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Niraparib (ovarian cancer) –

Addendum to Commission A19-88[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BRCA	breast cancer associated gene
BRCAmut	BRCA mutation
BRCAwt	BRCA wild type
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
gBRCAmut	germline BRCA mutation
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
non-gBRCAmut	without germline BRCA mutation
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SOC	System Organ Class

1 Background

On 24 February 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-88 (Niraparib – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented results of an adjusted indirect comparison versus olaparib using the common comparator placebo on the basis of randomized controlled trials (RCTs) for the assessment of the added benefit of niraparib as maintenance treatment in 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. For this comparison, the company had included the NOVA study on the niraparib side, and the 2 studies 19 and SOLO2 on the olaparib side. This adjusted indirect comparison was used for the benefit assessment.

In its dossier, the company had presented analyses of the indirect comparison on adverse event (AE) outcomes. For the NOVA study, discrepancies in the event time analyses presented were found between the data on patients at risk and the corresponding Kaplan-Meier curves as well as the median observation periods in the study arms. Therefore, the indirect comparison on these outcomes could not be considered. With its written comments [3,4], the company now presented corrected analyses (event time analyses and Kaplan-Meier curves) of the NOVA study.

The G-BA commissioned IQWiG with the assessment of the analyses on AEs submitted by the company in the commenting procedure under consideration of the information provided in the dossier.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

In its dossier for the assessment of niraparib as maintenance treatment in 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, the company had presented analyses on the basis of an indirect comparison versus olaparib using the common comparator placebo (see Figure 1). This was used for the benefit assessment.

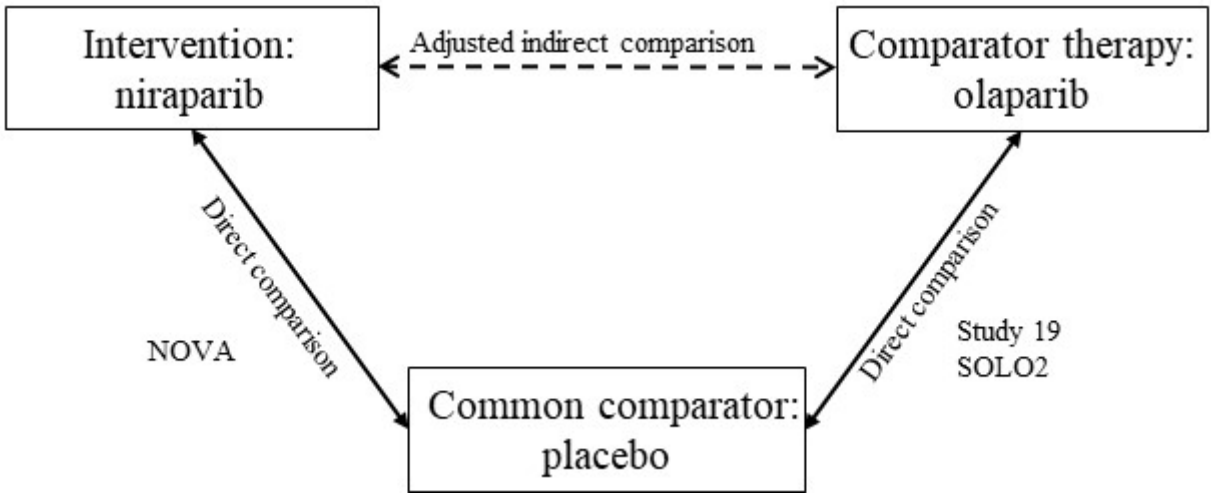

Figure 1: Study pool for the indirect comparison between niraparib and the ACT olaparib

For the niraparib side of the adjusted indirect comparison, the company had also presented analyses on AE outcomes, in particular event time analyses on serious AEs (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) and discontinuation due to AEs. Discrepancies were found between the data on patients at risk over time and the Kaplan-Meier curves as well as the median observation periods in the study arms. Therefore, the indirect comparison on these outcomes could not be considered.

2.1 Analyses subsequently submitted

The company described in its comments [3,4] that the patients at risk were not reflected adequately in the presented Kaplan-Meier curves for safety outcomes. According to the explanations of the company, patients who had no event, e.g. no severe AE (CTCAE grade ≥ 3), were considered "under observation" for this event until the last contact in the study, and censoring in the analysis was as late as this time point. However, observation of AE outcomes was not continued until the end of the study, but only until the end of study medication intake or, in the case of serious events, over a period of 30 days after the end of study medication intake. Thus, in the event time analyses and the corresponding Kaplan-Meier curves of the company, patients who were no longer under observation for the respective outcome were erroneously classified as under observation. With its comments, the company now presented analyses on AE outcomes that correct this error and in which the patients are censored according to the actual end of observation. These analyses are:

- Event time analyses and the corresponding Kaplan-Meier curves of the NOVA study on the overall rate of the outcomes on AEs, severe AEs (CTCAE grade ≥ 3), SAEs, and discontinuations due to AEs of the NOVA study
- Event time analyses and the corresponding Kaplan-Meier curves of the NOVA study for common AEs (≥ 10% in at least one study arm), common severe AEs (CTCAE grade ≥ 3) (≥ 5% in at least one study arm) and common SAEs (≥ 1% in at least one study arm) by System Organ Classes (SOCs) and Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA), and further AE operationalizations presented by the company as AEs of special interest. These also contain analyses on the AEs of special importance for the disease, which were used for the dossier assessment of niraparib (acute myeloid leukaemia, myelodysplastic syndrome and pneumonitis).
- New calculations of the indirect comparison for these outcomes

However, the company did not present any analyses for the total population of the NOVA study, but only separated according to the following subpopulations:

- cohort of the patients with germline breast cancer associated gene mutation [gBRCAmut] and without germline BRCA mutation (non-gBRCAmut) of their ovarian cancer, and
- patients with BRCA mutation (BRCAm) and with BRCA wild type (BRCAwt) of their ovarian cancer

This is incomprehensible insofar as it is clear from the dossier assessment that the assessment was based on analyses of the total population of the NOVA study. No new arguments against a joint consideration have emerged from the written comments of the company. Rather, the company itself described that it accepted this approach in principle. Likewise, the discussion in the oral hearing confirmed that a joint consideration of the populations is meaningful [5].

