Single Technology assessment

ID2017_059

Niraparib (Zejula) for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

This STA is restricted to BRCA mutation positive patients

03-10-2019

Norwegian Medicines Agency

PREFACE

Implementation of the National System for the introduction of new technologies in the specialist healthcare system will help ensure that assessment of appropriate new technologies happens in a systematic manner with respect to efficacy and safety, as well as impacts on health and society. The main aim of the new system is described in the National Health and Care Plan 2011-2015 and the White Paper 10 (2012-2013), Good quality - safe services. The regional health authorities, the Norwegian Knowledge Centre for Health Services, the Norwegian Medicines Agency and the Directorate of Health collaborate on tasks related to the establishment and implementation of the new system. Eventually, the National System for the introduction of new technologies in the specialist healthcare system will assist in the rational use of health care resources.

The Norwegian Medicines Agency has been assigned the responsibility to evaluate Single Technology Assessments (STA) of individual pharmaceuticals. A Single Technology Assessment is a systematic summary of evidence based on research on efficacy, safety and impact assessment. For pharmaceuticals, this will usually revolve around budgetary consequences or resource allocation. The burden of proof relating to the documentation of efficacy, safety and cost-effectiveness is borne by the MA-holder for the pharmaceutical under review. NoMA can, when necessary, provide guidance to pharmaceutical companies.

NoMA assesses the submitted evidence for all important clinical outcomes, resource use as well as the assumptions made in the analysis presented by the MA-holder and the presented results. NoMA does not perform its own health economic analyses. If required, NoMA may request additional information and perform additional calculations of the costs and cost effectiveness using the submitted model.

NoMA evaluates the relative efficacy and incremental costs in relation to a relevant comparator. The cost-effectiveness ratio will be weighed against the severity of the relevant condition/disease. NoMA does not assess the benefit risk balance already assessed under the market-authorisation procedure. Information about this is provided by EMA (SmPC).

Single Technology Assessment of pharmaceuticals is intended to support sound decision making on potential introductions of new technologies, and prioritisation made at the Health Authority level. NoMA has no decision-making authority in this system.

All assessments are published and available to the public (www.legemiddelverket.no).

SUMMARY

Rationale
NoMA has assessed the relative effectiveness and safety of Zejula according to the request specifications from the Ordering Forum (request number ID2017_059).

NoMA has evaluated maintenance treatment with niraparib (Zejula) of BRCA mutation-positive advanced, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to first-line platinum-based chemotherapy in adults. The restriction to only include BRACA mutation-positive patients was made to provide a basis for a comparison of Zejula with olaparib (Lynparza) which has already been introduced in the Norwegian Specialist Health Service for the same patient population.

Evaluation of maintenance treatment of the BRCA wild-type patient population will be carried out separately.

Number of patients in Norway
There are about 20-40 patients that can be treated with niraparib for this indication each year.

Norwegian clinical practice
According to the Norwegian guidelines, olaparib is used as maintenance therapy in patients with relapsed platinum-sensitive ovarian cancer.

Efficacy
The efficacy of niraparib in BRCA mutated patients with ovarian cancer was demonstrated through the NOVA trial, where niraparib showed a median PFS of 21.0 months compared to 5.5 months for placebo and a hazard ratio of 0.27 (95 % CI: 0.173, 0.410; $p < 0.0001$). The PFS results were compared, in an indirect treatment comparison, to olaparib based on data from the BRCA mutated subpopulation in Study 19. In Study 19 olaparib showed a median PFS of 11.2 months compared to 4.3 months for placebo and a hazard ratio of 0.18 (95 % CI: 0.10, 0.31; $p<0.0001$). The submitted analysis indicates that there are no clinically relevant differences in efficacy between olaparib and niraparib in this patient population.

Safety
The available safety data indicates that more patients will experience severe adverse reactions at the recommended dose of niraparib, when compared to olaparib, but that these reactions can be managed through dose reductions. Based on the feedback from the clinical experts and the expert group for the oncology tender, the differences in safety are deemed acceptable.

NoMA´s overall appraisal
The submitted data does not show clinically relevant differences in the efficacy of niraparib as compared to olaparib in BRCA mutated platinum-sensitive relapsed ovarian cancer. However, there appears to be a higher proportion of severe adverse reactions associated to niraparib when compared to olaparib at the recommended dose. Based on the feedback from the clinical experts and the expert group for the

oncology tender, the differences in safety can be considered acceptable, and the products comparable in clinical practice.

INNHOLDFORTEGNELSE

LOGG

Bestilling:	*ID_nr 2017_059: Niraparib (Zejula) til behandling av kreft i eggstokk, eggleder og bukhinne*
Forslagstiller:	Myndighet, Statens legemiddelverk
Legemiddelfirma:	GSK og Tesaro
Preparat:	Zejula
Virkestoff:	Niraparib
Indikasjon:	Zejula er indisert som monoterapi til vedlikeholdsbehandling av voksne pasienter med tilbakefall av platinasensitiv, høygradig serøs kreft i ovarieepitel eller eggleder eller primær peritonealkreft, med respons (fullstendig eller delvis) på platinabasert kjemoterapi.
ATC-nr:	L01X X54

Prosess

Dokumentasjon bestilt av Legemiddelverket	21-04-2017
Fullstendig dokumentasjon mottatt hos Legemiddelverket	22-12-2017
Klinikere kontaktet for første gang	20-02-2018
LIS kontaktet for første gang av Legemiddelverket.	22-09-2019
Legemiddelverket bedt om ytterligere dokumentasjon	22-02-2018
Ytterligere dokumentasjon mottatt av Legemiddelverket	03-07-2019
Rapport ferdigstilt:	03-10-2019
Saksbehandlingstid:	650 dager hvorav 495 dager i påvente av ytterligere opplysninger fra GSK/Tesaro. Dette innebærer en reel saksbehandlingstid hos legemiddelverket på 155 dager.
Saksutredere:	Bjørn Oddvar Strøm David Mwaura Ania Urbaniak
Kliniske eksperter:	Liv Cecilie V. Thomsen Expert group for the oncology tender

Kliniske eksperter har bidratt med avklaringer av sentrale forutsetninger i analysen (bl.a. sammenlignende behandling, pasientgrunnlag og overførbarhet av studiedata til norsk klinisk praksis). Legemiddelverket er ansvarlig for rapportens innhold. Kliniske eksperter har ikke vært involvert i noen konsensusprosess eller hatt noen «peer-review» funksjon ved utarbeidelse av rapporten.

ORDLISTE

APT	Absolutt prognosetap
AIC	Akaike information criterion
AUP	Apotekenes utsalgspris
BIC	Bayesian information criterion
BRCA	Breast cancer gene
ECOG	European cooperative oncology group
IKER	Inkrementell kostnadseffektivitetsratio
MVA	Merverdiavgift
OS	Overal survival, totaloverlevelse
PFS	Progression free survival, progresjonsfri overlevelse
QALY	Quality adjusted life years, kvalitetsjustert leveår
TFST	Time to first subsequent therapy
TSST	Time to second subsequent therapy
IRC	Independent review committee
ICR	Independent central review
RCC	Renal cell carsinoma, nyrecellekreft
RECIST	Response evaluation criteria in solid tumors
SmPC	Summary of product characteristics

1 BACKGROUND

1.1 SCOPE

This single technology assessment (STA) concerns maintenance treatment with niraparib of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

Health service interventions are to be evaluated against three prioritisation criteria; the benefit criterion, the resource criterion and the severity criterion. The priority-setting criteria are to be evaluated together. NoMA´s assessment is primarily based on the documentation presented by GSK.

In this assessment, NoMA has chosen to restrict the evaluation of niraparib to maintenance treatment of BRCA mutation-positive advanced, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to first-line platinum-based chemotherapy in adults. This restriction enables NOMA to evaluate a comparison with olaparib (Lynparza) that has already been introduced in the Norwegian Specialist Health Service for the same patient population. Evaluation covering maintenance treatment of the BRCA wild-type patient population will be carried out separately.

1.2 OVARIAN CANCER

Ovarian cancer originates from the cells of the ovary, but also includes primary peritoneal cancer and cancer in the fallopian tube. Ovarian cancer is the most common gynaecological cancer in Norway. Approximately 5 % to 10 % of ovarian cancer cases are assumed to be inheritable [1]. This is because mutations in the BRCA1 and BRCA2-gene have been found in families with ovarian cancer [2]. Women with a family history of mammary or ovarian cancer, and a known BRCA-mutation have a lifetime risk of about 40 % to 50 % of developing BRCA1 ovarian cancer, and about 20 % to 30 % lifetime risk for BRCA2. In comparison, the lifetime risk for the general population is approximately 2 %. The average age at diagnosis is 59 years. The disease is often asymptomatic in the early stages, and 60 % - 70 % of the patients have advanced disease at the time of diagnosis [3].

