Feasibility Study of a Network Meta-Analysis and Unanchored Population-Adjusted Indirect Treatment Comparison of Niraparib, Olaparib, and Bevacizumab as Maintenance Therapies in Patients with Newly Diagnosed Advanced Ovarian Cancer

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Background

Although rare, OC is a leading cause of cancer death in women, and with up to 85% of patients relapsing after standard 1L CT, there remains a high unmet need in 1L OC treatment[1,2]

Patients with newly diagnosed advanced OC after 1L CT receiving niraparib (a PARP inhibitor) maintenance therapy in the Phase 3 PRIMA trial (NCT02655016) experienced significantly longer PFS, regardless of biomarker status, compared with patients receiving placebo[1]

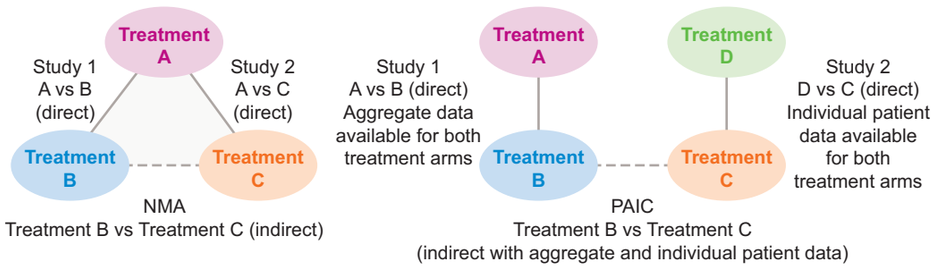
In the absence of head-to-head trials, the comparative efficacy of treatments can be informed using an indirect treatment comparison (ITC), including a network meta-analysis (NMA, **Figure 1A**) and population-adjusted ITC (PAIC, **Figure 1B**)[3]

An NMA is a statistical technique for determining the relative benefits of treatments, provided that RCT evidence for the interventions forms a connected network of evidence for the outcome of interest, and that the RCTs are sufficiently similar in terms of design, population, interventions and outcomes[3,4]

A PAIC estimates the relative treatment effects in which individual patient data in one or more trials are used to adjust for differences in the distribution of variables that influence outcomes. Unanchored PAIC can be used when the interventions do not form a connected network (**Figure 1B**)[5]

An NMA requires the presence of a connected network, whereas a PAIC can be used for either anchored or unanchored comparisons

Figure 1. Example schematics for NMA and PAIC



NMA, network meta-analysis; PAIC, population-adjusted indirect treatment comparison.

Objective

To assess the feasibility for estimating the relative efficacy of niraparib monotherapy following 1L CT in patients with advanced OC compared with other maintenance therapies in an NMA, or compared with olaparib plus bevacizumab in an unanchored PAIC

Methods

Trials included in the ITC (NMA and PAIC) analyses were based on a SLR conducted in February 2020 (additional details on the SLR methodology will be presented in Poster 373 at this congress)

Guidelines from the Cochrane Handbook for Systematic Reviews of Interventions were used to assess the level of heterogeneity across studies by comparing study designs, population characteristics, treatment arms, and outcome measures (**Table 1**)[6]

The feasibility of an unanchored PAIC for the PRIMA and PAOLA-1 (NCT02477644) trials was assessed based on the four key assumptions outlined in the guidance by the Decision Support Unit in NICE DSU Technical Support Document 18.[7] Violations of these assumptions result in biased or spurious estimates

In addition to the assumptions required for standard NMAs, unanchored PAIC requires conditional constancy of absolute effects. This assumption is much stronger than that made for anchored comparisons (which require only conditional constancy of relative effects). It requires that all effect modifiers and prognostic variables are known and accounted for in the adjustment model. Identification of these factors and their availability in the trials was therefore the key consideration of the feasibility assessment[7]

Treatment effect modifiers are baseline patient characteristics that influence response to a specific treatment.[8] These differ from prognostic factors, in which the prognostic value is independent of the treatment being evaluated. The potential treatment effect modifiers and prognostic factors considered in the feasibility analysis included:

- Age (mean)
- Tumour histology (% serous histology)
- ECOG performance status (% status 0)
- FIGO stage (% stage IV)
- History of cytoreductive surgery/best response to most recent platinum-based CT (% partial response)
- *BRCA*m status (% positive)
- HRd status (% positive)
- Prior treatment exposure alongside CT (% received bevacizumab)
- Receipt of NACT (% receiving)
- CA-125 ≤ ULN (%)

Table 1. Sources of heterogeneity that hinder comparability of studies[6]