If necessary, the Institute therefore conducted its own calculations both for a meta-analytical summary of the subpopulations presented by the company and for the respective adjusted indirect comparison. However, due to the lack of analyses for the total population of the NOVA study, it was not possible for the present addendum to make a choice of specific AEs based on the frequencies and differences between the treatment arms. For the chosen AEs with special importance for the disease (acute myeloid leukaemia, myelodysplastic syndrome and pneumonitis), no adjusted indirect comparison was calculated due to the very few events, since no sufficiently large statistically significant effect can result in each case (see Section 2.2). For these reasons, the present addendum only considers the results presented on the overall rates of the AE outcomes.

2.2 Risk of bias

As described in the benefit assessment of niraparib, due to potentially informative censorings and, for Study 19 additionally due to the high risk of bias across outcomes, there was a high risk of bias for the AE outcomes “SAEs” and “severe AEs” (CTCAE grade ≥ 3) of the studies

NOVA, 19 and SOLO2. In all 3 studies, the certainty of results for the outcome "discontinuation due to AEs" was restricted despite a low risk of bias. In addition, there were the described discrepant data between the median observation periods and the patients at risk in the Kaplan-Meier curves of the event time analyses [1]. Since the submitted indirect comparison for the side of niraparib versus placebo included only one study, there was no sufficient certainty of results in the dossier assessment that fulfilled the minimum requirement of the certainty of results for the derivation of a hint in the indirect comparison presented for the outcomes mentioned.

The restrictions of the certainty of results described above also apply to the recalculated analyses. The discrepant data of the analyses were resolved, however. In the present data situation, however, there is sufficient certainty of results for deriving an indication from the indirect comparison only in those cases in which sufficiently large observed effects exist in the indirect comparison so that these cannot be called into question by potential bias alone.

2.3 Results

The following Table 1 shows the results for the overall rates of SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuations due to AEs for the adjusted indirect comparison of niraparib versus olaparib in 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. The corresponding Kaplan-Meier curves of the cohorts of the NOVA study can be found in Appendix A. The Kaplan-Meier curves of the studies 19 and SOLO2 can be found in Appendix A.1 of dossier assessment A18-36 on olaparib [6]. Results on common AEs of the NOVA study are presented in Appendix B. Results on common AEs of the studies 19 and SOLO2 can also be found in dossier assessment A18-36.

The results for the total population of the NOVA study are based on Institute's calculations from a meta-analysis with fixed effects. The results of the adjusted indirect comparison according to Bucher were also calculated by the Institute.

Table 1: Results (SAEs, severe AEs [CTCAE grade ≥ 3], discontinuation due to AEs) – RCT, indirect comparison using common comparators: niraparib vs. olaparib (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Niraparib or olaparib** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Placebo** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Group difference** **HR [95% CI]; p-value**
Side effects					
SAEs					
Niraparib vs. placebo					
NOVA (gBRCAmut cohort)[a]	136	NA [22.8; NA] 42 (30.9)	65	NA [11.0; NA] 7 (10.8)	2.36 [1.04; 5.34]; 0.034
NOVA (cohort: non-gBRCAmut)[a]	231	NA [NA; NA] 68 (29.4)	114	NA [NA; NA] 20 (17.5)	1.69 [1.02; 2.81]; 0.040
Total					1.85 [1.21; 2.85]; 0.005[b]
Olaparib vs. placebo					
Study 19[c]	136	67.9 [ND] 31 (22.8)	128	42.0 [ND] 11 (8.6)	1.61 [0.79; 3.46]; 0.218[d]
SOLO2[e]	195	NA 35 (17.9)	99	NA 8 (8.1)	1.64 [0.79; 3.84]; 0.234[f]
Total					1.62 [0.94; 2.81]; 0.083[b]
Indirect comparison using a common comparator[h]:					
Niraparib vs. olaparib					_[i]
Severe AEs (CTCAE grade ≥ 3)					
Niraparib vs. placebo					
NOVA (gBRCAmut cohort)[a]	136	1.2 [0.8; 2.0] 108 (79.4)	65	NA [11.0; NA] 14 (21.5)	5.82 [3.32; 10.22]; < 0.001
NOVA (non-gBRCAmut cohort)[a]	231	1.6 [1.0; 2.7] 164 (71.0)	114	NA [20.1; NA] 27 (23.7)	4.61 [3.06; 6.96]; < 0.001
Total					5.00 [3.59; 6.97]; < 0.001[b]
Olaparib vs. placebo					
Study 19[c]	136	22.9 [ND] 59 (43.4)	128	NA 28 (21.9)	1.88 [1.20; 3.01]; 0.013[d]
SOLO2[e]	195	NA 72 (36.9)	99	NA 18 (18.2)	1.92 [1.17; 3.33]; 0.012[f]
Total					1.90 [1.34; 2.68]; < 0.001[b, g]
Indirect comparison using a common comparator[h]:					
Niraparib vs. olaparib					2.63 [1.63; 4.25]; < 0.001

Table 1: Results (SAEs, severe AEs [CTCAE grade ≥ 3], discontinuation due to AEs) – RCT, indirect comparison using common comparators: niraparib vs. olaparib (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Niraparib or olaparib** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Placebo** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Group difference** **HR [95% CI]; p-value**
Discontinuation due to AEs					
Niraparib vs. placebo					
NOVA (gBRCAmut cohort)[a]	136	NA [23.6; NA] 18 (13.2)	65	NA [NA; NA] 1 (1.5)	6.00 [0.79; 45.54]; 0.049
NOVA (non-gBRCAmut cohort)[a]	231	NA [NA; NA] 36 (15.6)	114	NA [NA; NA] 3 (2.6)	5.99 [1.84; 19.55]; < 0.001
Total					5.99 [2.16; 16.64]; < 0.001[b]
Olaparib vs. placebo					
Study 19[c]	136	NA 8 (5.9)	128	NA 2 (1.6)	1.96 [0.44; 13.68]; 0.528[d]
SOLO2[e]	195	NA 21 (10.8)	99	NA 2 (2.0)	3.71 [1.07; 23.40]; 0.063[f]
Total					2.79 [0.89; 8.80]; 0.080[b]
Indirect comparison using a common comparator[h]:					
Niraparib vs. olaparib					_[i]

