estimate olaparib PFS and OS)



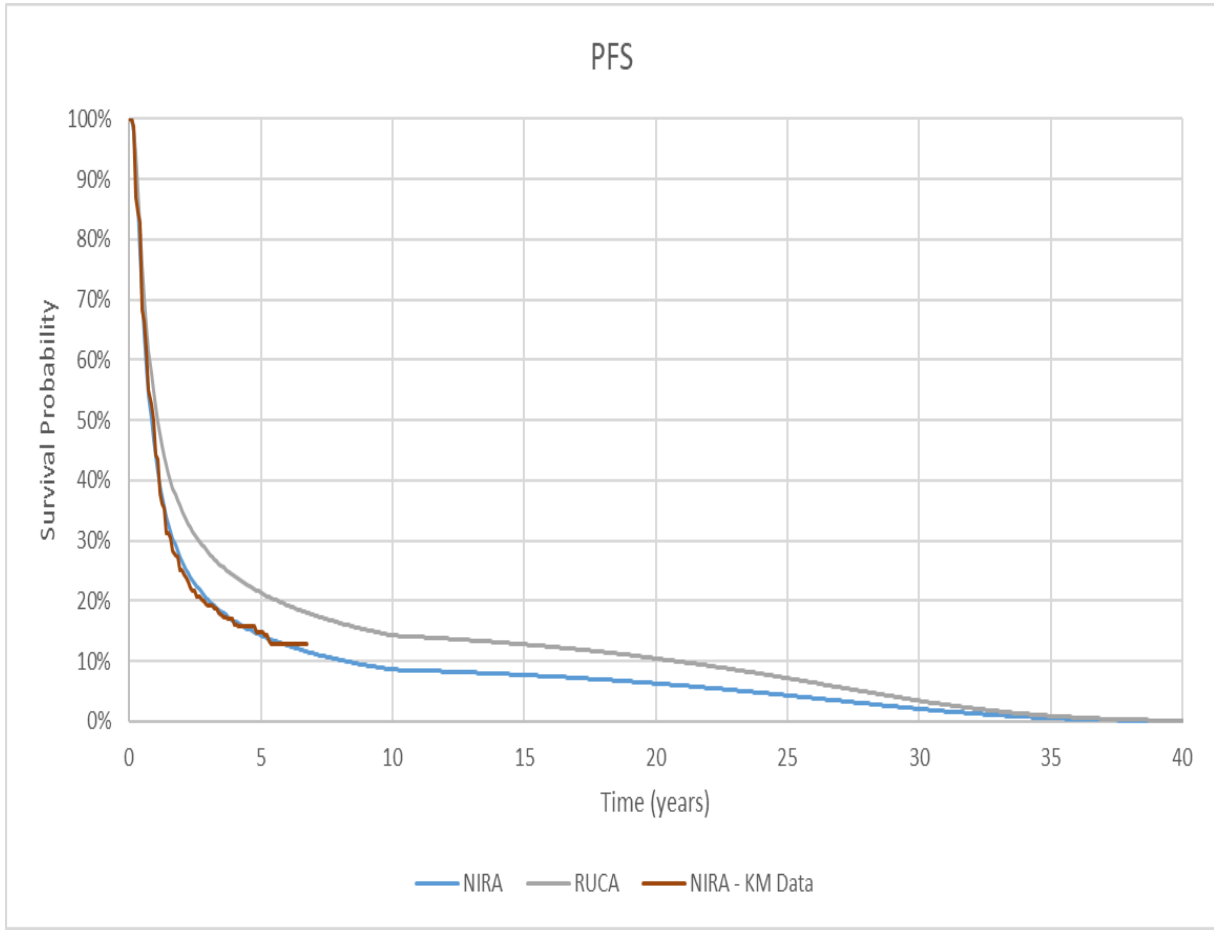
BRCAm, Breast cancer gene mutation; EAG, External Assessment Group; KM, Kaplan meier; HR, hazard ratio; OS, overall survival

PFS survival curves: BRCAwt

Progression-free survival in the company's base case for the BRCAwt population (generalised gamma, long-term remission assumption)

[redacted]