BRCA1 is associated with earlier disease presentation when compared to BRCA2, in addition to containing the largest proportion of ovarian cancer mutations [4, 5].

1.3 SEVERITY AND SHORTFALL

NoMA has previously calculated the absolute shortfall for the same patient population treated with current standard of care to be 11.9 QALYs [4]. In this assessment, olaparib is the relevant comparator. NoMA, considers therefore, that the absolute shortfall calculated in the STA for olaparib also applies for this assessment given that it covers the same patient population.

1.4 TREATMENT OF PLATINUM-SENSITIVE OVARIAN CANCER

1.4.1 Treatment with niraparib

- Indication
  Niraparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

- Mechanism of action
  Niraparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, PARP-1 and PARP-2, which play a role in DNA repair. In vitro studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis, and cell death. Increased niraparib-induced cytotoxicity was observed in tumour cell lines with or without deficiencies in the BReast CAncer (BRCA) 1 and 2 tumour suppressor genes. In orthotropic high-grade serous ovarian cancer patient-derived xenograft tumours (PDX) grown in mice, niraparib has been shown to reduce tumour growth in BRCA 1 and 2 mutations, BRCA wild-type but homologous recombination (HR) deficient, and in tumours that are BRCA wild-type and without detectable HR deficiency

- Posology
  The dose is three 100 mg hard capsules once daily, equivalent to a total daily dose of 300 mg. Should patients experience severe adverse reactions, then treatment can be withheld for up to 28 days, before being resumed at a lower dose (first 200 mg, then 100 mg). Should adverse reactions persist for more than 28 days, or reappear more than twice, then treatment should be discontinued.

- Adverse reactions
  In the pivotal ENGOT-OV16 (NOVA) study [6], adverse reactions (ADRs) occurring to ≥ 10 % of patients receiving Zejula monotherapy were as follows; nausea, thrombocytopenia, fatigue/asthenia, anaemia, constipation, vomiting, abdominal pain, neutropenia, insomnia, headache, decreased appetite, naso-pharyngitis, diarrhoea, dyspnoea, hypertension, dyspepsia, back pain, dizziness, cough, urinary tract infection, arthralgia, palpitations, and dyspepsia. The most common serious adverse reactions > 1 % (treatment-emergent frequencies) were thrombocytopenia and anaemia.

For more information, please see the approved Summary of Product Characteristics (SmPC) [7]

1.4.2 Treatment guidelines

According to the Norwegian guidelines (page 31), the current treatment standard used as maintenance therapy for BRCA-mutated patients with relapsed platinum-sensitive ovarian cancer is olaparib [5].

1.4.3 Comparator

Based on the treatment guidelines, olaparib is considered the appropriate comparator for this evaluation.

1.4.4 Treatment with olaparib (50 mg capsules)

- Indication
  Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

- Posology
  The recommended dose of olaparib is 400 mg (eight capsules) taken twice daily, equivalent to a total daily dose of 800 mg.
  Treatment with olaparib may be interrupted or a dose reduction considered in order to manage adverse reactions such as nausea, vomiting, diarrhoea and anaemia.

- Adverse reactions
  The most frequently observed adverse reactions across clinical trials for patients receiving Olaparib monotherapy (≥ 10 %) were nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, upper abdominal pain, cough, dyspnoea, anaemia, neutropenia, thrombocytopenia, and leukopenia. Grade ≥ 3 adverse reactions occurring in > 2 % of patients were anaemia (16 %), neutropenia (6 %), fatigue/asthenia (6 %), leukopenia (3 %), thrombocytopenia (2 %) and vomiting (2 %). Adverse reactions that most commonly led to dose interruptions and/or reductions were anaemia (13.9 %), vomiting (7.1 %), nausea (6.6 %), fatigue/asthenia (6.1 %) and neutropenia (5.8 %). Adverse reactions that most commonly led to permanent treatment discontinuation were anaemia (1.3 %), nausea (0.8 %) and thrombocytopenia (0.5 %).

  For more information, please see the approved SmPC [8].

2 RELATIVE EFFECTIVENESS

2.1 SUBMITTED STUDIES

The available data on maintenance treatment of recurrent ovarian cancer consists of one study for niraparib (NOVA) and two studies for olaparib; Study 19 and SOLO-2.

- NOVA (PR-30-5011-C or ENGOT-OV16) [7] was a phase III, randomized, double-blind trial of maintenance with niraparib versus placebo in patients with platinum-sensitive ovarian cancer. The primary endpoint was independent review committee (IRC) - assessed PFS as per RECIST 1.1 criteria. The gBRCAmut and non-gBRCAmut cohorts were treated as 2 independent cohorts/studies and the patients were randomized separately within each cohort.
- Study 19 (D0810C00019) [8] was a phase II randomised, double-blind, multicentre study to assess the efficacy of olaparib (400 mg bd, capsule formulation) in the treatment of patients with platinum-sensitive relapsed high grade serous ovarian cancer following treatment with two or more platinum-containing regimens. The primary endpoint was investigator-assessed PFS as per RECIST 1.0 criteria. Patients were not stratified (hence not randomized) by BRCA mutation status.
- SOLO-2 (D0816C00002) [9] is an ongoing phase III, randomised, double-blind, placebo-controlled, multicentre study to assess the efficacy of olaparib maintenance monotherapy (300 mg bd, tablet formulation) in the treatment of patients with platinum-sensitive relapsed high grade serous ovarian cancer patients (including patients with primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer with BRCA mutations. The primary endpoint is investigator-assessed PFS as per RECIST 1.1 criteria.

Olaparib 400 mg, capsule formulation, was previously assessed by NoMA based on Study 19 (STA Lynparza). A study comparing the newer tablet formulation of olaparib 300 mg vs the capsule formulation has now been published [10]. However, the new tablet formulation is yet to be evaluated by NOMA, hence the comparison based on SOLO-2 is for supportive purposes only.

Table 1 Overview of relevant studies

Study	Population	Intervention	Comparator	Primary endpoint	Secondary endpoint
NOVA (ENGOT-OVA16) [6, 7]	Patients with platinum-sensitive, relapsed, high-grade ovarian cancer who had received at least 2 platinum-based chemotherapy and were in response to their last platinum-based chemotherapy	Niraparib 300 mg QD	Placebo	Progression-free survival (PFS), defined as the time from the date of treatment randomization to the date of first documentation of progression or death by any cause, was assessed by IRC per RECIST v.1.1 criteria.	Time to first subsequent treatment (TFST), Chemotherapy free interval (CFI), Time to second subsequent treatment (TSST), Patient reported outcomes (PRO) including EQ-5D-5L, PFS2, OS
Study 19 (D0810C00019) [8]	Patients with platinum-sensitive relapsed (PSR) high grade serous ovarian cancer following treatment with two or more platinum-containing regimens.	Olaparib capsule, 400 mg BD	Placebo	PFS, defined as the time from randomisation to the earlier date of objective assessment of progression (per RECIST 1.0 criteria) or death (by any cause in the absence of progression).	OS, Best overall response, Response rate, Disease control rate, Duration of response, Tumour size, Time to progression *Exploratory:* Time to discontinuation of olaparib/placebo treatment (TDT), TFST, TSST
SOLO-2 (D0816C00002) [9]	Relapsed high grade serous ovarian cancer (HGSOC) patients (including patients with primary peritoneal and / or fallopian tube cancer) or high grade endometrioid cancer with BRCA mutations (documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function)) who have responded following platinum based chemotherapy	Olaparib 300 mg tablets BD	Placebo	PFS using investigator assessment according to RECIST 1.1	OS, Time from randomization to second progression, HRQoL, TFST, TSST, TDT

GSK has attempted to make a comparison of the studies in order to determine similarity of the patient cohorts as well as study endpoints and data maturity. However, GSK argues/claims that the studies cannot be robustly compared via ITC due to the following reasons:

- The primary endpoint of PFS was not the same across the studies. In the NOVA study, the assessment of PFS by IRC included all radiological and clinical progression events and deaths. While in Study 19, PFS by investigator assessment included only radiologic events and death – see Table 2.
- The scanning interval was different in the NOVA study compared to Study 19 and SOLO-2. NOVA study scans were performed every 8 weeks through week 52 then every 12 weeks until treatment discontinuation, whilst scans were performed every 12 weeks through week 60 in Study 19 and week 72 in SOLO-2 followed by every 24 weeks until progression or withdrawal of patient consent.
- Heterogeneity of patient characteristics: less BRCAmut patients in the NOVA study had ECOG 0 (65.9 % niraparib vs. 73.8 % placebo) compared to Study19 (83.8 % olaparib vs. 72.6 % placebo)