a. Results of the first data cut-off from 30 May 2016 (primary analysis) based on the corrected analyses on AE outcomes of this data cut-off presented with the company's comments.
b. Institute's calculation from meta-analysis with fixed effect (inverse variance method).
c. Results of the last data cut-off on 9 May 2016 (final analysis).
d. Cox proportional hazards model with profile likelihood method for estimation of the 95% CI; p-value: log-rank test; both analyses by the company adjusted for Jewish family origin (yes/no), time to progression after the penultimate platinum-containing chemotherapy (> 6–12 months vs. > 12 months), and objective response to the last platinum-containing chemotherapy before inclusion in the study (complete vs. partial).
e. Results of the first data cut-off on 19 September 2016 (primary analysis).
f. Cox proportional hazards model with profile likelihood method for estimation of the 95% CI; p-value: log-rank test; both analyses adjusted for objective response to the last platinum-containing chemotherapy before inclusion in the study (complete vs. partial) and time to progression after the penultimate platinum-containing chemotherapy (> 6–12 months vs. > 12 months).
g. Inverse effect estimation for the estimation of the size of the effect: HR [95% CI]: 0.38 [0.24; 0.61].
h. Effect, CI and p-value: Institute's calculation (adjusted indirect comparison according to Bucher [7]).
i. The results are not interpretable due to an insufficient certainty of results for this data constellation.

AE: adverse event; BRCA: breast cancer associated gene; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; gBRCAmut: germline BRCA mutation; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; ND: no data; non-gBRCAmut: without germline BRCA mutation; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Severe adverse events (CTCAE grade ≥ 3)

For the outcome "severe AEs" (CTCAE grade ≥ 3), only the result from a study with outcome-specific high risk of bias was available on the niraparib side of the adjusted indirect comparison. The prerequisites for the derivation of conclusions on the added benefit from an adjusted indirect comparison were therefore initially not fulfilled. However, a large effect for this outcome was shown both in the comparison of niraparib with placebo in the NOVA study and in the adjusted indirect comparison with olaparib using the common comparator placebo. It is not assumed in the present data situation that the statistically significant effect in the indirect comparison to the disadvantage of niraparib is completely called into question by potential bias. Hence, despite the high outcome-specific risk of bias, the qualitative certainty of results is sufficiently high in the NOVA study to be able to interpret the present effect and derive a hint of greater or lesser harm from niraparib.

Overall, there is therefore a hint of greater harm from niraparib in comparison with olaparib. Due to the uncertainties, the extent of the effect cannot be quantified, however.

Serious adverse events and discontinuation due to adverse events

As for the outcome "severe AEs" (CTCAE grade ≥ 3), there are only results from a study with outcome-specific high risk of bias for the outcomes "SAEs" and "discontinuation due to AEs" on the niraparib side of the indirect comparison. The prerequisites for drawing conclusions on the added benefit from an adjusted indirect comparison were therefore initially not fulfilled also for these outcomes. In addition, a statistically significant difference between niraparib and olaparib was neither shown for the outcome "SAEs" nor for the outcome "discontinuation due to AEs" in the adjusted indirect comparison (HR [95% confidence interval (CI)]; SAEs: 1.14 [0.57; 2.30]; discontinuation due to AEs: 2.15 [0.46; 9.97]). The results are not interpretable due to an insufficient certainty of results for this data constellation. In each case, this resulted in no hint of greater or lesser harm of niraparib in comparison with olaparib; an added benefit is therefore not proven for either outcome.

2.4 Overall conclusion on added benefit

Table 2 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 2: Positive and negative effects from the assessment of niraparib in comparison with olaparib

Positive effects	**Negative effects**
—	Serious/severe side effects Overall rates of severe AEs (CTCAE grade ≥ 3): hint of greater harm – extent: "non-quantifiable"
There are no usable data for the outcomes on morbidity, health-related quality of life and further AE outcomes.	

Overall, usable data for the indirect comparison are available for 2 outcomes (overall survival and severe AEs [CTCAE grade ≥ 3]). There was no statistically significant difference between niraparib and olaparib for the outcome "overall survival" (HR [95% CI]: 0.99 [0.61; 1.60]) [1]. Thus, only a negative effect of niraparib in severe AEs (CTCAE grade ≥ 3) remains, resulting in a hint of non-quantifiable greater harm of niraparib in comparison with olaparib.

In summary, there is therefore a hint of lesser benefit of niraparib versus olaparib for 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.

2.5 Summary

The data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of niraparib from dossier assessment A19-88 for the assessment of the added benefit of niraparib as maintenance treatment in 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.

The following Table 3 shows the result of the benefit assessment of niraparib under consideration of dossier assessment A19-88 and the present addendum.

Table 3: Niraparib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with platinum-sensitive relapsed high-grade[b] serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy and require maintenance treatment	**Olaparib** or watchful waiting	**Hint of lesser benefit**
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. Designation taken from the English SPC. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics		

The G-BA decides on the added benefit.

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The reference list contains citations provided by the company in which bibliographical information may be missing.

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Appendix A – Kaplan-Meier curves on adverse event outcomes of the NOVA study

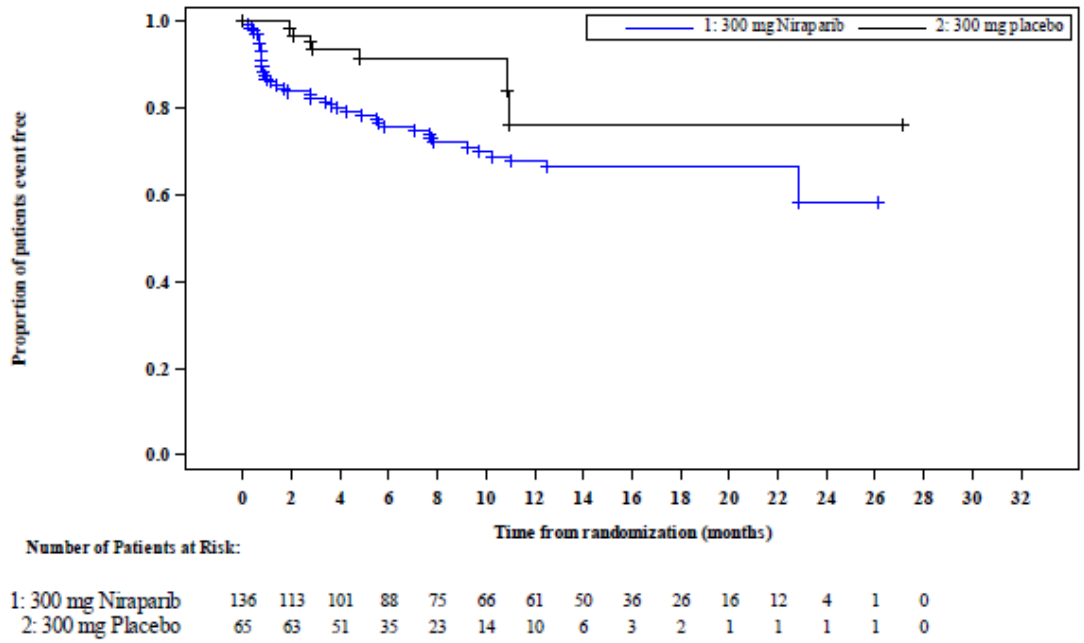

Figure 2: Kaplan-Meier curve on SAEs – RCT, direct comparison: niraparib vs. placebo, study NOVA, gBRCAmut cohort