Category	Factor
Different quality or methods of randomised trials	• Adequate concealment of randomisation • Blinding • Duration of follow-up • Treatment groups
Confounding factors in relation to participant population	• Age • Genetic variation • Diagnostic workup • Intensity of surveillance • Severity of disease or condition • History of surgery and residual disease • Previous therapy
Confounding factors in relation to circumstances	• Geography • Date of trials
Different treatment	• Dose • Duration • Timing
Different outcome measures and methods of statistical analysis	• Definition of outcomes • Rating instrument • Frequency of measurement • Start point of measurement • End point of measurement • Availability of data

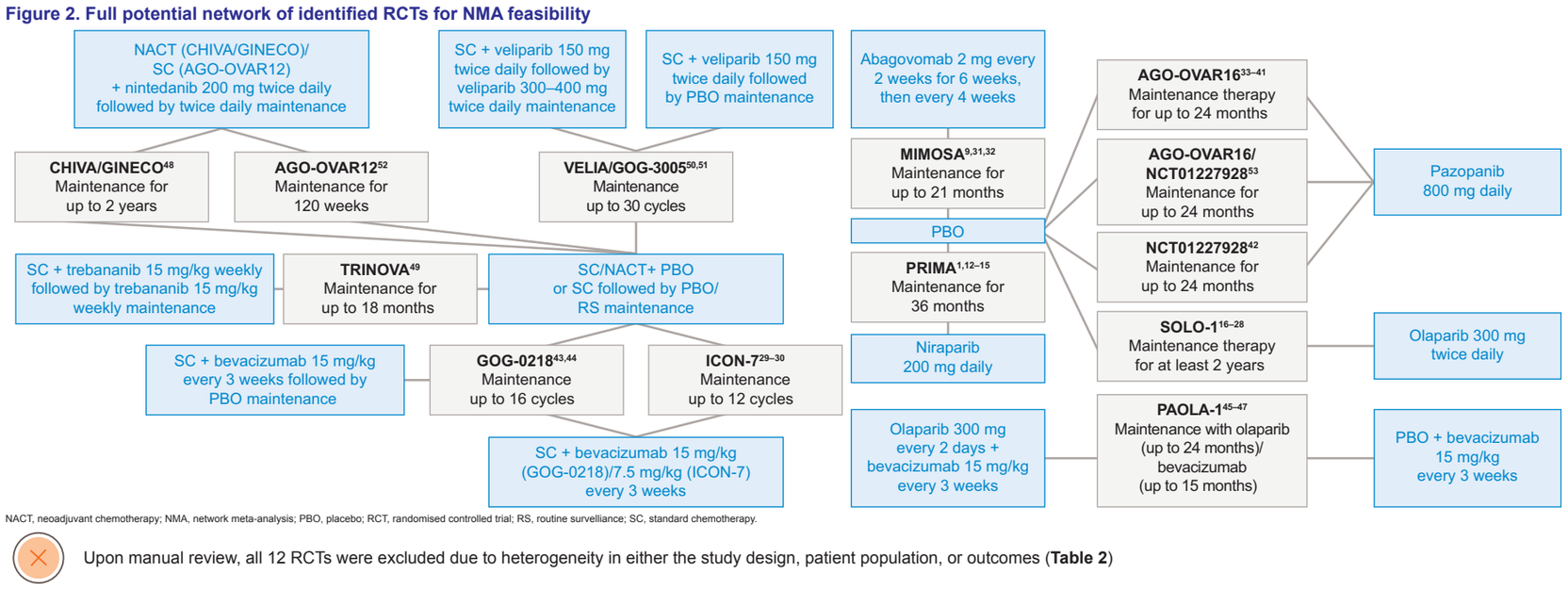
In subsequent clinician validation meetings, held in March 2020, 8 OC clinical experts (7 from the US, 1 from the UK) identified visible residual disease (VRD, based on history of cytoreductive surgery) as a key treatment effect modifier that would influence PFS in this NMA

Results

NMA feasibility assessment

The SLR identified 12 RCTs of OC maintenance treatment following 1L CT for inclusion in the PRIMA NMA feasibility assessment (**Figure 2**)

Figure 2. Full potential network of identified RCTs for NMA feasibility



NACT, neoadjuvant chemotherapy; NMA, network meta-analysis; PBO, placebo; RCT, randomised controlled trial; RS, routine surveillance; SC, standard chemotherapy.