Table 2 Comparison of primary endpoints

	Investigator Led PFS				Independent Central Review PFS			
	Primary endpoint	Radiologic PD	Clinical PD	Death	Primary Endpoint	Radiologic PD	Clinical PD	Death
ENGOT-OV16/NOVA	×	✓	✓	✓	✓	✓	✓	✓
Study 19	✓	✓	×	✓	×	✓	×	×
SOLO-2	✓	✓	×	✓	×	✓	×	×

Abbreviations: PFS – Progression-free survival; PD – Progressed disease

NoMA's assessment

GSK claims that the study heterogeneity is too great to conduct an ITC, and instead argues that a side-by-side comparison is the most appropriate approach. NoMA considers a side-by-side comparison inappropriate as it ignores the benefits of randomization. A side-by-side comparison is based on a comparison of individual PARP inhibitor arm-data, as opposed to a relative effect estimate of a PARP inhibitor versus placebo estimated in an ITC. When randomization holds within a trial, the comparison of those relative effects account for differences in prognostic factors between the NOVA trial and Study 19. However, NoMA is in agreement that an ITC cannot adjust for heterogeneity (effect modification) and differences in trial design.

NoMA agrees that the ITC on its own does not present a reliable estimate and the conclusion on similarity cannot be solely based on the PFS analysis. However, BRCAmut patient characteristics are similar between NOVA and Study 19 in terms of age, race, primary tumor location and respons to prior therapy. Additionally, ECOG performance status is an important prognostic factor [11], even though GSK has not

provided evidence of effect modification. Generally, there is no need to account for prognostic factors in an ITC if the randomization worked [12]. NoMA notes, however, that there was an imbalance in the ECOG status between arms in both studies which might have favoured olaparib when compared to niraparib. At the same time, it is not possible to make a complete comparison of patient characteristics between the trials, as a limited numer of characteristics are reported and some are not reported in the same way.

NoMA also acknowledges that there are differences in the PFS definition and, most importantly, time of PFS assessment. The NOVA PFS primary endpoint by an IRC included all radiological and clinical progression events, determined by RECIST v1.1 and clinical criteria i.e. increase in CA-125 with confirmed response by other test e.g. ultrasound or clinical symptoms, and deaths, while the Study 19 and SOLO-2 PFS primary endpoints by investigator assessment per RECIST 1.0 criteria included only radiologic events and death. Estimates of median PFS tend to be longer when assessed by independent central review (vis-à-vis site investigators). The NOVA study used RECIST criteria 1.1 where additional criteria were introduced as compared to RECIST 1.0. These additional RECIST criteria potentially increase the time to progression and hence bias the results in favour of niraparib. The comparability of RECIST criteria has been assessed in patients receiving targeted therapy in advanced or metastatic cancer via a pooled analysis conducted by Kim et al [13]. The authors concluded that RECIST 1.1 shows highly concordant response assessment with RECIST 1.0 in patients treated with targeted agents. However, patients with ovarian cancer were not included in this analysis.

The scanning interval was different between NOVA, Study 19 and SOLO-2. In NOVA, PFS was assessed every 8 weeks up to Week 56, and then at 12-week intervals until disease progression. In Study 19, PFS was assessed every 12 weeks up to Week 60, and then at 24-week intervals until disease progression. Significant CA-125 elevation could also trigger an unscheduled tumour assessment in Study 19, potentially leading to a shorter median time to progression than would be otherwise be observed. On the other hand, the shorter scan interval in NOVA may potentially result in a shorter median PFS than in Study 19 or SOLO-2.

Overall, NoMA acknowledges that there are substantial differences between the trials and that the results of an indirect treatment comparison (chapter 3.3.3) must be interpreted with caution. At the same time, NoMA has not identified a clear direction of bias in the design and patient characteristics that favors one PARP inhibitor over another.

3 PICO[1]

3.1 PATIENT POPULATION

Norwegian clinical practice

The patients in Norwegian clinical practice are currently receiving olaparib as standard care. Based on data from the Norwegian prescription database, patients receiving olaparib have median age between 60 and 64 years [14]. The patient population in the current STA is limited to patients who have responded to platinum-based therapy at least two times at time of initiation of treatment. Given that olaparib has been available for some years, it is assumed that most patients will start a PARP inihibitor after their second response to platinum-based therapy.

Submitted clinical documentation

The patient characteristics from the NOVA study are shown below.

Table 3 Patient characteristics from the NOVA trial [6]

Characteristic	Germline *BRCA* Mutation		No Germline *BRCA* Mutation	
	Niraparib (N=138)	Placebo (N=65)	Niraparib (N=234)	Placebo (N=116)
Median age (range) — yr	57 (36–83)	58 (38–73)	63 (33–84)	61 (34–82)
Eastern Cooperative Oncology Group performance status — no. (%)				
0	91 (65.9)	48 (73.8)	160 (68.4)	78 (67.2)
1	47 (34.1)	17 (26.2)	74 (31.6)	38 (32.8)
Cancer stage — no. (%)†				
I or II	23 (16.7)	10 (15.4)	22 (9.4)	5 (4.3)
III	95 (68.8)	46 (70.8)	173 (73.9)	86 (74.1)
IV	20 (14.5)	9 (13.8)	38 (16.2)	24 (20.7)
Time to progression after penultimate platinum therapy — no. (%)				
6 to <12 mo	54 (39.1)	26 (40.0)	90 (38.5)	44 (37.9)
≥12 mo	84 (60.9)	39 (60.0)	144 (61.5)	72 (62.1)
Best response to most recent platinum therapy — no. (%)				
Complete	71 (51.4)	33 (50.8)	117 (50.0)	60 (51.7)
Partial	67 (48.6)	32 (49.2)	117 (50.0)	56 (48.3)
Previous bevacizumab use — no. (%)	33 (23.9)	17 (26.2)	62 (26.5)	30 (25.9)
Germline *BRCA* mutation — no. (%)				
BRCA1	85 (61.6)	43 (66.2)	NA	NA
BRCA2	51 (37.0)	18 (27.7)	NA	NA
BRCA1, *BRCA2* rearrangement, or both	9 (6.5)	4 (6.2)	NA	NA
Previous lines of chemotherapy — no. (%)‡				
1	1 (0.7)	0	0	0
2	70 (50.7)	30 (46.2)	155 (66.2)	77 (66.4)
≥3	67 (48.6)	35 (53.8)	79 (33.8)	38 (32.8)

* There were no significant differences between the niraparib group and the placebo group. NA denotes not applicable.
† Staging was performed with the use of the International Federation of Gynecology and Obstetrics system. Among the patients without a germline *BRCA* mutation, data with respect to staging were not available for one patient in the placebo group, and one patient in the niraparib group had stage 0 disease at the time of diagnosis.
‡ Among the patients without a germline *BRCA* mutation, data with respect to previous lines of therapy were not available for one patient in the placebo group.

[1] Patients, Intervention, Comparator, Outcome.

In the ITC, patients from the gBRCAmut cohort were compared to relevant patients from Study 19. Patient characteristics for BRCA mutated subgroup from Study 19 are presented below.

Table 4 Baseline characteristics from Study 19 [15]