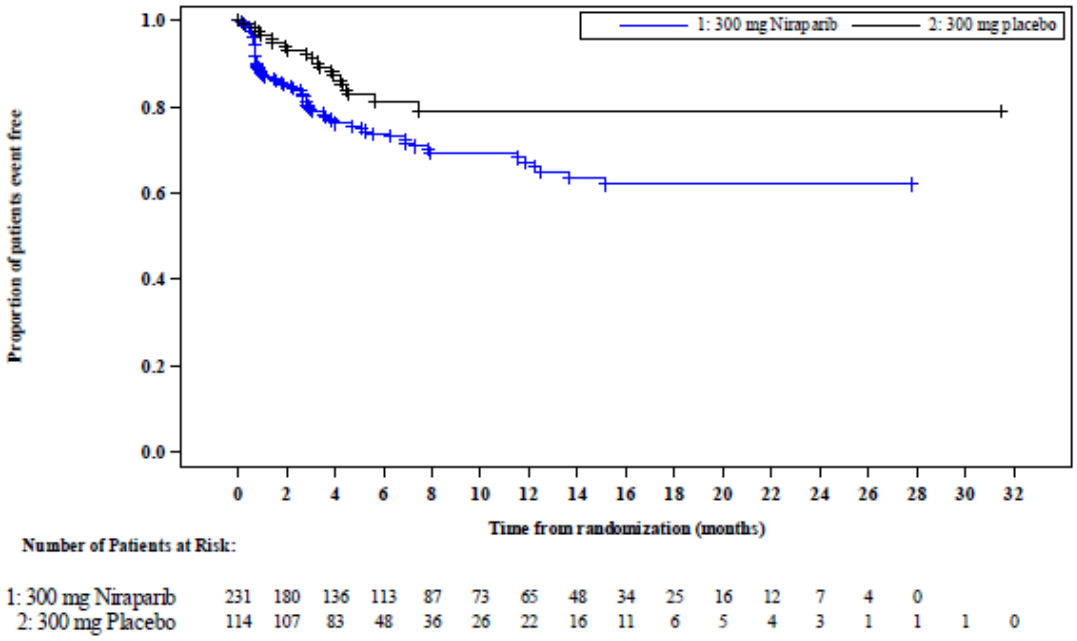

Figure 3: Kaplan-Meier curve on SAEs – RCT, direct comparison: niraparib vs. placebo, study NOVA, non-gBRCAmut cohort

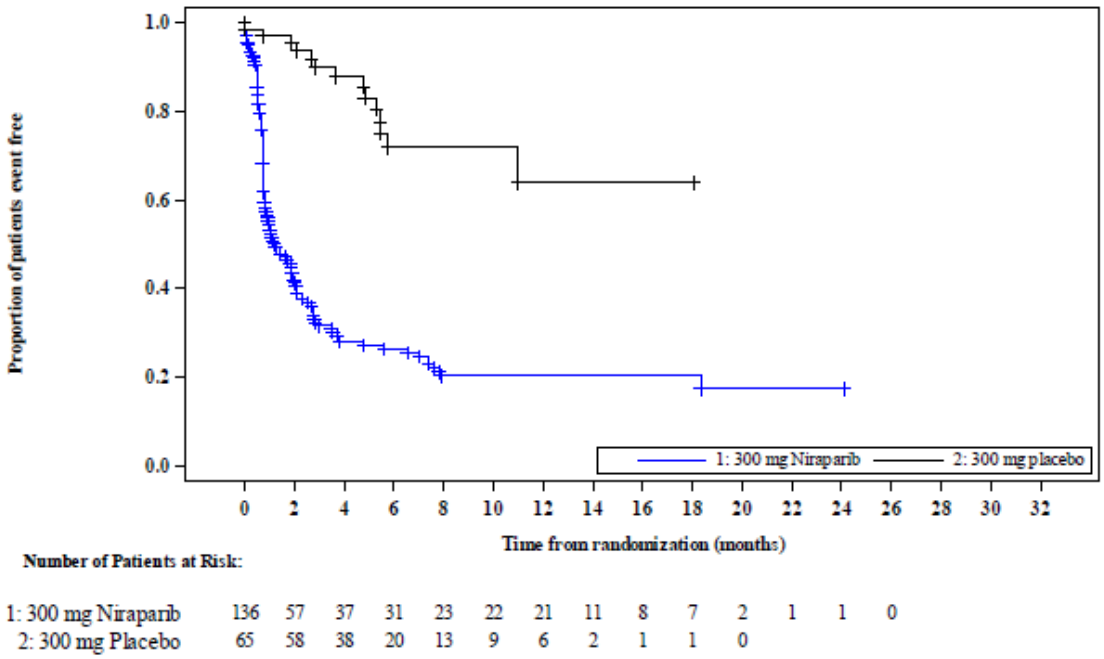

Figure 4: Kaplan-Meier curve on severe AEs (CTCAE grade 3 and 4) – RCT, direct comparison: niraparib vs. placebo, study NOVA, gBRCAmut cohort