Upon manual review, all 12 RCTs were excluded due to heterogeneity in either the study design, patient population, or outcomes (**Table 2**)

Table 2. Reasons for exclusion for each trial from NMA with PRIMA

Trial	Study design heterogeneity: lack of common comparator within the network	Patient population heterogeneity: inclusion of patients with FIGO Stage III disease with no VRD following PDS	Outcome heterogeneity: Interim or immature OS data	Outcome heterogeneity: Differing measurement of PFS and OS starting time point due to trial design
SOLO-1[16–28]		✓*	✓	
ICON-7[29,30]	✓			✓
MIMOSA[9,31,32]		✓	✓	PFS was not assessed
AGO-OVAR16[33–41]		✓		
NCT01227928[42]		✓		
GOG-0218[43,44]	✓			✓
PAOLA-1[45–48]	✓	✓	✓	
CHIVA/GINECO[49]	✓	✓	✓	✓
TRINOVA-3[50]	✓	✓		✓
VELIA/GOG-3005[51,52]	✓	✓	✓	✓
AGO-OVAR12[53]	✓			✓

*This study was also excluded due to a disparity between *BRCA*m disease biomarker status. *BRCA*, breast cancer gene; *BRCA*m, *BRCA* mutated; FIGO, International Federation of Gynaecology Oncology; OS, overall survival; PDS, primary debulking surgery; PFS, progression-free survival; VRD, visible residual disease.

Study design heterogeneity

Therapies that were evaluated as maintenance therapies initiated alongside 1L CT, followed by a maintenance phase, cannot be compared against PRIMA (niraparib maintenance treatment following 1L CT) because of the inability to elucidate the contribution of the agent to the maintenance phase from that in the 1L CT phase

Therefore, ICON-7, GOG-0218, TRINOVA-3, VELIA/GOG-3005, CHIVA/GINECO, and AGO-OVAR12 were excluded

Time on treatment could vary based on the maximum treatment duration specified in the treatment discontinuation rules. For instance, the maximum treatment duration was 24 months in PAOLA-1 and 36 months in PRIMA

If a large proportion of patients terminated therapy prior to disease progression, the outcome of PFS may be impacted by the shorter treatment regimen

The maximum treatment durations were substantially shorter for AGO-OVAR16, NCT01227928, and TRINOVA-3 compared with PRIMA. ICON-7, SOLO-1, PAOLA-1, and TRINOVA-3 all reported a longer median follow-up compared with PRIMA

Despite comparable treatment arms, MIMOSA was excluded as treatment was discontinued based on recurrence (defined as the appearance of any lesion or development of tumour-related symptoms evaluated by medical examination and must be confirmed by a documented CT-scan) rather than disease progression (per RECIST version 1.1) used in PRIMA[1,9]

ICON-7, GOG-0218, CHIVA/GINECO, TRINOVA-3, VELIA/GOG-3005, and AGO-OVAR12 were excluded as patients received an active CT as part of the control arm

Patient population heterogeneity

When considering heterogeneity within the intention-to-treat patient population at baseline, all RCTs had confounding factors

MIMOSA, AGO-OVAR16, PAOLA-1, SOLO-1, VELIA/GOG-3005, NCT01227928, CHIVA/GINECO and TRINOVA-3 were excluded on the basis of including patients with no residual disease following debulking surgery

A connected NMA is not feasible if there are differences in patient population that cause an imbalance in treatment effect modifiers. VRD was identified as a treatment effect modifier in this analysis

SOLO-1 only included patients with *BRCA*m, which is a treatment effect modifier, leading to exclusion of this trial

Outcome heterogeneity

Following a review of the heterogeneity of the PFS outcome across the 12 RCTs, all RCTs were excluded

PFS assessed by a BICR was the primary endpoint in PRIMA, but in SOLO-1, AGO-OVAR16 and PAOLA-1, PFS was assessed by the investigators

PFS was not assessed in MIMOSA and insufficient PFS data were reported in CHIVA/GINECO and AGO-OVAR12

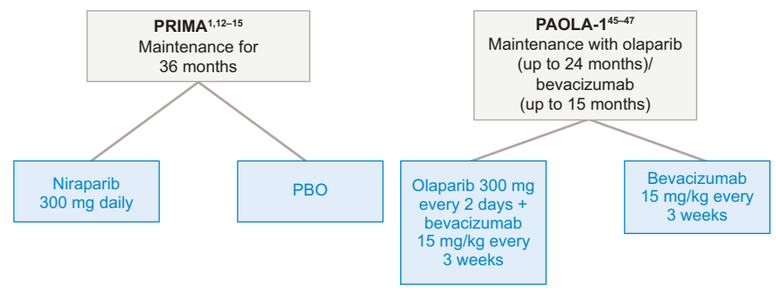
ICON-7, GOG-0218, TRINOVA-3, VELIA/GOG-3005, CHIVA/GINECO, and AGO-OVAR12 were excluded on the basis that PFS included the time patients were receiving standard CT, and as such the PFS timings are not consistent

OS data were inconsistent with PRIMA (i.e. some studies included the time period when patients received 1L CT) or were immature at the time of this analysis, and as such all 12 RCTs were excluded

PAIC feasibility assessment

A PAIC between PRIMA and PAOLA-1 was not feasible due to significant differences in trial outcomes, as well as differences in the inclusion/exclusion criteria, use of bevacizumab prior to the study, and use of NACT in these trials (**Figure 3**)

Figure 3. Network of identified RCTs for PAIC feasibility



PAIC, population-adjusted indirect treatment comparison; PBO, placebo; RCT, randomised controlled trial.