	FAS		*BRCAm*	
	Olaparib 400 mg bd (n=136)	**Placebo (n=129)**	**Olaparib 400 mg bd (n=74)**	**Placebo (n=62)**
Age (years)				
Mean (SD)	58.9 (10.95)	58.5 (9.89)	57.6 (10.37)	55.5 (10.53)
Median (range)	58.0 (21-89)	59.0 (33-84)	57.5 (38-89)	55.0 (33-84)
Age group (years), n (%)				
<50	30 (22.1)	20 (15.5)	19 (25.7)	16 (25.8)
≥50 to <65	61 (44.9)	74 (57.4)	38 (51.4)	35 (56.5)
≥65	45 (33.1)	35 (27.1)	17 (23.0)	11 (17.7)
Race, n (%)				
White	130 (95.6)	126 (97.7)	70 (94.6)	61 (98.4)
Black/African American	2 (1.5)	1 (0.8)	2 (2.7)	0
Asian	2 (1.5)	2 (1.6)	1 (1.4)	1 (1.6)
Other	2 (1.5)	0	1 (1.4)	0
Ethnic population, n (%)				
Jewish descent[a]				
No	115 (84.6)	112 (86.8)	60 (81.1)	48 (77.4)
Yes	21 (15.4)	17 (13.2)	14 (18.9)	14 (22.6)
Ashkenazi Jewish	17 (12.5)	12 (9.3)	12 (16.2)	10 (16.1)
Sephardic Jewish	1 (0.7)	1 (0.8)	1 (1.4)	1 (1.6)
Mizrahim Jewish	2 (1.5)	1 (0.8)	1 (1.4)	0
Other	0	3 (2.3)	0	3 (4.8)
Missing	1 (0.7)	0	0	0
ECOG performance status, n (%)				
(0) Normal activity	110 (80.9)	95 (73.6)	62 (83.8)	45 (72.6)
(1) Restricted activity	23 (16.9)	30 (23.3)	11 (14.9)	15 (24.2)
(2) In bed <50% of the time	1 (0.7)	2 (1.6)	0	1 (1.6)
Unknown	2 (1.5)	2 (1.6)	1 (1.4)	1 (1.6)
Primary tumour location				
Ovary	119 (87.5)	109 (84.5)	65 (87.8)	54 (87.1)
Fallopian Tube	3 (2.2)	3 (2.3)	1 (1.4)	2 (3.2)
Primary peritoneal	14 (10.3)	16 (12.4)	8 (10.8)	6 (9.7)
Other	0	1 (0.8)[d]	0	0
Tumour grade				
Well Differentiated (G1)	0	0	0	0
Moderately Differentiated (G2)	36 (26.5)	34 (26.4)	17 (23.0)	15 (24.2)
Poorly Differentiated (G3)	97 (71.3)	89 (69.0)	55 (74.3)	46 (74.2)
Undifferentiated (G4)	2 (1.5)	4 (3.1)	1 (1.4)	0
Unassessable (GX)	1 (0.7)	2 (1.6)	1 (1.4)	1 (1.6)
Platinum sensitivity[b]				
>6 to ≤12 months	53 (39.0)	54 (41.9)	28 (37.8)	26 (41.9)
>12 months	83 (61.0)	75 (58.1)	46 (62.2)	36 (58.1)
Objective response[c]				
CR	57 (41.9)	63 (48.8)	36 (48.6)	34 (54.8)
PR	79 (58.1)	66 (51.2)	38 (51.4)	28 (45.2)

a In the FAS, one patient was classified as not of Jewish descent at the previous data cut-off (30 June 2010) and is now classified as being of Jewish (Ashkenazi) descent.
b Platinum sensitivity = time to progression after the completion of platinum therapy. Note: Platinum sensitivity refers to the penultimate platinum not the platinum regimen that was just completed by the patient.
c Objective Response: CR = Patients with no target lesions and no non-target lesions at baseline; PR = Patients with target lesions and/or non-target lesions at baseline. Note: This is the response from the platinum regimen just prior to therapy. Data for 1 patient who did not receive platinum therapy are also included.
d One Patient had location of Other – FIMBRIA
bd Twice daily; ***BRCA*** Breast cancer susceptibility gene; ***BRCAm gBRCA*** and/or ***tBRCA*** mutated; CR Complete response; CSR Clinical study report; ECOG Eastern Cooperative Oncology Group; FAS Full analysis set; ***gBRCA*** Germline ***BRCA***; PR Partial response; SD Standard deviation; ***tBRCA*** Tumour ***BRCA***

NoMA's assessment

Patients in both studies (NOVA and Study 19) are slightly younger than in Norwegian clinical practice, but this is common in clinical trials. The other patient characteristics are as expected for this population. It is noted that more patients treated with olaparib (80.9%) were in good general condition (ECOG 0) than patients treated with niraparib (64.9%). This has a potential to bias the efficacy estimate in favour of olaparib. The response to last platinum-based treatment and duration of that response were similar between the patients treated with olaparib and niraparib. The NOVA study only included patients with germline BRCA-mutation, whereas Study 19 also included patients with somatic mutations. In Study 19, only 8 of 74 patients in the active arm had a somatic mutation [15]. There is no indication that these patients had a different response from the overall population, and this is therefore unlikely to introduce further bias in the comparison.

3.2 INTERVENTION AND COMPARATOR

Norwegian clinical practice

It is assumed that patients will be treated with niraparib according to the SmPC with an initial dose of 300 mg daily (qd). A lower starting dose of 200 mg may be considered for patients weighing under 58 kg. The dose can be reduced based on adverse reactions. Should patients experience any grade 3 or higher adverse reactions, the treatement should be interrupted until the reaction resolves. Niraparib should then be resumed at lower dose (200 mg the first time, and 100 mg the second). However, niraparib treatment should be discontinued if patients experience severe adverse reactions at a dose of 100 mg.

For haematological events, dosing should be interrupted at platelet levels below 100 000/µL. haemoglobin < 8 g/dL, or neutrophil count below 1000/µl. The platelets should be at least 100 000/µL, haemoglobin more than 9g/dL, or neutrophils above 1500/µl before reassuming treatment. Niraparib may be continued at the same dosage, or at a reduced dose, depending on the judgement of the treating clinician for patients experiencing low platelet count, in addition to a reduced dose for patients with low haemoglobin or neutrophils. If patients have platelets, haemoglobin, or neutrophils below the stated threshold while on 100mg niraparib daily, niraparib should be discontinued [7]. Treatment with niraparib is expected to continue until disease progression or unacceptable toxicity.

Based on the experience from the NOVA trial [6] , and US data provided by GSK, it is assumed that most patients will reduce their dose during the course of treatment.

Norwegian patients with platinum-sensitive BRCA mutation-positive ovarian cancer who have responded to platinum-based chemotherapy are currently treated with olaparib according to the SmPC, with an initial dose of 400 mg twice daily (bd). If patients experience adverse reactions such as nausea, vomiting, diarrhoea and anaemia, dose interruption may be considered. Patients may then start treatment again on a reduced dose of 200 mg twice daily, with a further reduction to 100 mg twice daily if required. Patients will be treated until disease progression or unacceptable toxicity.

Submitted documentation
In the pivotal NOVA trial, the patients started with a dose of 300 mg niraparib once daily. Dose reduction was based on adverse events, with a mean dose usage of 195 mg daily. More than 70 % of the patients had to reduce their dose, and 15 % of the patients discontinued treatment due to adverse events.

A real-world study submitted by GSK found that 2 % of the patients starting on dosage of 200 mg niraparib once daily had to discontinue treatment, while 15 % had a dose reduction [16]. GSK has also submitted a publication where the authors recommends a lower starting dose for patients with body weight <77 kg [17].

In Study 19, 41.9 % of the patients had to reduce their olaparib dose, mostly due to adverse events, while 10.6 % of the patients discontinued olaparib treatment [15].

NoMA's assessment
There are more frequent dose reductions in the clinical trials for niraparib compared to the olaparib trial. GSK has provided data showing that there is less need for dose modifications in patients starting with 200 mg niraparib daily. However, this reduced starting dose is not aligned with the approved indication, and hence NoMA's assessment will only take to account the submitted study and approved indication i.e a starting dose of 300 mg once daily.

3.3 OUTCOMES

3.3.1 Efficacy

The NOVA study
The primary endpoint in the NOVA study was IRC-assessed PFS per RECIST 1.1. A total of 553 patients (ITT population) were enrolled in the NOVA study where 372 were randomized to niraparib and 181 to placebo. The study was designed to evaluate niraparib as maintenance treatment in two independent cohorts of patients: those with germline BRCA mutation (gBRCAmut cohort, 203 patients) and those who were not germline BRCA mutation carriers (non-gBRCAmut cohort, 350 patients) [18].

In the gBRCAmut cohort, median PFS as determined by the IRC was 21.0 months in the niraparib arm vs. 5.5 months in the placebo arm with a HR of 0.27 (95 % CI: 0.173, 0.410) ($p < 0.0001$). The effect was consistent between subgroups. A sensitivity analysis based on investigator assessment resulted in a median PFS of 14.8 (95 %CI 12.0, 16.6) for niraparib vs. 5.5 (4.9, 7.2) and a similar HR of 0.27 (0.182, 0.401). In terms of secondary endpoints, niraparib demonstrated a benefit in terms of time to first subsequent therapy (TFST) with a HR of 0.31 (0.205, 0.481), Chemotherapy-free interval (CFI) with a HR of 0.26 (0.166, 0.409) and Progression-free survival 2 (PFS2) with a HR of 0.48 (0.280, 0.821). Baseline symptoms and QoL were equivalent between placebo and niraparib patients in the cohort [18].