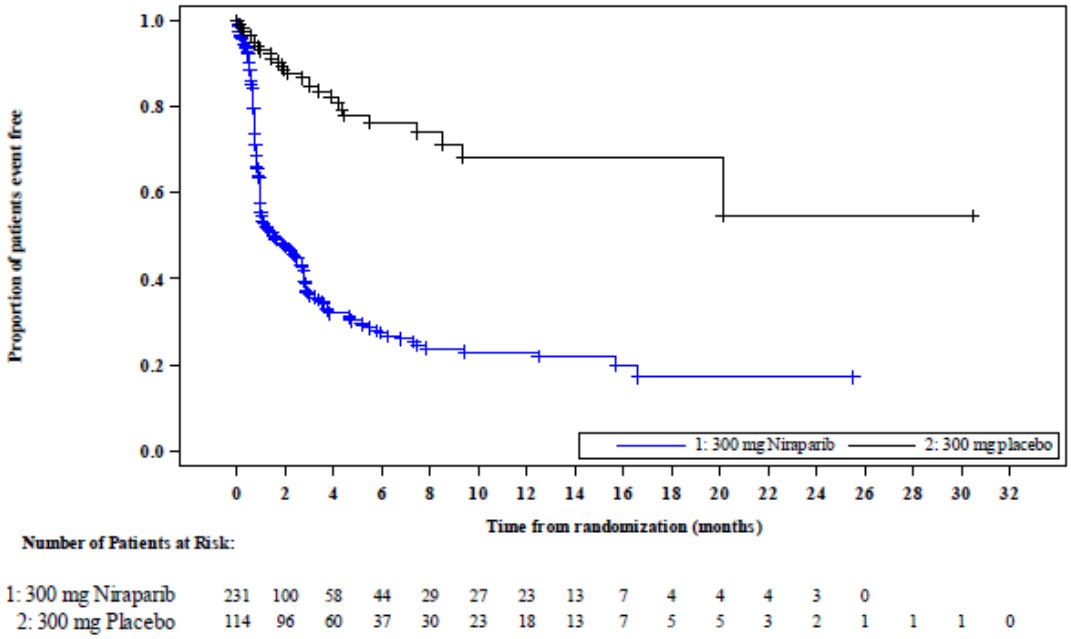

Figure 5: Kaplan-Meier curve on severe AEs (CTCAE grade 3 and 4) – RCT, direct comparison: niraparib vs. placebo, study NOVA, non-gBRCAmut cohort

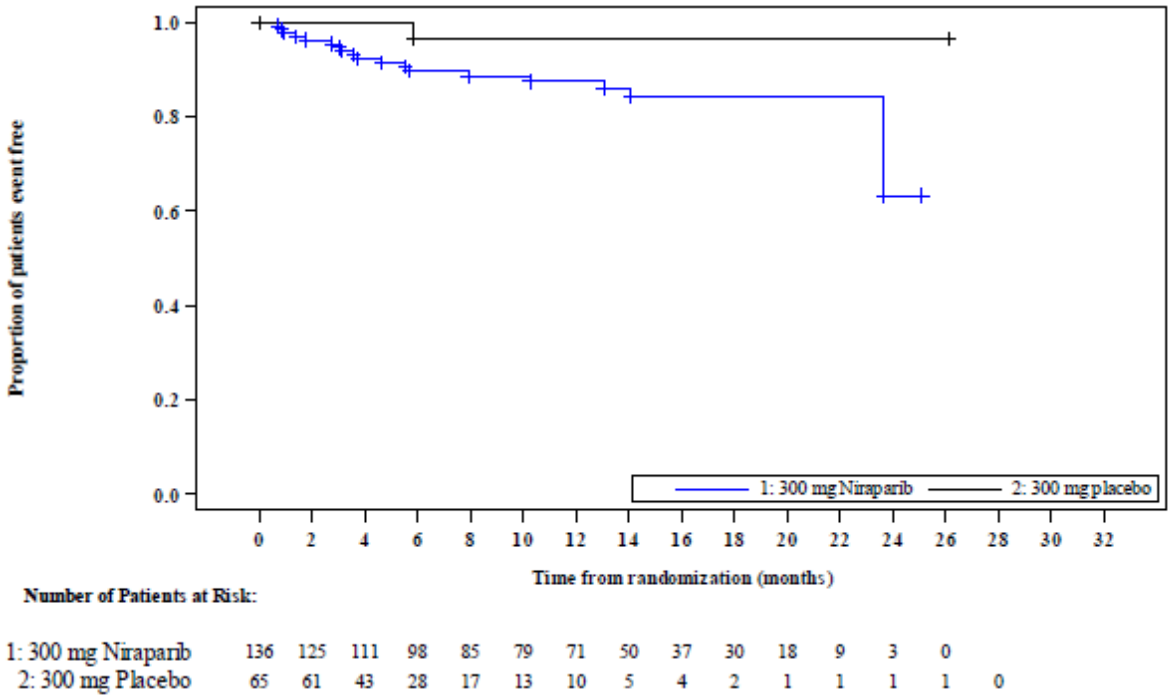

Figure 6: Kaplan-Meier curve on discontinuation due to AEs – RCT, direct comparison: niraparib vs. placebo, study NOVA, gBRCAmut cohort

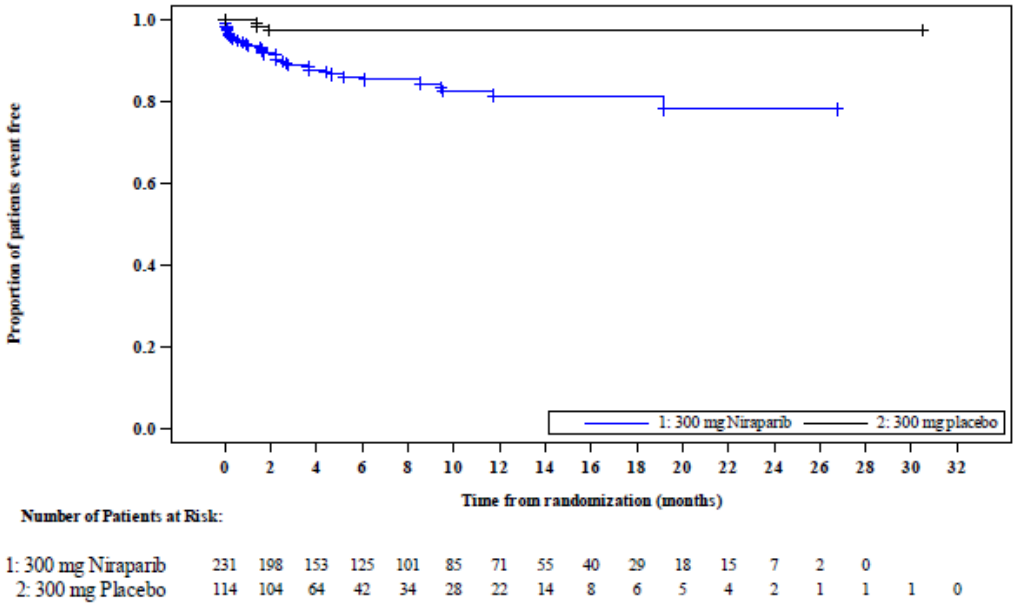

Figure 7: Kaplan-Meier curve on discontinuation due to AEs – RCT, direct comparison: niraparib vs. placebo, study NOVA, non-gBRCAmut cohort