Inclusion/exclusion criteria

The wider inclusion criteria in PAOLA-1 (including patient cytoreductive surgery history and best response to most recent platinum-based therapy) means that a proportion of the PAOLA-1 population is expected to have a 'better prognosis' than the PRIMA population. In PAOLA-1, patients were enrolled regardless of surgical results, such that there were FIGO Stage III patients with no VRD after PDS. However, the requirement in PRIMA for FIGO Stage III disease with no VRD following PDS meant that PRIMA patients had a 'worse prognosis' at baseline compared with PAOLA-1 patients

PAOLA-1 included patients with Stage III disease and no VRD following PDS. This population was excluded from PRIMA and has been shown to have a better prognosis compared with patients with VRD.[1,10] This lack of overlap between the trial populations violates the 'conditional constancy of absolute effects' assumption for unanchored PAICs

54% and 52% of patients in PAOLA-1, in experimental and control arms, respectively, had no no evidence of disease after 1L CT.[10] In PRIMA, 'no evidence of disease' was not reported

Receipt of NACT

Receipt of NACT was identified as a confounding factor which would bias the comparison of PRIMA and PAOLA-1. Patients who received NACT have a worse prognosis[11]

Bevacizumab treatment prior to study entry

Patients in PAOLA-1 received bevacizumab in combination with platinum-based CT, prior to study entry and continued with bevacizumab as a maintenance therapy with or without olaparib. Few patients in PRIMA received bevacizumab, prior to commencing niraparib maintenance therapy

This difference between the two studies is a potential confounding factor and source of bias and uncertainty when considering an ITC between niraparib and olaparib plus bevacizumab

PFS method of assessment and frequency of measurements

The primary endpoint for PRIMA was PFS by BICR; for PAOLA-1 the primary endpoint was investigator-assessed PFS. Disparities in these two types of assessments may exist and comparative efficacy estimates based on secondary or exploratory endpoints should be treated with caution given that the clinical trials may not be powered to detect significance beyond the primary endpoint(s)

The more frequent scanning intervals in PRIMA (performed every 12 weeks) may have led to shorter median PFS estimates compared with PAOLA-1 (scans performed every 24 weeks, or every 12 weeks if there was evidence of disease progression) and this is therefore a source of bias

Implications for Field of OC

Cross-trial comparisons of therapeutic agents investigated in 1L OC should be made with caution as this study demonstrates that several confounding factors can preclude an objective systematic comparison between RCTs

Study Limitations

The clinical studies identified for the NMA were informed by a SLR, and as such the list was influenced by the search strategy and selection criteria of the review

The PAIC feasibility assessment was limited to the comparison of PRIMA and PAOLA-1

The feasibility assessments were based largely on PFS, due to limited common outcomes across the clinical studies

Conclusions

- **Based on the evidence presented here, neither an NMA nor PAIC would meet current guidelines, such as those outlined by ISPOR, for objective comparative clinical effectiveness analyses**
- **The PRIMA clinical trial enrolled patients with a high risk of disease recurrence, and as such the study population differed markedly from several of the other 1L OC maintenance studies**
- **Indirect comparisons of 1L OC maintenance RCTs are subject to uncontrolled heterogeneity and should not be considered appropriate evidence for use in clinical decision making or reimbursement decisions**

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Abbreviations

1L, first line; CA-125, cancer antigen-125; CT, chemotherapy; CT-scan, computed tomography scan; BICR, blinded independent central review; *BRCA*m, breast cancer gene mutated; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; HRd, homologous recombination deficiency; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; ITC, indirect treatment comparison; IV, intravenous; NACT, neoadjuvant chemotherapy; NICE DSU, National Institute for Health and Care Excellence Decision Support Unit; NMA, network meta-analysis; OC, ovarian cancer; OS, overall survival; PAIC, population-adjusted indirect treatment comparison; PARP, poly(ADP-ribose) polymerase; PDS, primary debulking surgery; PFS, progression-free survival; RCT, randomised controlled trial; RECIST, Response evaluation criteria in solid tumors; RS, routine surveillance; SLR, systematic literature review; ULN, upper limit of normal; VRD, visible residual disease.

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