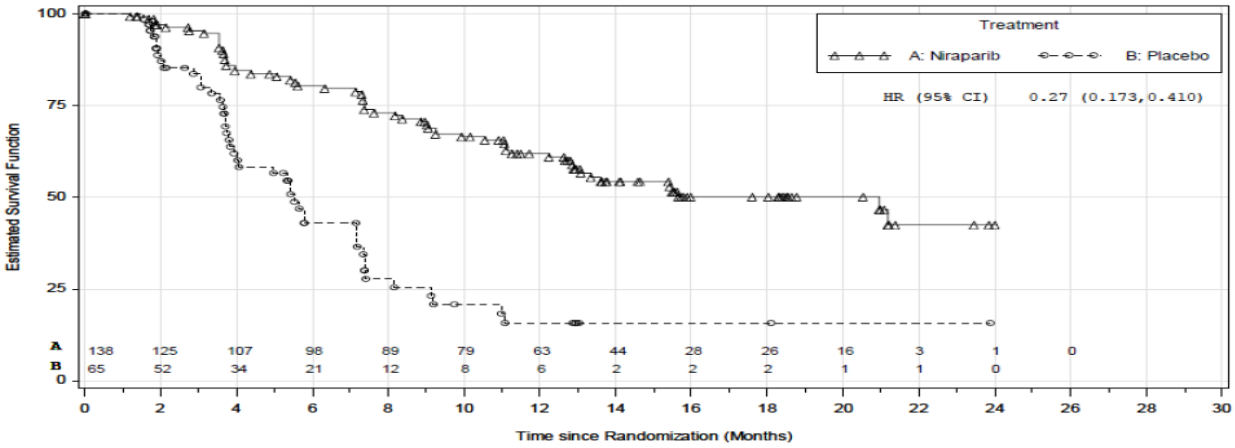

Figure 1 Kaplan-Meier plot for IRC-assessed PFS in the gBRCAmut Cohort (NOVA study)

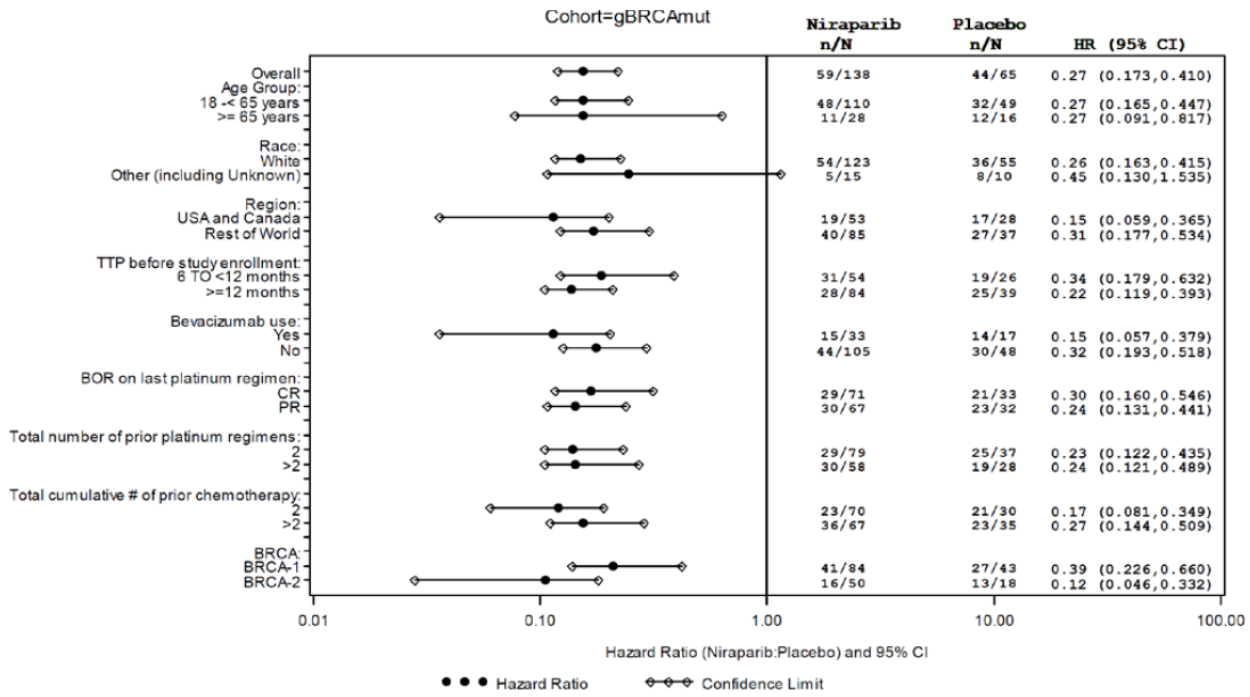

Figure 2 Forest plot of HR (95% CI) for PFS by Patient Subgroups for the gBRCAmut Cohort (ITT Population) (NOVA study)

As of 30th May 2016 (the most recent data cut-off) for the primary analysis of PFS, the OS data were immature. At that time, a total of 24 patients in the gBRCAmut cohort had died, including 16 (12 %) of the 138 patients randomized to niraparib and 8 (12 %) of the 65 patients randomized to placebo; thus, median OS was not reached in either randomized treatment arm with an HR of 0.91 (95 % CI: 0.360, 2.282).

Study 19

The primary endpoint in Study 19 was Investigator-assessed PFS per RECIST 1.0. Among patients with BRCA mutation status, 26/74 (35.1 %) patients progressed or died in the olaparib group and 46/62 (74.2 %) progressed or died in the placebo group. The HR was reported as 0.18 (95 % CI: 0.10, 0.31; p<0.0001) which corresponds to an 82 % reduction in the risk of disease progression or death. The median PFS time was 11.2 months for olaparib compared with 4.3 months for placebo. The investigator-assessed PFS benefit in patients with BRCA mutation status was confirmed by blinded independent central radiological review (HR 0.22; 95 % CI: 0.12,0.40; p<0.00001; median not reached versus 4.8 months). The data cut-off date was 30 June 2010 and no adjustment was made for treatment crossover [15]. In the most recent analysis (data cutoff of September 2015) the HR for OS was reported at 0.62 (95 % CI: 0.41, 0.94; nominal p=0.025) in patients with BRCAmut which corresponds to a 38 % reduction in the risk of death. Median OS was 34.9 months (95 % CI: 29.2, 54.6) for olaparib vs 30.2 months (23.1, 40.7) for placebo [19].

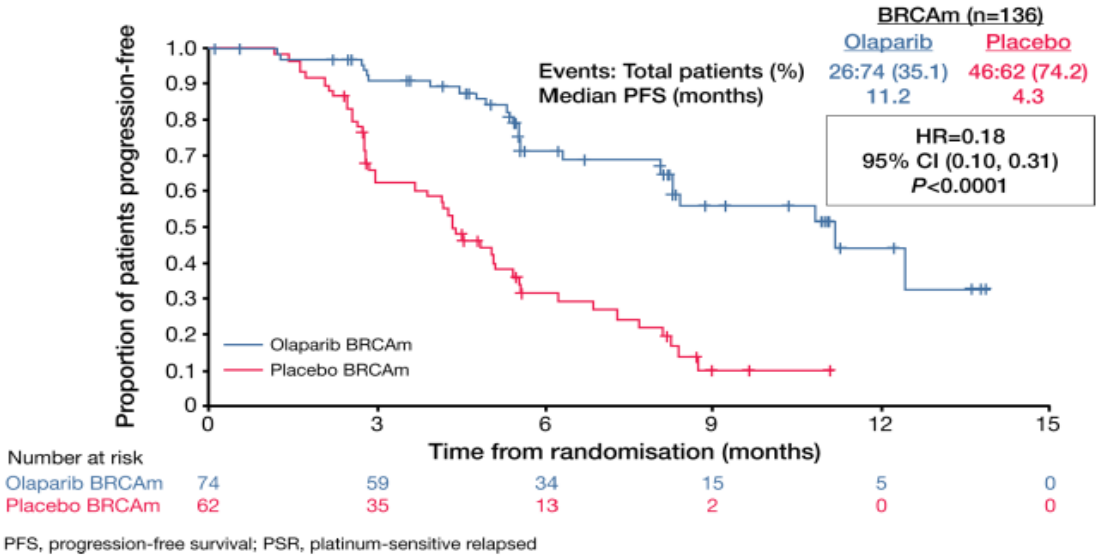

Figure 3 Kaplan-Meier plot of Investigator-assessed PFS for the olaparib 400mg bd and placebo groups: patients with BRCA mutation (Study 19) [20]