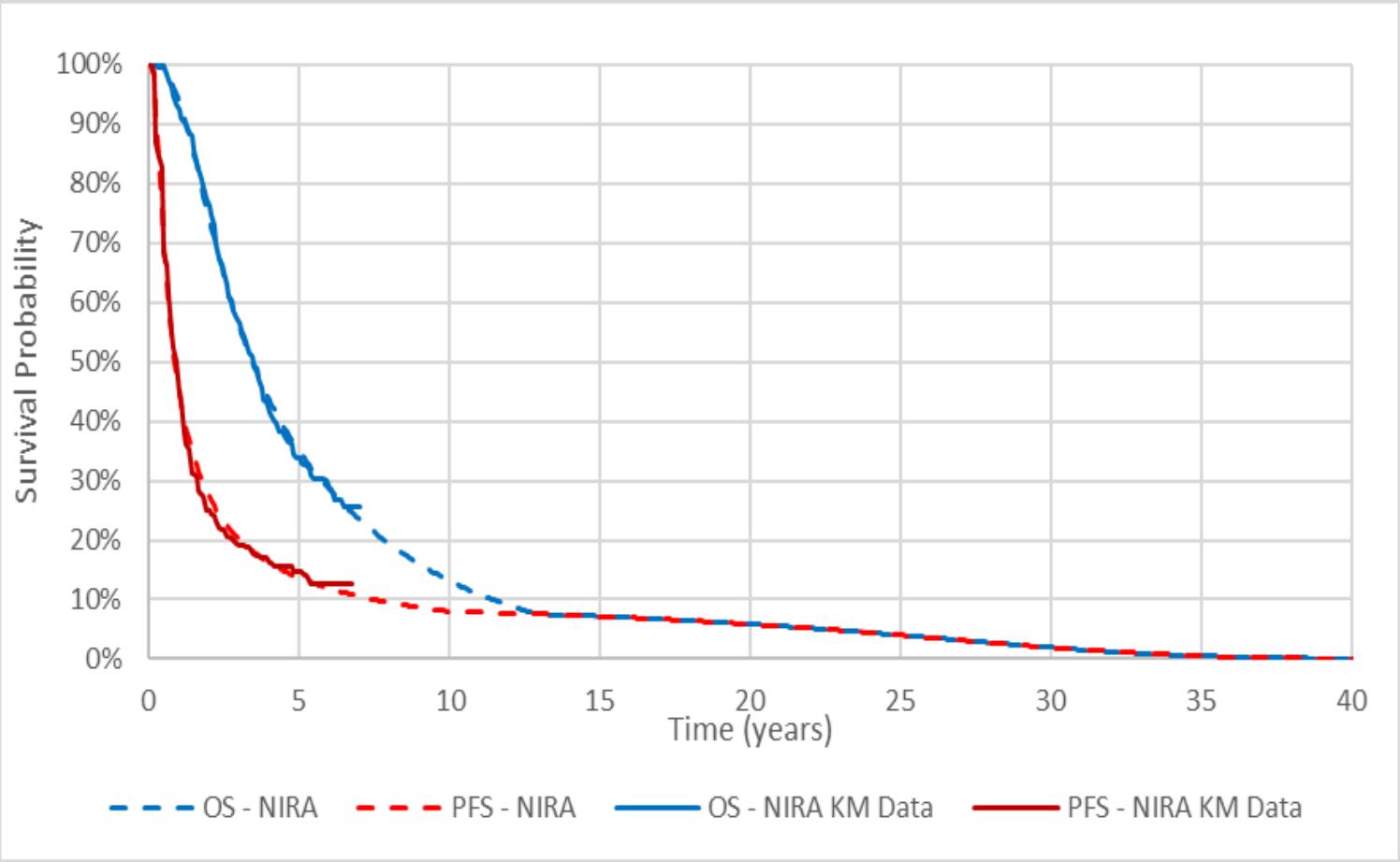
Progression-free survival using EAG preferred analysis for BRCAwt population (generalised gamma, long-term remission assumption applied) with HR applied to estimate rucaparib



BRCAwt, Breast cancer gene wild type; EAG, External Assessment Group; KM, Kaplan meier; HR, hazard ratio; PFS, progression-free survival