Appendix B – Results on side effects of the NOVA study (separated by cohorts)

Table 4: Common AEs[a] – RCT, direct comparison: niraparib vs. placebo, gBRCAmut cohort (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	Niraparib N = 136	Placebo N = 65
NOVA		
Overall AE rate	136 (100)	61 (93.8)
Gastrointestinal disorders	127 (93.4)	48 (73.8)
Nausea	105 (77.2)	22 (33.8)
Vomiting	54 (39.7)	10 (15.4)
Constipation	52 (38.2)	12 (18.5)
Diarrhoea	33 (24.3)	15 (23.1)
Abdominal pain	28 (20.6)	15 (23.1)
Dyspepsia	23 (16.9)	8 (12.3)
Dry mouth	18 (13.2)	2 (3.1)
Abdominal pain upper	14 (10.3)	7 (10.8)
Blood and lymphatic system disorders	104 (76.5)	11 (16.9)
Thrombocytopenia	74 (54.4)	2 (3.1)
Anaemia	70 (51.5)	5 (7.7)
Neutropenia	24 (17.6)	3 (4.6)
Leukopenia	11 (8.1)	4 (6.2)
General disorders and administration site conditions	101 (74.3)	31 (47.7)
Fatigue	64 (47.1)	19 (29.2)
Asthenia	24 (17.6)	3 (4.6)
Oedema peripheral	11 (8.1)	2 (3.1)
Pyrexia	11 (8.1)	3 (4.6)
Musculoskeletal and connective tissue disorders	63 (46.3)	27 (41.5)
Back pain	22 (16.2)	7 (10.8)
Arthralgia	21 (15.4)	8 (12.3)
Myalgia	13 (9.6)	6 (9.2)
Pain in extremity	12 (8.8)	3 (4.6)
Muscle spasms	11 (8.1)	1 (1.5)
Investigations	64 (47.1)	15 (23.1)
Platelet count decreased	31 (22.8)	1 (1.5)
Neutrophil count decreased	21 (15.4)	3 (4.6)
White blood cell count decreased	17 (12.5)	5 (7.7)
Increased blood creatinine	10 (7.4)	3 (4.6)

Table 4: Common AEs[a] – RCT, direct comparison: niraparib vs. placebo, gBRCAmut cohort (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Niraparib** **N = 136**	**Placebo** **N = 65**
Nervous system disorders	84 (61.8)	17 (26.2)
Headache	47 (34.6)	5 (7.7)
Dizziness	24 (17.6)	6 (9.2)
Dysgeusia	18 (13.2)	1 (1.5)
Peripheral neuropathy	11 (8.1)	4 (6.2)
Infections and infestations	64 (47.1)	25 (38.5)
Nasopharyngitis	18 (13.2)	3 (4.6)
Urinary tract infection	15 (11.0)	6 (9.2)
Upper respiratory tract infection	12 (8.8)	3 (4.6)
Skin and subcutaneous tissue disorders	62 (45.6)	13 (20.0)
Rash	13 (9.6)	1 (1.5)
Alopecia	12 (8.8)	4 (6.2)
Pruritus	10 (7.4)	3 (4.6)
Metabolism and nutrition disorders	52 (38.2)	19 (29.2)
Decreased appetite	30 (22.1)	9 (13.8)
Hypomagnesaemia	14 (10.3)	8 (12.3)
Respiratory, thoracic and mediastinal disorders	53 (39.0)	7 (10.8)
Dyspnoea	23 (16.9)	3 (4.6)
Cough	22 (16.2)	1 (1.5)
Psychiatric disorders	40 (29.4)	11 (16.9)
Insomnia	24 (17.6)	4 (6.2)
Anxiety	13 (9.6)	7 (10.8)
Vascular disorders	43 (31.6)	11 (16.9)
Hypertension	29 (21.3)	5 (7.7)
Injury, poisoning and procedural complications	25 (18.4)	3 (4.6)
Cardiac disorders	25 (18.4)	1 (1.5)
Palpitations	12 (8.8)	0 (0)
Tachycardia	10 (7.4)	1 (1.5)
Renal and urinary disorders	15 (11.0)	2 (3.1)
Reproductive system and breast disorders	12 (8.8)	3 (4.6)
Eye disorders	12 (8.8)	1 (1.5)
Ear and labyrinth disorders	11 (8.1)	4 (6.2)

a. Events that occurred in ≥ 10 patients in the intervention arm, in ≥ 10% patients in the comparator arm.
b. MedDRA version 18.0.

AE: adverse event; BRCA: breast cancer associated gene; gBRCAmut: germline BRCA mutation; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 5: Common AEs[a] – RCT, direct comparison: niraparib vs. placebo, non-gBRCAmut cohort (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Niraparib** **N = 231**	**Placebo** **N = 114**
NOVA		
Overall AE rate	231 (100.0)	110 (96.5)
Gastrointestinal disorders	209 (90.5)	81 (71.1)
Nausea	165 (71.4)	41 (36.0)
Constipation	94 (40.7)	24 (21.1)
Vomiting	72 (31.2)	19 (16.7)
Abdominal pain	55 (23.8)	38 (33.3)
Diarrhoea	37 (16.0)	22 (19.3)
Abdominal distension	24 (10.4)	18 (15.8)
Abdominal pain upper	22 (9.5)	8 (7.0)
Dyspepsia	19 (8.2)	9 (7.9)
Gastrooesophageal reflux disease	19 (8.2)	4 (3.5)
Dry mouth	16 (6.9)	5 (4.4)
General disorders and administration site conditions	155 (67.1)	65 (57.0)
Fatigue	104 (45.0)	39 (34.2)
Asthenia	34 (14.7)	13 (11.4)
Mucosal inflammation	19 (8.2)	2 (1.8)
Pyrexia	14 (6.1)	7 (6.1)
Oedema peripheral	13 (5.6)	6 (5.3)
Blood and lymphatic system disorders	158 (68.4)	14 (12.3)
Anaemia	108 (46.8)	7 (6.1)
Thrombocytopenia	95 (41.1)	4 (3.5)
Neutropenia	42 (18.2)	3 (2.6)
Leukopenia	16 (6.9)	5 (4.4)
Investigations	105 (45.5)	23 (20.2)
Platelet count decreased	43 (18.6)	3 (2.6)
Neutrophil count decreased	28 (12.1)	2 (1.8)
White blood cell count decreased	19 (8.2)	0 (0)
Gamma-glutamyltransferase increased	18 (7.8)	5 (4.4)
Alanine aminotransferase increased	14 (6.1)	2 (1.8)
Aspartate aminotransferase increased	14 (6.1)	2 (1.8)
Blood alkaline phosphatase increased	11 (4.8)	1 (0.9)
Increased blood creatinine	10 (4.3)	3 (2.6)