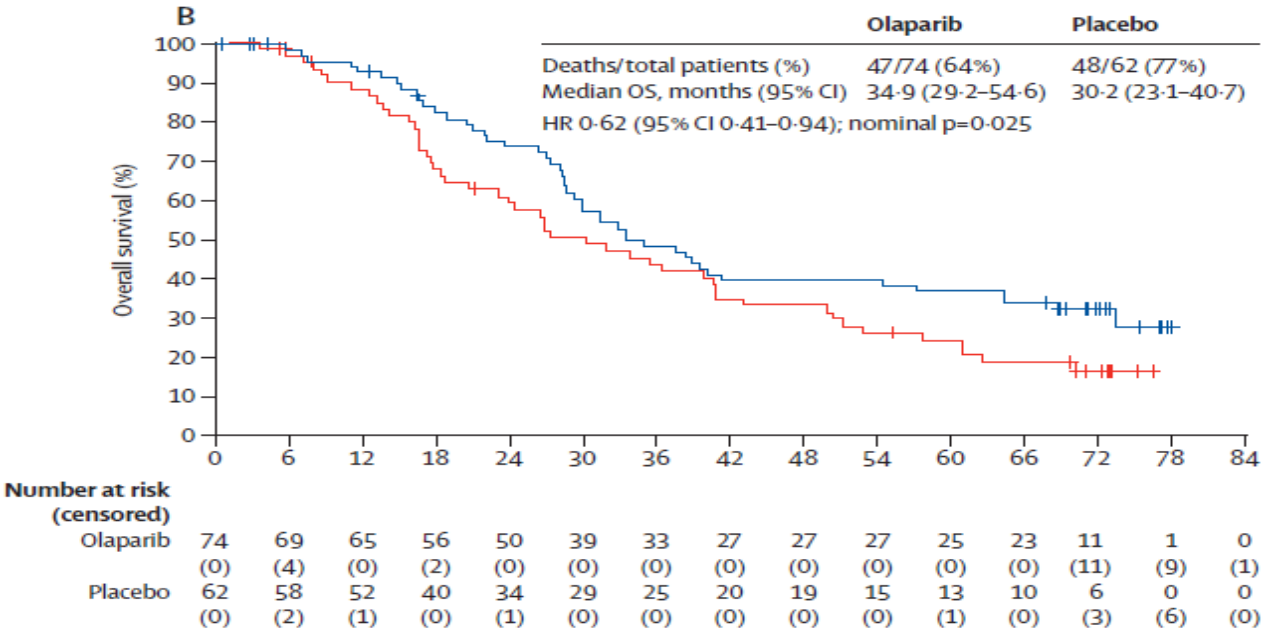

Figure 4 Kaplan-Meier curve for OS in BRCAmut subgroup (Study 19) [19].

SOLO-2 (supportive study)

The efficacy analyses were done in the intention-to-treat population (i.e. patients with a BRCA1 or BRCA2 (BRCA1/2) mutation using a tablet formulation of olaparib 300mg). Investigator-assessed median PFS was significantly longer with olaparib (19.1 months [95 % CI: 16.3, 25.7]) compared to placebo (5.5 months [5.2, 5.8]; HR 0.30 [0.22, 0.41], p<0·0001) (data cutoff September 2016). Similar results were obtained when PFS was assessed by blinded independent central review (HR 0.25 (95 % CI: 0.18,0.35), p<0·0001). In this sensitivity analysis, median PFS was significantly longer in patients receiving olaparib than in those given placebo (30.2 months [95 % CI: 19.8 to not calculable] vs 5.5 months [4.8, 5.6]). The findings for several secondary endpoints also showed significantly improved outcomes with olaparib compared with placebo. Median time to first subsequent therapy (171 events in 295 patients: 92 [47 %] in the olaparib group vs 79 [80 %] in the placebo group; 58 % maturity) was 27.9 months (95 % CI: 22.6 to not calculable) in the olaparib group versus 7.1 months (6.3–8.3) for placebo. Median time to second progression (119 events: 70 [36 %] in the olaparib group vs 49 [50 %] in the placebo group; 40 % maturity) was not reached (95 % CI: 24.1 to not calculable) in the olaparib group versus 18.4 months (15.4, 22.8) in the placebo group. Median time to second subsequent therapy (128 events: 68 [35 %] vs 60 [61 %]; 43 % maturity) was not reached (95 % CIs not calculable) compared with 18.2 months (15.0, 20.5) in the placebo group. The immature overall survival data (72 events: 45 [23 %] vs 27 [27 %]; 24 % maturity) showed no statistically significant difference between the groups (HR 0.80 [95 % CI: 0.50, 1.31], p=0.43; medians not reached in either group [95 % CIs not calculable]).

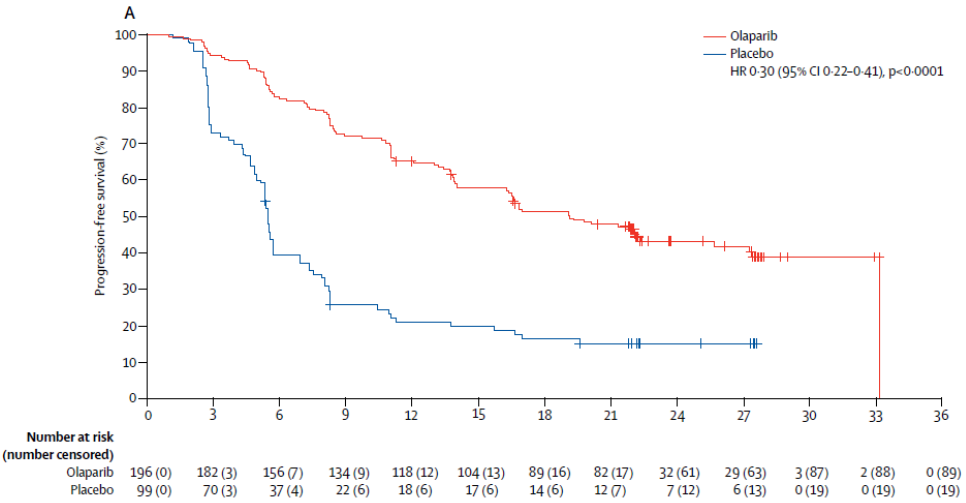

Figure 5 Kaplan-Meier plot of Investigator-assessed PFS for the olaparib 300mg bd and placebo groups (ITT population i.e patients with BRCA mutation, SOLO-2)

NoMA's assessment

The NOVA study

The effect of niraparib versus placebo is well documented in the NOVA study. This was a double -blinded, Phase III study with IRC-assessed PFS as the primary endpoint. The risk of assessment bias is low. Another strength of the study is that patients were stratified according to their germline BRCA mutation status (and hence maintaining randomisation within strata) and that the study was powered to detect a difference in each BRCA cohort.

Study 19

The effect of olaparib 400 mg vs placebo is well documented in Study 19. The study was previously assessed by NoMA in a separate STA [21]. The key difference to NOVA is that Study 19 was a Phase II study designed to compare the efficacy and safety of maintenance treatment with olaparib versus placebo, irrespective of BRCA status. Stratification and analysis by BRCA mutation status was not part of the initial study design and was only included as a post-hoc analysis. Despite the lack of stratified randomisation based on BRCA mutation statusp, patient characteristics are well balanced across the arms. The only noticeable difference is an imbalance in ECOG. More patients in the olaparib 400mg group had ECOG 0 at baseline (83.8 % vs 72.6 % for placebo), and consequently, fewer patients had ECOG 1 (14.9 % vs 24.2 % for placebo). Given the expected prognostic properties if the ECOG performance status, the observed imbalance might favour olaparib. The results from the SOLO-2 trial which included only BRCA mutation-positive patients supports the conclusions of olaparib efficacy in this population.

3.3.2 Safety

Submitted documentation

The company has not submitted a comparison of safety between olaparib and niraparib.