OS survival curves: BRCAwt (1)

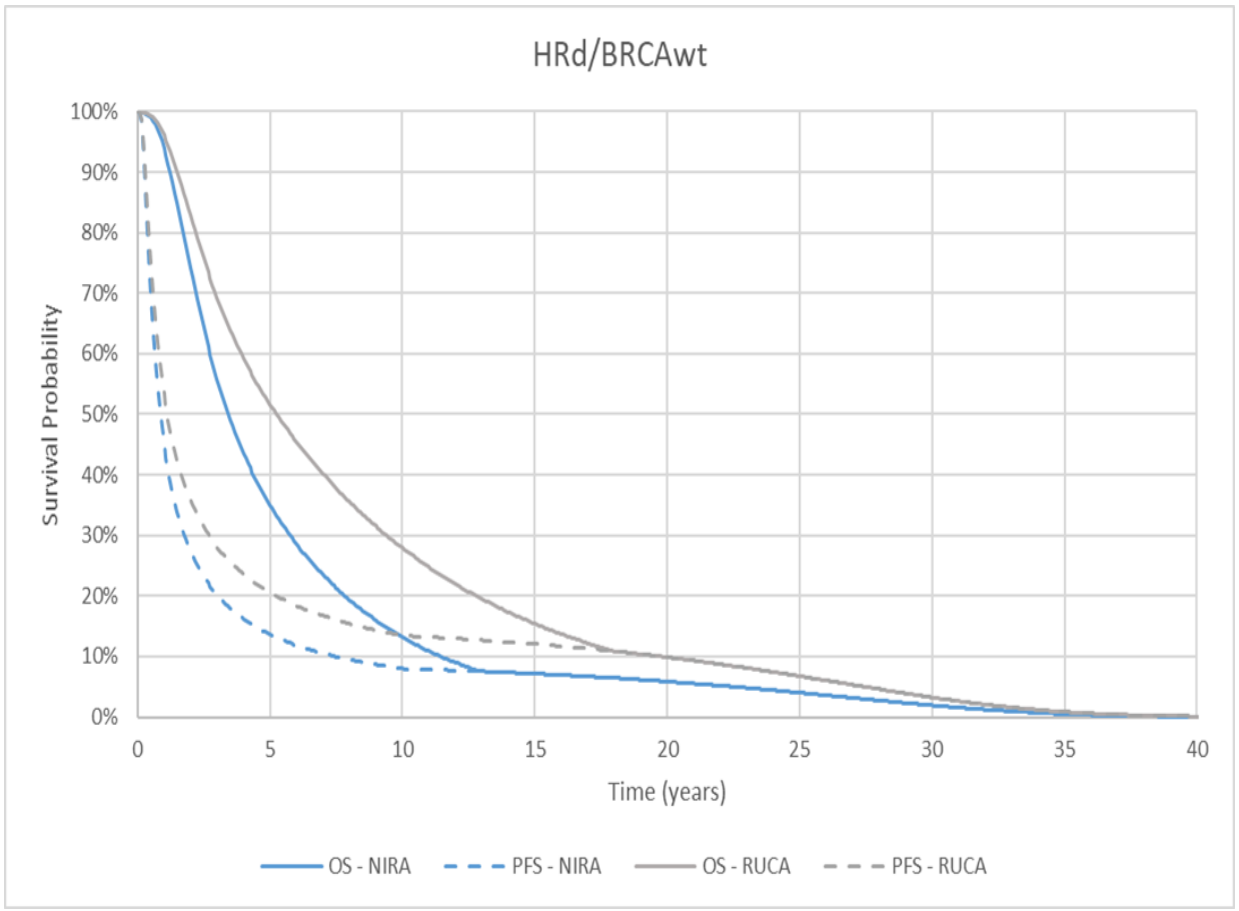
Overall survival in company's base case for the BRCAwt population (one-knot hazard spline), including base-case PFS extrapolation constraint



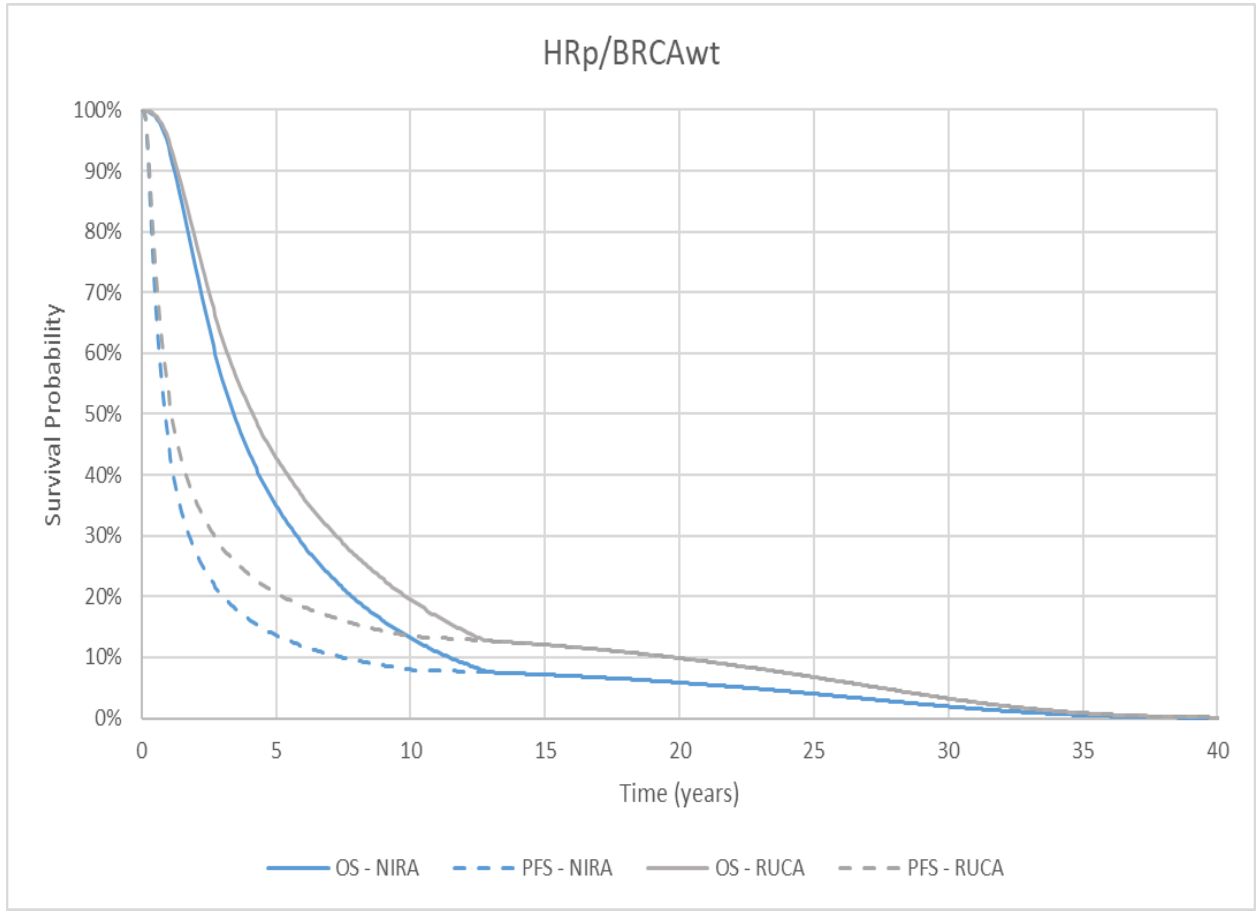
BRCAwt, Breast cancer gene wild type; KM, Kaplan meier; OS, overall survival; PFS, progression-free survival

OS survival curves: BRCAwt (2)

Overall survival for niraparib and rucaparib, applying EAG derived HR for HRd/BRCAwt population to baseline niraparib BRCAwt (all) curve



Overall survival for niraparib and rucaparib, applying EAG derived HR for HRp/BRCAwt population to baseline niraparib BRCAwt (all) curve



BRCAwt, Breast cancer gene wild type; EAG, External Assessment Group; HR, hazard ratio; HRd, homologous recombination deficient; HRp, homologous recombination proficient; OS, overall survival; PFS, progression-free survival