Table 5: Common AEs[a] – RCT, direct comparison: niraparib vs. placebo, non-gBRCAmut cohort (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Niraparib** **N = 231**	**Placebo** **N = 114**
Musculoskeletal and connective tissue disorders	96 (41.6)	53 (46.5)
Back pain	27 (11.7)	14 (12.3)
Arthralgia	22 (9.5)	14 (12.3)
Myalgia	17 (7.4)	12 (10.5)
Pain in extremity	13 (5.6)	10 (8.8)
Muscle spasms	12 (5.2)	5 (4.4)
Musculoskeletal pain	12 (5.2)	3 (2.6)
Infections and infestations	107 (46.3)	41 (36.0)
Nasopharyngitis	23 (10.0)	10 (8.8)
Urinary tract infection	23 (10.0)	5 (4.4)
Bronchitis	14 (6.1)	2 (1.8)
Sinusitis	10 (4.3)	2 (1.8)
Nervous system disorders	114 (49.4)	37 (32.5)
Headache	48 (20.8)	12 (10.5)
Dizziness	37 (16.0)	7 (6.1)
Dysgeusia	19 (8.2)	6 (5.3)
Peripheral neuropathy	14 (6.1)	8 (7.0)
Respiratory, thoracic and mediastinal disorders	99 (42.9)	29 (25.4)
Dyspnoea	48 (20.8)	12 (10.5)
Cough	33 (14.3)	7 (6.1)
Oropharyngeal pain	13 (5.6)	3 (2.6)
Epistaxis	10 (4.3)	4 (3.5)
Skin and subcutaneous tissue disorders	98 (42.4)	32 (28.1)
Photosensitivity reaction	23 (10.0)	1 (0.9)
Alopecia	16 (6.9)	8 (7.0)
Dry skin	16 (6.9)	4 (3.5)
Rash	11 (4.8)	5 (4.4)
Petechiae	10 (4.3)	0 (0)
Metabolism and nutrition disorders	97 (42.0)	31 (27.2)
Decreased appetite	63 (27.3)	17 (14.9)
Hypomagnesaemia	13 (5.6)	6 (5.3)
Hypokalaemia	12 (5.2)	4 (3.5)
Psychiatric disorders	91 (39.4)	19 (16.7)
Insomnia	65 (28.1)	9 (7.9)
Anxiety	17 (7.4)	4 (3.5)

Table 5: Common AEs[a] – RCT, direct comparison: niraparib vs. placebo, non-gBRCAmut cohort (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Niraparib** **N = 231**	**Placebo** **N = 114**
Vascular disorders	73 (31.6)	12 (10.5)
Hypertension	42 (18.2)	3 (2.6)
Hot flush	23 (10.0)	6 (5.3)
Cardiac disorders	48 (20.8)	6 (5.3)
Palpitations	26 (11.3)	3 (2.6)
Tachycardia	14 (6.1)	1 (0.9)
Reproductive system and breast disorders	20 (8.7)	11 (9.6)
Injury, poisoning and procedural complications	20 (8.7)	6 (5.3)
Renal and urinary disorders	17 (7.4)	6 (5.3)
Eye disorders	16 (6.9)	7 (6.1)
Ear and labyrinth disorders	13 (5.6)	3 (2.6)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 18.0.

AE: adverse event; BRCA: breast cancer associated gene; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; non-gBRCAmut: without germline BRCA mutation; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 6: Common SAEs[a] – RCT, direct comparison: niraparib vs. placebo, gBRCAmut cohort

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Niraparib** **N = 136**	**Placebo** **N = 65**
NOVA		
Overall rate of SAEs	42 (30.9)	7 (10.8)
Blood and lymphatic system disorders	22 (16.2)	0 (0)
Thrombocytopenia	18 (13.2)	0 (0)
Gastrointestinal disorders	10 (7.4)	2 (3.1)

a. Events that occurred in ≥ 5% patients in at least one study arm.
b. MedDRA version 18.0.

BRCA: breast cancer associated gene; gBRCAmut: germline BRCA mutation; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 7: Common SAEs[a] – RCT, direct comparison: niraparib vs. placebo, non-gBRCAmut cohort

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Niraparib** **N = 231**	**Placebo** **N = 114**
NOVA		
Overall rate of SAEs	68 (29.4)	20 (17.5)
Blood and lymphatic system disorders	31 (13.4)	0 (0)
Thrombocytopenia	22 (9.5)	0 (0)
Gastrointestinal disorders	12 (5.2)	12 (10.5)

a. Events that occurred in ≥ 5% patients in at least one study arm.
b. MedDRA version 18.0.

BRCA: breast cancer associated gene; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; non-gBRCAmut: without germline BRCA mutation; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event, SOC: System Organ Class; vs.: versus

Table 8: Common severe AEs (CTCAE grade ≥ 3)[a] – RCT, direct comparison: niraparib vs. placebo, gBRCAmut cohort

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Niraparib** **N = 136**	**Placebo** **N = 65**
NOVA		
Overall rate of severe AEs (CTCAE grade ≥ 3)	108 (79.4)	14 (21.5)
Blood and lymphatic system disorders	78 (57.4)	1 (1.5)
Anaemia	45 (33.1)	0 (0)
Thrombocytopenia	42 (30.9)	1 (1.5)
Neutropenia	17 (12.5)	1 (1.5)
Investigations	30 (22.1)	2 (3.1)
Neutrophil count decreased	13 (9.6)	1 (1.5)
Platelet count decreased	11 (8.1)	0 (0)
Gastrointestinal disorders	16 (11.8)	4 (6.2)
Nausea	7 (5.1)	2 (3.1)
Vascular disorders	14 (10.3)	3 (4.6)
Hypertension	11 (8.1)	3 (4.6)
General disorders and administration site conditions	12 (8.8)	2 (3.1)
Fatigue	7 (5.1)	0 (0)
Metabolism and nutrition disorders	7 (5.1)	1 (1.5)

a. Events that occurred in ≥ 5% patients in at least one study arm.
b. MedDRA version 18.0.