In the NOVA study, the most common grade 3 or 4 adverse events that were reported in the niraparib group were thrombocytopenia (in 33.8 %), anemia (in 25.3 %), and neutropenia (in 19.6 %). These were mostly managed through dose reductions. A summary of the reported adverse events in the trial is shown below:

Table 5 Adverse events reported in the NOVA trial[6]

Event	Niraparib (N = 367)		Placebo (N = 179)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Nausea	270 (73.6)	11 (3.0)	63 (35.2)	2 (1.1)
Thrombocytopenia†	225 (61.3)	124 (33.8)	10 (5.6)	1 (0.6)
Fatigue‡	218 (59.4)	30 (8.2)	74 (41.3)	1 (0.6)
Anemia§	184 (50.1)	93 (25.3)	12 (6.7)	0
Constipation	146 (39.8)	2 (0.5)	36 (20.1)	1 (0.6)
Vomiting	126 (34.3)	7 (1.9)	29 (16.2)	1 (0.6)
Neutropenia¶	111 (30.2)	72 (19.6)	11 (6.1)	3 (1.7)
Headache	95 (25.9)	1 (0.3)	17 (9.5)	0
Decreased appetite	93 (25.3)	1 (0.3)	26 (14.5)	1 (0.6)
Insomnia	89 (24.3)	1 (0.3)	13 (7.3)	0
Abdominal pain	83 (22.6)	4 (1.1)	53 (29.6)	3 (1.7)
Dyspnea	71 (19.3)	4 (1.1)	15 (8.4)	2 (1.1)
Hypertension	71 (19.3)	30 (8.2)	8 (4.5)	4 (2.2)
Diarrhea	70 (19.1)	1 (0.3)	37 (20.7)	2 (1.1)
Dizziness	61 (16.6)	0	13 (7.3)	0
Cough	55 (15.0)	0	8 (4.5)	0
Back pain	49 (13.4)	2 (0.5)	21 (11.7)	0
Arthralgia	43 (11.7)	1 (0.3)	22 (12.3)	0
Dyspepsia	42 (11.4)	0	17 (9.5)	0
Nasopharyngitis	41 (11.2)	0	13 (7.3)	0
Urinary tract infection	38 (10.4)	3 (0.8)	11 (6.1)	2 (1.1)
Palpitations	38 (10.4)	0	3 (1.7)	0
Dysgeusia	37 (10.1)	0	7 (3.9)	0
Myalgia	30 (8.2)	1 (0.3)	18 (10.1)	0
Abdominal distention	28 (7.6)	0	22 (12.3)	1 (0.6)

* Listed are the adverse events of any grade that occurred in at least 10% of the patients in either study group, along with the corresponding incidence of grade 3 or 4 events. No grade 5 events were observed in either study group.
† The category of thrombocytopenia includes reports of thrombocytopenia and decreased platelet count.
‡ The category of fatigue includes reports of fatigue, asthenia, malaise, and lethargy.
§ The category of anemia includes reports of anemia and decreased hemoglobin count.
¶ The category of neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia.

Adverse events reported in Study 19 are shown below:

Table 6 Adverse events reported in Study 19

Event	Olaparib (N=136)				Placebo (N=128)			
	Any Grade	Grade 1	Grade 2	Grade 3 or 4	Any Grade	Grade 1	Grade 2	Grade 3 or 4
	number of patients (percent)							
Any	130 (95.6)	NA	NA	48 (35.3)	116 (90.6)	NA	NA	26 (20.3)
Nausea	93 (68.4)	71 (52.2)	19 (14.0)	3 (2.2)	45 (35.2)	35 (27.3)	10 (7.8)	0
Fatigue	66 (48.5)	32 (23.5)	25 (18.4)	9 (6.6)	48 (37.5)	36 (28.1)	8 (6.3)	4 (3.1)†
Vomiting	43 (31.6)	27 (19.9)	13 (9.6)	3 (2.2)	18 (14.1)	12 (9.4)	5 (3.9)	1 (0.8)
Diarrhea	31 (22.8)	23 (16.9)	5 (3.7)	3 (2.2)	29 (22.7)	21 (16.4)	5 (3.9)	3 (2.3)
Headache	25 (18.4)	16 (11.8)	9 (6.6)	0	15 (11.7)	13 (10.2)	1 (0.8)	1 (0.8)
Decreased appetite	25 (18.4)	17 (12.5)	8 (5.9)	0	17 (13.3)	13 (10.2)	4 (3.1)	0
Abdominal pain	24 (17.6)	11 (8.1)	11 (8.1)	2 (1.5)	33 (25.8)	26 (20.3)	3 (2.3)	4 (3.1)
Anemia	23 (16.9)	3 (2.2)	13 (9.6)	7 (5.1)	6 (4.7)	3 (2.3)	2 (1.6)	1 (0.8)
Dyspepsia	22 (16.2)	19 (14.0)	3 (2.2)	0	11 (8.6)	9 (7.0)	2 (1.6)	0
Dysgeusia	19 (14.0)	17 (12.5)	2 (1.5)	0	8 (6.3)	8 (6.3)	0	0
Cough	18 (13.2)	14 (10.3)	4 (2.9)	0	12 (9.4)	11 (8.6)	1 (0.8)	0
Upper abdominal pain	18 (13.2)	12 (8.8)	6 (4.4)	0	10 (7.8)	6 (4.7)	3 (2.3)	1 (0.8)
Arthralgia	16 (11.8)	10 (7.4)	6 (4.4)	0	17 (13.3)	14 (10.9)	3 (2.3)	0
Nasopharyngitis	17 (12.5)	12 (8.8)	5 (3.7)	0	14 (10.9)	11 (8.6)	3 (2.3)	0
Constipation	17 (12.5)	12 (8.8)	5 (3.7)	0	13 (10.2)	11 (8.6)	2 (1.6)	0
Dizziness	17 (12.5)	14 (10.3)	3 (2.2)	0	9 (7.0)	9 (7.0)	0	0
Asthenia	16 (11.8)	10 (7.4)	5 (3.7)	1 (0.7)	12 (9.4)	11 (8.6)	1 (0.8)	0
Back pain	16 (11.8)	9 (6.6)	4 (2.9)	3 (2.2)	10 (7.8)	8 (6.3)	2 (1.6)	0
Hot flush	5 (3.7)	4 (2.9)	1 (0.7)	0	15 (11.7)	13 (10.2)	2 (1.6)	0
Abdominal distention	14 (10.3)	13 (9.6)	1 (0.7)	0	11 (8.6)	10 (7.8)	1 (0.8)	0

* Adverse events reported here occurred in at least 10% of patients in either study group. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. NA denotes not available.

† One patient in the placebo group inadvertently received olaparib at a dose of 400 mg twice daily for approximately 2 weeks between days 29 and 84. The exact dates and duration are unknown. It is not known whether the patient was receiving olaparib or placebo when the adverse event occurred on day 56. This adverse event was counted in the safety analysis for placebo, but the possibility that it was attributable to olaparib cannot be excluded.

In the NOVA trial, 14.7 % of the patients receiving niraparib discontinued treatment due to adverse effects, compared to 9.5 % in olaparib's Study 19.

NoMA's assessment

As would be expected of two medications with a similar mode of action, a side-by-side comparison of the adverse event profiles between niraparib and olaparib shows that both have similar adverse event profiles - with nausea, fatigue and haematological reactions being the most important events.

However, data on haematological events from one published indirect comparison between the safety profiles of niraparib and olaparib [22] suggests that adverse events are more frequent for niraparib than

for olaparib. The incidence of grade 3-4 adverse events was significantly higher in the niraparib population than in the olaparib population, and the same was true for dose interruptions. However, the difference is smaller, and not statistically significant for treatment discontinuation. This analysis is based on few events, and has to be interpreted with caution. Additionally, the data might indicate that the increased of adverse events for niraparib can be managed with more frequent dose reductions.

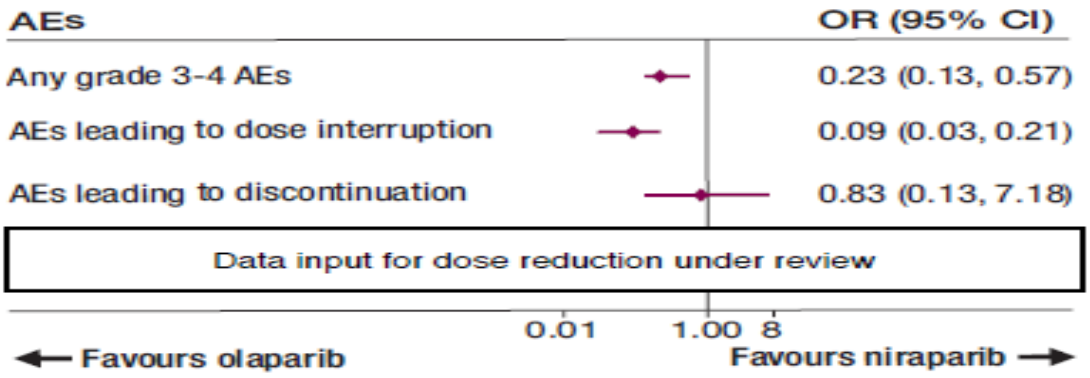

Figure 6 Comparison of safety between niraparib and olaparib [22]

It is clear from the data above that niraparib at the recommended dose has a less favourable safety profile than olaparib. However, given the feedback from clinicians, and the fact that the expert group for the oncology tender consideres the products to be similar enough, NoMA accepts that the differences in safety are manageable.

3.3.3 Results from indirect treatment comparison (ITC)

An ITC with fractional polynomials (FP) was conducted separately for the comparison of niraparib (NOVA) with a capsule formulation of olaparib (400 mg, Study 19), and the comparison of niraparib (NOVA) with a tablet formulation of olaparib (300 mg, SOLO-2).

Figure 7 below shows the evidence network for the indirect comparison of PFS between niraparib 300 mg qd and olaparib 400 mg bid, and a separate network for the niraparib 300 mg comparison with olaparib 300 mg (supportive analysis).

Figure 7 Evidence network of PFS; niraparib 300mg qd vs olaparib 400mg bid (top) and vs olaparib 300mg bid (bottom)

The FP methodology was chosen as the proportional hazard assumption was not met for the individual studies, and hence one constant hazard ratio (HR) for PFS could not be used as an output (see Figure 8 for visualization of variable HR over time). When FP is used, the difference in the parameters is considered the multidimensional treatment effect, which is synthesized (and indirectly compared) across studies. With this approach, the treatment effects (PFS) are represented by multiple parameters rather than a single parameter [23].

Figure 8 Hazard ratio of treatments compared to placebo for PFS; niraparib 300mg qd vs. olaparib 400mg bid (left), niraparib 300mg qd vs. olaparib 300mg bid (right)

Table 7 Estimates of hazard ratios from ITC of PFS; niraparib 300mg qd vs. olaparib 400mg bid. IRC-assessed PFS in NOVA, Investigator-assessed PFS in Study 19.

Table 8 Estimates of hazard ratios from ITC of PFS; niraparib 300mg qd vs. olaparib 300mg bid. IRC-assessed PFS in NOVA, Investigator-assessed PFS in SOLO-2.

The observed median PFS for BRCA mutated patients in the olaparib 400mg bid arm in Study 19 was 11.2 months compared to 4.3 months in the placebo arm. The observed median PFS for olaparib 300 mg bid in SOLO2 was 19.1, and the placebo arm was 5.5 months. In contrast, in the NOVA study, the median PFS in

the gBRCAmut cohort in the niraparib arm was 21.0 months vs 5.5 months in the placebo arm. However, it was the relative difference between the treatment arm and the placebo arm in terms of HR that was synthesized by means of Bayesian indirect comparisons. The modeled progression free survival of treatment compared to placebo is presented in Figure 9.

Figure 9 Modeled progression free survival of treatments compared to placebo; niraparib 300mg qd vs. olaparib 400mg bd (left) and vs olaparib 300mg bd (right)

GSK also has submitted a comparison of niraparib 300 mg with pooled data for olaparib based on Study 19 and SOLO-2.

Safety

There is no robust ITC performed on safety between olaparib and niraparib due to a lack of feasibility of comparable AE reporting.

NoMA assessment

The studies vary in the definition of PFS and the assessment interval (see chapter 2.1) making it difficult to conclude the similarity of olaparib and niraparib in the BRCAmut population solely based on PFS. The estimates are, however, highly

uncertain due to broad confidence intervals driven by low patients at risk and event numbers [redacted] follow-up time. The comparison of OS could not be conducted due to data immaturity.

ITC including secondary endpoints

To complement the PFS analysis, NoMA has conducted an ITC for time to first subsequent therapy or death (TFST) and time from randomisation to start of second subsequent therapy (TSST) as the endpoints were reported in NOVA and Study 19 for the BRCAmut populations (Table 9). The calculated HR should be interpreted with caution as the proportional hazard has not been assessed due to unavailability of survival curves. Heterogeneity in patient populations is present between the trials. The NOVA data are relatively immature. However, although the differences in PFS assessment still indirectly affect TFST and TSST, this impact is diluted especially in terms of the TSST endpoint. Both niraparib and olaparib significantly extend TFST and TSST when compared to placebo. There is no statistically significant difference between the PARP inhibitors.

Table 9 ITC of common secondary endpoints for niraparib (NOVA) and olaparib 400mg (Study 19) in the gBRCAmut population.

Analysis	Events:Patients	Median time (months)(95% CI)	HR vs placebo	95% CI	ITC*: HR niraparib vs olaparib	95% CI
Time to first subsequent therapy or death (TFST)**	Olaparib: 46/74 (62.2%)	15.6	0.33	0.22, 0.50	**0.93**	**0.52, 1.7** **(p=0.836)**
	Placebo: 54/62 (87.1%)	6.2				
	Niraparib: 58/138 (42%)	21.0 (17.5, NE)	0.31	0.205, 0.481		
	Placebo: 43/65 (66.2%)	8.4 (6.6, 10.6)				
Time from randomisation to start of second subsequent therapy (TSST)**	Olaparib: 42/74 (56.8%)	23.8	0.44	0.29, 0.67	**1.09**	**0.53, 2.21 (p=0.810)**
	Placebo: 49/62 (79.0%)	15.2				
***	Niraparib: 33/138 (23.9%)	25.8 (22.4,NE)	0.48	0.272,0.851		
***	Placebo: 23/65 (35.4%)	20.5 (16.0,NE)				

**Frequentist ITC, Stata 15.1*

*** definitions appear to be aligned between NOVA and Study 19; TFST is defined as the date of randomization to the earlier of the start date of first follow-up anti-cancer treatment (FUACT) or death. TSST is defined as the date of randomization to the earlier of the start date of second FUACT or death.*

**** values sourced from the CSR for NOVA*

The results of an indirect treatment comparison of olaparib 300 mg versus niraparib in gBRCAmut platinum-sensitive relapsed ovarian cancer have previously been published [22]. These results support the conclusion of similarity in terms of PFS (both IRC and Investigator-assessed) and TFST. The validity of the assumption of proportionality of hazards for the time to event endpoints has not been discussed.

Table 10 Indirect treatment comparison of olaparib versus niraparib in gBRCAm platinum-sensitive relapsed ovarian cancer [22].

Outcome (PARP inhibitor vs placebo)	Naïve cross-study comparison		Bayesian ITC (Olaparib vs Niraparib)
	SOLO2 Olaparib 300 mg tablets bid	NOVA Niraparib 300 mg capsules qd	
PFS by Independent Review Committee			
Hazard Ratio (95% CI)	0.25 (0.18, 0.35)	0.27 (0.17, 0.41)	Hazard ratio: **0.93**
Median, months	30.2 vs 5.5	21.0 vs 5.5	95% CI: 0.53, 1.61
PFS by Investigator Assessment			
Hazard Ratio (95% CI)	0.30 (0.22, 0.41)	0.27 (0.18, 0.40)	Hazard ratio: **1.11**
Median, months	19.1 vs 5.5	14.8 vs 5.5	95% CI: 0.67, 1.83
Time to first subsequent therapy			
Hazard Ratio (95% CI)	0.28 (0.21, 0.38)	0.31 (0.21, 0.48)	Hazard ratio: **0.90**
Median, months	27.9 vs 7.1	21.0 vs 8.4	95% CI: 0.54, 1.49

In conclusion, niraparib has not been shown to be more effective than olaparib in terms of PFS in BRCA mutation-positive ovarian cancer. A comparison of OS (potentially more unbiased outcome) could not be conducted due to the immaturity of niraparib data.

4 DISCUSSION

The present assessment is limited to patients with BRCA-mutated platinum-sensitive relapsed ovarian cancer. For patients without BRCA-mutation, a separate assessment will be presented later.

Another PARP inhibitor, olaparib is already approved for treatment of these patients, and the scope of this assessment is limited to considering whether olaparib and niraparib can be considered similar enough to be included in the same tender.

Overall , the submitted clinical efficacy data and different indirect treatment comparisons indicate no clinically relevant efficacy differences between olaparib and niraparib in this patient population. Data on overall survival for niraparib are immature, but given the similar mode of action and similarity of PFS and time to subsequent treatment, there is no reason to assume that there is a difference.

However, the available safety data indicates that more patients will experience severe adverse reactions at the recommended dose of niraparib, when compared to olaparib, but that these reactions can be managed through dose reduction. Based on the feedback from the clinical experts and the expert group for the oncology tender, NoMA considers the differences in safety to be within an acceptable range.

Norwegian Medicines Agency, 03-10-2019

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VEDLEGG 1 KOMMENTARER FRA PRODUSENT (VEDLAGT SEPARAT)

- Vi gjør oppmerksom på at PFS-tallene i tabell 10 fra Hettle et al 2017 er basert på en sensitivitetsanalyse fra SOLO-studien. Investigator-assessed primary endpoint er 19.1 vs 5.5 (mens det I tabell 10 fremkommer 30.2 vs. 5.5)
- ITC omtalt i 3.3.3 er ikke publisert. Denne ble etter vår forståelse utarbeidet på forespørsel fra SLV. Tesaro mente at det ikke var metodologisk riktig med en slik analyse og hadde ikke utarbeidet denne om det ikke var for forespørselen. Den ble ikke utarbeidet for offentlig bruk. Vi ber derfor om at denne unntas offentlighet (markert i gult).