AE: adverse event; BRCA: breast cancer associated gene; CTCAE: Common Terminology Criteria for Adverse Events; gBRCAmut: germline BRCA mutation; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 9: Common severe AEs (CTCAE grade ≥ 3)[a] – RCT, direct comparison: niraparib vs. placebo, non-gBRCAmut cohort

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Niraparib** **N = 231**	**Placebo** **N = 114**
NOVA		
Overall rate of severe AEs (CTCAE grade ≥ 3)	164 (71.0)	27 (23.7)
Blood and lymphatic system disorders	107 (46.3)	1 (0.9)
Thrombocytopenia	62 (26.8)	0 (0)
Anaemia	46 (19.9)	0 (0)
Neutropenia	24 (10.4)	0 (0)
Investigations	52 (22.5)	7 (6.1)
Neutrophil count decreased	19 (8.2)	1 (0.9)
Platelet count decreased	16 (6.9)	0 (0)
Gastrointestinal disorders	15 (6.5)	12 (10.5)
Vascular disorders	25 (10.8)	1 (0.9)
Hypertension	19 (8.2)	1 (0.9)
General disorders and administration site conditions	22 (9.5)	1 (0.9)
Fatigue	14 (6.1)	0 (0)
Metabolism and nutrition disorders	8 (3.5)	6 (5.3)

a. Events that occurred in ≥ 5% patients in at least one study arm.
b. MedDRA version 18.0.

AE: adverse event; BRCA: breast cancer associated gene; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; non-gBRCAmut: without germline BRCA mutation; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 10: Discontinuation due to AEs – RCT, direct comparison: niraparib vs. placebo, gBRCAmut cohort

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Niraparib** **N = 136**	**Placebo** **N = 65**
NOVA		
Overall rate of discontinuations due to AEs	18 (13.2)	1 (1.5)
Blood and lymphatic system disorders	9 (6.6)	1 (1.5)
Thrombocytopenia	4 (2.9)	1 (1.5)
Anaemia	3 (2.2)	0 (0)
Neutropenia	1 (0.7)	0 (0)
Pancytopenia	1 (0.7)	0 (0)
Investigations	5 (3.7)	0 (0)
Neutrophil count decreased	4 (2.9)	0 (0)
Platelet count decreased	1 (0.7)	0 (0)
Gastrointestinal disorders	1 (0.7)	0 (0)
Intestinal obstruction	1 (0.7)	0 (0)
General disorders and administration site conditions	1 (0.7)	0 (0)
Fatigue	1 (0.7)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.7)	0 (0)
Myelodysplastic syndrome	1 (0.7)	0 (0)
Vascular disorders	1 (0.7)	0 (0)
Hypertensive crisis	1 (0.7)	0 (0)

a. MedDRA version 18.0.

AE: adverse event; BRCA: breast cancer associated gene; gBRCAmut: germline BRCA mutation; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 11: Discontinuation due to AEs – RCT, direct comparison: niraparib vs. placebo, non-gBRCAmut cohort (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Niraparib** **N = 231**	**Placebo** **N = 114**
NOVA		
Overall rate of discontinuations due to AEs	36 (15.6)	3 (2.6)
General disorders and administration site conditions	11 (4.8)	0 (0)
Fatigue	9 (3.9)	0 (0)
Asthenia	2 (0.9)	0 (0)
Pain	1 (0.4)	0 (0)
Gastrointestinal disorders	8 (3.5)	1 (0.9)
Nausea	6 (2.6)	0 (0)
Vomiting	3 (1.3)	0 (0)
Constipation	1 (0.4)	0 (0)
Small intestinal obstruction	0 (0)	1 (0.9)
Blood and lymphatic system disorders	7 (3.0)	0 (0)
Thrombocytopenia	3 (1.3)	0 (0)
Anaemia	2 (0.9)	0 (0)
Neutropenia	2 (0.9)	0 (0)
Investigations	6 (2.6)	0 (0)
Platelet count decreased	4 (1.7)	0 (0)
Gamma-glutamyltransferase increased	1 (0.4)	0 (0)
Lymph node palpable	1 (0.4)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.9)	2 (1.8)
Myelodysplastic syndrome	1 (0.4)	0 (0)
Undifferentiated sarcoma	1 (0.4)	0 (0)
Breast cancer	0	1 (0.9)
Metastases to central nervous system	0	1 (0.9)
Nervous system disorders	4 (1.7)	0 (0)
Dizziness	2 (0.9)	0 (0)
Headache	2 (0.9)	0 (0)
Metabolism and nutrition disorders	3 (1.3)	0 (0)
Decreased appetite	3 (1.3)	0 (0)
Hepatobiliary disorders	2 (0.9)	0 (0)
Cholestasis	1 (0.4)	0 (0)
Hepatic failure	1 (0.4)	0 (0)
Musculoskeletal and connective tissue disorders	2 (0.9)	0 (0)
Myalgia	1 (0.4)	0 (0)
Neck pain	1 (0.4)	0 (0)

Table 11: Discontinuation due to AEs – RCT, direct comparison: niraparib vs. placebo, non-gBRCAmut cohort (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Niraparib** **N = 231**	**Placebo** **N = 114**
Psychiatric disorders	2 (0.9)	0 (0)
Hallucination	1 (0.4)	0 (0)
Insomnia	1 (0.4)	0 (0)
Respiratory, thoracic and mediastinal disorders	2 (0.9)	0 (0)
Dyspnoea	1 (0.4)	0 (0)
Pleural effusion	1 (0.4)	0 (0)
Cardiac disorders	1 (0.4)	0 (0)
Palpitations	1 (0.4)	0 (0)
Skin and subcutaneous tissue disorders	1 (0.4)	0 (0)
Hyperhidrosis	1 (0.4)	0 (0)

a. MedDRA version 18.0.

AE: adverse event; BRCA: breast cancer associated gene; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; non-gBRCAmut: without germline BRCA mutation; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus