Non-Interventional study (NIS) protocol

Ch**a**racteristics **r**elated to Assessments of disease, patient and treatment ass**o**ciated with **l**ong-term surv**i**val in ovaria**n** cancer patients (CAROLIN)- Intergroup study NOGGO / A-AGO

Sponsor:
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Version: 2.0

The study will be conducted as described herein and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements including but not limited to Institutional Review Board/Ethics Committee (IRB/EC) approval.

Confidentiality Statement

LIST OF STUDY CONTACTS

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SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: Characteristics related to Assessments of disease, patient and treatment related characteristics associated with long-term survival in ovarian cancer patients (CAROLIN)

This observational plan was subjected to critical review and has been approved by the Sponsor. The information contained herein is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice (GCP).

Sponsor Signature **Date**

INVESTIGATOR SIGNATURE PAGE

Declaration of the investigator

Title: Characteristics related to Assessments of disease, patient and treatment related characteristics associated with long-term survival in ovarian cancer patients (CAROLIN)
I have read this study in its entirety, including all appendices. By signing this study, I agree to conduct the study in accordance with the plan described herein, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB). I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study and will receive all instructions necessary to perform the study as described herein.

Investigator

Investigator Signature	**Date**

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LIST OF ABBREVIATIONS AND DEFINITIONS

Table 1: List of Abbreviations

Abbreviation	Definition
ADP	adenosine diphosphate
ADR	adverse drug reaction
AE	adverse event
AESI	adverse even of special interest
AML	acute myeloid leukemia
AUC	area under the curve
BER	base excision repair
BRCA	breast cancer gene
CA-125	cancer antigen 125
CAPAN-1	Human Pancreatic Adenocarcinoma Cell Line
CBC	complete blood count
CFI	Chemotherapy free interval
CL	oral clearance
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CUP	Compassionate Use Program
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DDR	DNA damage repair
DSB	double strand breaks
e	electronic
EC	Ethical Committee
eCRF	electronic case report form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
e.g.	for example
EMA	European Medicines Agency
EOT	end of treatment
EQ-5D	standardized instrument for measuring generic health status
FACIT	Functional Assessment of Chronic Illness Therapy
FACT	Functional Assessment of Cancer Therapy
FDA	Federal Drug Administration

Abbreviation	Definition
FE	food effect
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
FLIE	Functional Living Index-Emesis
FPI	First patient in
gBRCA	germline breast cancer gene
GCP	Good Clinical Practice
GCSF	granulocyte-colony stimulating factor
GBM	glioblastoma multiforme
CTCAE	Common Terminology Criteria for Adverse Events
hCG	human chorionic gonadotropin
HR	homologous recombination
HRD	homologous recombination deficiency
IB	investigators brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	International Ethic Committee
irAEIs	immune-related adverse events of interest
IRB	Institutional Review Boards
IUD	intrauterine device
LLN	lower limit of normal
LPLV	Last patient last visit
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHEJ	non-homologous end joining
NIS	non-interventional study
NOGGO	North-Eastern German Society of Gynecological Oncology
OD	once daily
ORR	overall response rate
OS	overall survival
PARP	Poly-(ADP-ribose) polymerase
PFI	platinum free interval
PFS	progression-free survival
P-gp	P-glycoprotein
PI	Principal Investigator

Abbreviation	Definition
PIC	patients informed consent
PK	pharmacokinetics
PR	partial response
PRO	patient reported outcomes
PS	performance status
OC	ovarian cancer
QD	once a day
QoL	quality of life
QTc	corrected QT interval
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SDV	source data verification
SPM	second primary malignancy
TEAS	treatment-emergent adverse events
TFI	therapy free interval
TFST	time to first subsequent therapy
ULN	upper limit of normal
VAS	visual analogue scales
WBDC	Web-based Data Capture

1. SYNOPSIS

Title	Characteristics related to Assessments of disease, patient and treatment associated with long-term survival in ovarian cancer patients (CAROLIN)
Coordinating investigator in Germany	[redacted]
Coordinating investigator in Austria	[redacted]
Sponsor	NOGGO e.V.
Financing	[redacted]
Indication	Patients with platinum-sensitive relapsed OC who are eligible for Niraparib treatment
Rationale	Niraparib is a selective Poly-(ADP-ribose) polymerase (PARP) 1 and 2 inhibitor which selectively kills tumor cells in vitro and in mouse xenograft models. PARP inhibition leads to irreparable double strand breaks (DSBs), use of the error-prone DNA repair pathway, resultant genomic instability, and ultimately cell death. Additionally, PARP trapped at genetic lesions as a result of the suppression of autoparalysation can contribute to cytotoxicity (1). The safety and efficacy of Niraparib as maintenance therapy was studied in a Phase 3 randomized, double-blind, placebo-controlled international trial (ENGOT - OV16 / NOVA) in patients with platinum-sensitive recurrent predominantly high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. In the NOVA study, Niraparib met the primary endpoint of prolonging progression-free survival (PFS) versus placebo regardless of BRCA mutation or HRD tumor status (2). Based on the results of the ENGTO-OV 16/NOCA study, Niraparib has been approved for

	marketing authorization with the FDA and EMA. Therefore, , we thought to perform a fully prospective study characterizing the long-term experience of patients with OC that receive maintenance treatment with Niraparib. With this project we will be able to prospectively validate the experience of patients with cancer undergoing maintenance treatment through specific evaluation of the long-term use of Niraparib.
Objective (primary)	Identification of disease, patient and treatment factors associated with long term survival
Secondary objectives	• Evaluation of therapy management of Niraparib with focus on long term survival (including dose, adverse events, duration of treatment, QoL) • Identification of treatment specific factors associated with long-term survival (<5 vs >5 years)
Study type and study design	In this Non-interventional study (NIS) patients with platin-sensitive relapsed ovarian cancer (OC) will be included who are eligible for Niraparib treatment (treatment decision by physician independently before inclusion of the patients into the study). The Niraparib treatment will be according to SmPC. During the NIS study data will be collected at baseline and every six months for up to eight years follow-up (long term survival) or patient's death whatever comes first.
Patient number	300 adult patients including 200 subjects with BRCA-wild type (negative) and 100 subjects who are BRCA-mutant (positive)
Number of centers	about 30 sites in Germany and Austria
Patient eligible, if:	• Female, age at least 18 years • Participant must be able to understand the study procedures and agree to participate in the study by providing written informed consent • Histologically diagnosed OC, fallopian tube cancer, or primary peritoneal cancer

	• For the last chemotherapy course prior to inclusion in the NIS the patient must have achieved a partial (PR) or complete (CR) tumor response • Patients eligible for Niraparib maintenance therapy according to SmPC • Patient is able to take oral medications
Patient not eligible, if:	• Known hypersensitivity to the components of the product • Pregnant or breast-feeding patients
Milestones	Enrollment Rate (patients/month): 10-15 Duration: 24 months enrollment FPI (date): Q1 2019 LPI (date) : Q1 2021 LPLV (date): Q1 2028 Publications and/or other reports: end of 2029 (final study report) Interim analysis are planned after 100 patient enrollment, 1-year follow-up from LPI, 3-years follow-up from LPI, 5-years enrollment from LPI.

2. BACKGROUND AND SIGNIFICANCE

2.1. Background of PARP and Homologous Recombination Deficiency

Poly-(ADP-ribose) polymerase (PARP)1 and PARP2 are zinc-finger deoxyribonucleic acid (DNA)-binding enzymes that play a crucial role in DNA repair (Fong et al., 2009). Upon formation of DNA breaks, PARP binds at the end of broken DNA strands, a process that activates its enzymatic activity.

Activated PARP catalyzes the addition of long polymers of adenosine diphosphate (ADP)-ribose onto PARP and several other proteins associated with chromatin, including histones and various DNA repair proteins (De Lorenzo et al., 2013; Jones et al., 2015). This results in chromatin relaxation, fast recruitment of DNA repair proteins, and efficient repair of DNA breaks. In this manner, PARP plays a key role in sensing DNA damage and converting it into intracellular signals that activates the base excision repair (BER) and single-strand break repair pathways. Normal cells repair up to 10,000 DNA defects daily, and single-strand breaks are the most common form of DNA damage. Cells that are unable to repair this burden of DNA damage, such as those with defects in the homologous recombination or BER-pathways, are at risk for accumulating multiple lesions that will ultimately trigger apoptosis. They enter the S-phase (DNA replication) of the cell cycle with unrepaired single- and double-strand breaks. Pre-existing single-strand breaks are converted to double-strand breaks as the replication machinery passes. Accumulated double-strand breaks present during S-phase are repaired by homologous recombination. Homologous recombination is the preferred repair pathway because it is associated with a much lower error rate than other forms of repair. Cells that are unable to perform DNA repair via homologous recombination (e.g., due to inactivation of genes required for homologous recombination, such as breast cancer [*BRCA1*]- or breast cancer 2 [*BRCA2*]-mutated cells) are at risk for accumulating multiple lesions that will ultimately trigger apoptosis. These cells accumulate stalled replication forks during S-phase and are more likely to use the error-prone non-homologous end joining (NHEJ) or alternative (alt)-NHEJ-pathways to repair double-strand breaks in DNA. Accumulation of errors in DNA by NHEJ contributes to mutation burden that promotes the development of cancer. Over time, the buildup of excessive DNA errors in combination with the inability to complete S-phase (because of stalled replication forks) contributes to cell death (De Lorenzo et al., 2013; Jones et al., 2015).

Treatment with PARP inhibitors could represent a novel opportunity to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways. For example, a tumor arising in a patient with a germline *BRCA* mutation (g*BRCA*mut) has a defective homologous recombination DNA repair pathway and would be increasingly dependent on NHEJ, alt-NHEJ, and BER for maintenance of genomic integrity. PARP inhibitors block alt-NHEJ and BER, forcing tumors with BRCA deficiencies to use the error-prone NHEJ to fix double-strand breaks (Fong et al., 2009). Non-*BRCA* deficiencies in homologous recombination DNA repair

genes could also enhance tumor cell sensitivity to PARP inhibitors (Gelmon et al., 2011). The rationale for anticancer activity in a subset of non-g*BRCA*mut tumors is that they share distinctive DNA repair defects with g*BRCA*mut carriers, a phenomenon broadly described as "BRCAness." (Turner et al., 2004) DNA repair defects can be caused by germline or somatic alterations to the homologous recombination DNA repair pathway. In a recent analysis of approximately 500 high-grade serous ovarian adenocarcinoma tumors, approximately 50% contained homologous recombination defects (Cancer Genome Atlas Research Network, 2011). A subset of these tumors had biologically plausible molecular alterations that may make them sensitive to PARP-inhibition by Niraparib. A similar analysis of triple-negative breast cancer indicates that 43% to 44% of these patients have tumors with homologous recombination defects (Timms et al., 2014). Homologous recombination is a complex pathway, and several genes other than *BRCA1* and *BRCA2* are required either to sense or repair DNA double-strand breaks via the homologous recombination pathway. Therefore, PARP-inhibitors are also selectively cytotoxic for cancer cells with deficiencies in DNA repair proteins other than *BRCA1* and *BRCA2* (Fong et al., 2009; Turner and Ashworth, 2011; Turner et al., 2004). Recent clinical studies have shown PARP-inhibitors to be active in breast and OC. Clinical anticancer activity with PARP-inhibitors has been seen in both patients with g*BRCA*mut and without g*BRCA*mut; however, activity is more robust in patients with the germline mutation (Fong et al., 2009; Gelmon et al., 2011; Kummar et al., 2012; Ledermann et al., 2012; Mirza et al., 2016; Robson et al., 2017; Sandhu et al., 2013; Tutt et al., 2010). In summary, treatment with PARP1/2-inhibitors represents a novel opportunity to selectively kill a subset of cancer cell types by exploiting their deficiencies in DNA repair. Human cancers exhibit genomic instability and an increased mutation rate due to underlying defects in DNA repair. These deficiencies render cancer cells more dependent on the remaining DNA repair pathways, and targeting these pathways is expected to have a much greater impact on the survival of the tumor cells than that of normal cells.

2.2. Background of Niraparib

Niraparib is a potent, orally active PARP1 and PARP2-inhibitor being developed as a treatment for patients with tumors that harbor defects in the homologous recombination DNA repair pathway or that are driven by PARP-mediated transcription factors.

2.2.1. Nonclinical Experience

Non-clinical data on Niraparib are discussed in detail in the Niraparib Investigator's Brochure (IB). Briefly, in non-clinical models, Niraparib has been observed to inhibit normal DNA repair mechanisms and induce synthetic lethality when administered to cells with homologous recombination defects. In a *BRCA1*-mutant xenograft study, Niraparib dosed orally caused tumor regression, which was mirrored by a >90% reduction in tumor weight compared with control. In a *BRCA2*-mutant xenograft study, Niraparib-dosed mice showed 55% to 60% growth inhibition, both by tumor volume and weight.

Niraparib displayed strong antitumor activity in *in vivo* studies with *BRCA1*-mutant breast cancer (MDA-MB-436), *BRCA2*-mutant pancreatic cancer (CAPAN-1), and with patient-derived Ewing sarcoma mice models. Utilizing patient-derived ovarian and breast cancer xenograft models, Niraparib demonstrated response in both *BRCAmut* and *BRCA* wild-type tumors.

2.2.2. Clinical Experience

Niraparib clinical data are discussed in detail in the Niraparib IB. In the phase 1 clinical program, Niraparib as a monotherapy or in combination with chemotherapy, has been administered to 144 patients.

2.2.2.1. Phase 1 Study of Niraparib Monotherapy in Advanced Solid Tumors

Clinical activity data for Niraparib administered as monotherapy in patients with OC are available from 1 early-phase clinical study. In parts A and B of the phase 1 study PN001 (ClinicalTrials.gov identifiers: MK-4827-001 and 2008_501), 100 patients with advanced solid tumors who had received a median of three prior therapies were enrolled; 49 patients had OC (13 platinum-sensitive, 35 platinum-resistant, and one platinum-refractory) (Sandhu et al., 2013). An additional four patients were enrolled in part D of the study, which assessed pharmacokinetics only.

The most common non-hematological TEAEs were nausea, fatigue, anorexia, constipation, vomiting, and insomnia. These TEAEs were mainly mild to moderate in severity, self-limiting, and manageable with standard treatments. Hematological toxicity appeared to be dose proportional and most frequently arise in the setting of cumulative doses. Anemia was reported in 48 (48%) of 100 patients and was grade ≥3 in 10 (10%) of 100 patients. Thrombocytopenia was less common (35 [35%] of 100 patients) and was grade ≥3 in 15 (15%) of 100 patients. Neutropenia was the least commonly reported (24 [24%] of 100 patients), and was grade 3 in 4 (4%) of 100 patients at Niraparib doses of 300 and 400mg. In all cases, hematological TEAEs were uncomplicated and reversible. Twenty patients required dose reductions (usually by one dose level) for recurrent anemia or thrombocytopenia. Treatment was discontinued due to AEs in seven patients, including the four patients who had DLTs during the first cycle and three patients who had grade 3 vomiting, Grade 2 prolongation of QT interval, and Grade 3 prolongation of QT interval. No treatment-related deaths occurred.

Of the 49 patients, 22 had confirmed *BRCA1* or *BRCA2*-mutation, of whom twenty were radiologically assessable. Eight (40%) of these twenty patients achieved a confirmed partial response (PR) by Response Evaluation Criteria in Solid Tumors (RECIST) and cancer antigen 125 (CA-125) Gynecologic Cancer Intergroup criteria at doses ranging from 80 to 400mg per day. Median response duration was 387 days (range: 159 to 518 days). Three (33%) of nine patients with platinum-resistant *BRCA*-mutation OC had PR by RECIST and CA-125 criteria. In patients with platinum-sensitive disease, five (50%) of ten patients (95% CI: 19 to 81) with *BRCA1* or *BRCA2*-mutations had RECIST and CA-125 responses.

2.2.2.2. Phase 3 Study of Niraparib Monotherapy in Platinum-sensitive, Recurrent Ovarian Cancer (OC)

In the randomized, double-blind phase 3 NOVA trial (Niraparib maintenance therapy in platinum-sensitive, recurrent OC), a total of 553 patients were randomized at 107 centers worldwide. Patients were categorized according to the presence or absence of a g*BRCA*-mutation (g*BRCA* cohort and non-g*BRCA* cohort) within their tumors and the type of non-g*BRCA*-mutation and were randomly assigned in a 2:1 ratio to receive Niraparib (300mg) or placebo once daily (QD). The primary end point was progression-free survival (PFS). The study enrolled 203 patients in the g*BRCA*-mutation cohort and 350 patients in the non-g*BRCA*-mutation cohort. Among the 350 patients in the non-g*BRCA*-mutation cohort, 162 had tumors that were identified as homologous recombination deficiency positive (HRDpos), and 134 had tumors that were HRD negative (HRDneg). HRD status was not determined for 54 patients.
Demographic and baseline characteristics were well balanced. Table 2 below shows the results for the PFS primary endpoint for each of the three primary efficacy populations (i.e., g*BRCA*-mutation cohort, HRD-positive cohort, and overall non-g*BRCA*-mutation cohort). In addition, median PFS in patients with HRD-negative tumors was 6.9 months (95% confidence interval [CI]: 5.6, 9.6) in the Niraparib arm, versus 3.8 months (95% CI: 3.7, 5.6) in the placebo arm, with a HR of 0.58 (95% CI: 0.361, 0.922) (p = 0.0226).

Table 2: Progression-Free Survival in Ovarian Cancer Patients in NOVA

	gBRCAmut Cohort		**Non-gBRCAmut Cohort (Regardless of HRD Status)**		**HRDpos (Within non-gBRCAmut Cohort)**	
	Niraparib (n = 138)	**Placebo (n = 65)**	**Niraparib (n = 234)**	**Placebo (n = 116)**	**Niraparib (n = 106)**	**Placebo (n = 56)**
Median PFS (95% CI)[a] (months)	21.0 (12.9, NE)	5.5 (3.8, 7.2)	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)	12.9 (8.1, 15.9)	3.8 (3.5, 5.7)
p-value[b]	< 0.0001		< 0.0001		< 0.0001	
HR (Niraparib:placebo) (95% CI)[c]	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)		0.38 (0.243, 0.586)	

Source: PR-30-5011-C (NOVA main) CSR

Abbreviation: CI = confidence interval; CSR = clinical study report; gBRCAmut = germline BRCA mutation; HR = hazard ratio; HRD = homologous recombination deficiency; HRDpos = homologous recombination deficiency positive; NE = not evaluated; PFS = progression-free survival.

[a] PFS is defined as the time in months from the date of randomization to progression or death.

[b] Based on stratified log-rank test using randomization stratification factors.

[c] Based on the stratified Cox proportional hazards model using randomization stratification factors.

The primary data to support the safety of treatment with Niraparib are derived from the NOVA main study in which a total of 546 patients received study treatment.

All 367 patients who received Niraparib and 171 (96%) of 179 patients who received placebo experienced at least one treatment-emergent adverse event (TEAE). The high rate of TEAEs in the placebo group indicates the burden of prior chemotherapy and the patient's underlying OC. Review of the data across study cohorts for TEAE incidence showed that, in general, the results were similar in the g*BRCA*-mutation and non-g*BRCA*-mutation cohorts. In the overall safety population, for the Niraparib versus placebo treatment arms, the incidences of grade 3 or 4 TEAEs (74% vs. 23%), serious adverse events (SAEs) (30% vs. 15%), TEAEs leading to treatment interruption (67% vs. 15%), TEAEs leading to dose reduction (69% vs. 5%), and TEAEs leading to treatment discontinuation (15% vs. 2%) were higher for Niraparib than for placebo. There were no on-treatment deaths reported.

The most commonly observed non-hematologic TEAEs (all grades) observed in Niraparib-treated compared with placebo-treated patients were nausea (74% vs. 35%), fatigue (46% vs. 32%), constipation (40% vs. 20%), and vomiting (34% vs. 16%). The majority of the non-hematological TEAEs were mild to moderate in severity. The most commonly observed hematologic TEAEs (all grades) of Niraparib were anemia (49%), thrombocytopenia (46%), decreased platelet count (20%), and neutropenia (18%). Although grade 3 or 4 hematologic laboratory AEs were common at the initiation of study treatment, no severe clinical sequelae were observed, and relatively few patients discontinued study treatment due to these AEs. Dose adjustment based on individual tolerability during the first three cycles substantially reduced the incidence of these AEs beyond cycle three, indicating the overall effectiveness of the approach to dose modification. These TEAEs can be monitored routinely using standard assessments of hematological laboratory parameters, as is routine for patients with OC receiving anticancer therapies. In the NOVA study, Niraparib dose adjustment tended to occur early with most patients reaching their individual adjusted dose level at the end of month three (i.e., cycle 3) of treatment.

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been observed in patients receiving treatment with Olaparib, a PARP inhibitor; given the common mechanism of action, MDS and AML therefore represent a potential risk to patients receiving Niraparib. In the phase 3 NOVA study, the incidence of MDS/AML in patients who received Niraparib (5 of 367; 1.4%) was similar to its incidence in patients who received placebo (2 of 179; 1.1%). Guidance on monitoring patients for new AEs of MDS/AML and the follow-up of patients with suspected MDS/AML is provided.

Study PR-30-5011-C1 (NOVA corrected QT interval [QTc] sub-study; n = 26) is an open-label evaluation of the effects of Niraparib on QTc measurements in patients with histologically diagnosed OC, fallopian tube cancer, or primary peritoneal cancer. There were no reports of clinically significant abnormal electrocardiogram (ECG) changes, including QTc interval prolongation, attributed to Niraparib. Administration of Niraparib at the therapeutic dose did not prolong the QT interval. There was no correlation between the exposure level (i.e., plasma

concentration) of Niraparib and QTc changes (i.e., change in corrected QT interval calculated using Fridericia's formula [ΔQTcF]).

2.2.2.3. Baseline Platelet Count and Weight as Predictors of Thrombocytopenia.

An analysis was conducted using the data collected in ENGOT-OV16/NOVA and the initial phase I study, PN001. This analysis determined that baseline platelets had an impact on platelet nadir; lower baseline platelets (<180 10^9/L) were associated with an increased frequency of thrombocytopenia grade ≥1 (76%) or grade ≥ 3 (45%) compared to patients with higher baseline platelet counts. Further, an exploratory analysis of clinical data versus baseline body weight from ENGOT-OV16/NOVA was conducted. For this analysis, the weight categories were based on quartiles with the lowest quartile (patients with a body weight less than 58 kg at baseline) compared to the highest quartile (patients with a body weight greater than or equal to 77 kg at baseline). While TEAEs occurred in most patients regardless of body weight, grade ≥3 TEAEs, SAEs, and TEAEs leading to dose modification or treatment discontinuation occurred more commonly in the weight <58 kg cohort than in the ≥77 kg cohort. In the cohort of patients with a body weight <58kg, approximately 80% of patients had a dose reduction compared to 59% of patients with a weight greater than or equal to 77 kg. Treatment discontinuations were increased in the subjects with lower body weight (24%) compared to patients in the highest quartile (10%).

The potential relationship between body weight and TEAEs was further explored in an analysis to evaluate the correlation of grade 3 or 4 thrombocytopenia and baseline body weight. The lowest platelet count in the first 30 days was plotted versus baseline body weight to determine if low body weight identified a subgroup of patients with higher levels of thrombocytopenia during cycle 1. In the first 30 days of treatment, a baseline body weight ≥77 kg is associated with a lower incidence of grade 3 or 4 thrombocytopenia (14%) relative to the group with body weight <58 kg (43%).

Finally, a classification of tree approach was used to refine the best cut-off points for predicting the likelihood of a patient developing ≥grade 3 thrombocytopenia within 30 days after the first dose of Niraparib. The results of the model show that the subgroup of patients with a baseline body weight <77 kg **or** baseline platelet count <150,000µL had a grade 3/4 thrombocytopenia rate in the first 30 days of 35.4% compared to 11.5% in the group of patients with a body weight >77 kg **and** a platelet count >150,000µL. Furthermore, the average daily dose was 258 mg through the first two cycles for patients with a body weight >77 kg and platelet count >150,000µL, and was only 206mg for patients with body weight < 77 kg or platelet count <150,000µL. Thus, the actual delivered dose approximated a starting dose of 200 mg despite the intended delivery of a starting dose of 300 mg.

3. STUDY RATIONALE

Niraparib is a selective Poly-(ADP-ribose) polymerase (PARP) 1 and 2 inhibitor which selectively kills tumor cells in vitro and in mouse xenograft models. PARP inhibition leads to irreparable double strand breaks (DSBs), use of the error-prone DNA repair pathway, resultant genomic instability, and ultimately cell death. Additionally, PARP trapped at genetic lesions as a result of the suppression of autoparaylation can contribute to cytotoxicity1 (Mirza et al., 2016).

The safety and efficacy of Niraparib as maintenance therapy was studied in a phase 3 randomized, double-blind, placebo-controlled international trial (ENGOT-OV16/NOVA) in patients with platinum-sensitive recurrent predominantly high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. In the NOVA study, Niraparib met the primary endpoint of prolonging progression-free survival (PFS) versus placebo regardless of BRCA mutation or HRD tumor status 2.

Based on the results of the ENGOT-OV16 / NOVA study, Niraparib (Zejula®) was filed by [redacted] and gained marketing authorization with the FDA and EMA.

We have previously investigated patients' preferences and expectations from cancer maintenance treatment regimens (Expression IV project). The results from this project were recently published (Rohr et al. 2017) and indicated that patients choose maintenance therapy primarily to improve therapeutic outcome and secondarily to improve quality of life. Further, we estimated that 30 % of patients prefer an oral administration and over 50% will tolerate a 2-year administration of maintenance therapy if the delay of tumor growth will be more than six months.

Based on these results, we thought to perform a fully prospective study characterizing the long-term experience of patients with OC that receive maintenance treatment with Niraparib. With this project we will be able to prospectively validate the experience of patients with cancer undergoing maintenance treatment through specific evaluation of the long-term use of Niraparib.

3.1. STUDY DESIGN

3.2. Study Design

It is planned to enroll 300 patients with platin-sensitive relapsed OC who are eligible for Niraparib treatment by about 30 sites in Germany and Austria, who are eligible for Niraparib treatment.

Treatment decision has to be determined independently by the physician before inclusion of the patients into the study. The Niraparib treatment should be planned according to current SmPC.

For collection of best quality data we will include only patients that start Niraparib treatment at time of enrollment. During this NIS data will be collected at baseline and every 3 months for up to 7 years follow-up (long term survival with every 6 months visits) or patient's death whatever comes first.

3.2.1. Primary Objective

- Identification of disease, patient and treatment factors associated with long term survival

3.2.2. Secondary Objectives

- Evaluation of therapy management of Niraparib with focus on long term survival (including dose, adverse events, duration of treatment, QoL)
- Identification of Niraparib specific factors associated with long-term survival (<5 vs >5 years)

3.2.3. Population and Sample Size

300 subjects will be recruited by physicians of specialized hospitals/practice who are participating in the NIS. It is planned, that about 30 sites will participate. 200 subjects should be *BRCA*-wild type (negative) and 100 subjects should be *BRCA*-mutant (positive).
Adult patients with platinum sensitive relapsed OC who are in response to platinum-based chemotherapy meeting the criteria for treatment with Niraparib in accordance with the terms of its EMA marketing authorization as documented in the SmPC.

4. PARTICIPANT SELECTION

4.1. Inclusion Criteria

- Female, age at least 18 years
- Participant must be able to understand the study procedures and agree to participate in the study by providing written informed consent
- Histologically diagnosed OC, fallopian tube cancer, or primary peritoneal cancer
- For the last chemotherapy course prior to inclusion in the NIS the patient must have achieved a partial (PR) or complete (CR) tumor response
- Patients eligible for Niraparib maintenance therapy according to current SmPC
- Patient is able to take oral medications

4.2. Exclusion Criteria

- Known hypersensitivity to the components of the product
- Pregnant or breast-feeding patients

The patient is not allowed to participate in another interventional clinical trial.

5. OUTCOME MEASURES

5.1. REQUIRED MEASURES

Before any assessments starts:

- Verification of eligibility of study participation
- Written informed consent

5.1.1 At baseline - Patient demographics and disease/treatment history

- Demographic: age, weight, height
- ECOG (Eastern Cooperative Oncology Group, see Appendix 1)
- Medical/family history of cancer: history of other cancers, family history of cancers; OC diagnosis history and treatment history: age of patient at cancer diagnosis, tumor histology, FIGO stage, primary tumor location, timepoint of primary surgery, (and all other surgeries regarding OC), optimal debulking (yes, no), description of prior chemo/platinum lines (including drugs/regimens, start and end dates, and frequency) and response to last chemo/platinum line, treatment with other maintenance therapy/ PARP-inhibitors prior to enrollment (duration, dose, and reason for (premature) discontinuation), additional treatments received for cancer prior to enrollment (specify date, duration, type of treatment and reason for interruption), duration of chemotherapy free intervals (CFI) all lines, responses during last lines of chemotherapy, response to recent platinum-based chemotherapy (e.g. thrombocytopenia, grad 4 adverse events, GCSF administration)
- Biomarker data collected per clinical routine and reported as available from medical charts: BRCAstatus
- Clinical symptoms and co-morbidities (e.g. hypertension, ascites, nausea, fatigue, pain)
- Co-medication
- Physical examination as standard of care
- Pregnancy
- Smoking and alcohol use
- Complete blood count (CBC)

- Glomerular filtration rate (GFR)
- Serum biochemistry
- CA125 levels as collected per standard of care
- General patient expectations of Niraparib (see Appendix 3)
- Quality of life questionnaires including:
  - Individual patient questionnaire (see appendix 2) including state of health, distress, activity and the falling history
  - SF-12 questionnaire
  - FACT questionnaires: fatigue by FACT-F questionnaire
  - EORTC questionnaires: EORTC QLQ-C30, QLQ-OV28
  - Patient reported outcome with PRO CTCAE
- Grip strength via dynamometer (hand force): see 5.1.4
- Adverse Events: see section 9

5.1.2 Required measures during Niraparib treatment

The Niraparib treatment will be examined every 3 months:

- Age at Niraparib initiation (will be ask once)
- Weight at Niraparib treatment
- ECOG
- Clinical symptoms and co-morbidities (e.g. hypertension, ascites, nausea, fatigue, pain)
- Co-medication
- Physical examination as standard of care
- Complete blood count as assessed per standard of care
- Serum Biochemistry
- Glomerular filtration rate (GFR)
- CA125 levels as collected per standard of care
- Time between last chemotherapy cycle and Niraparib therapy
- Starting Niraparib dose; time, duration and reason for dose interruption, reduction(s), including new dose prescribed; time and reason for treatment termination, if patient has to stop during observation time
- Pregnancy

- Quality of life questionnaires including:
  - SF-12 questionnaire
  - FACT questionnaires: fatigue by FACT-F questionnaire
  - EORTC questionnaires: EORTC QLQ-C30, QLQ-OV28
  - Patient reported outcome with PRO CTCAE
- Adverse Events (including ADR, AE, AESI, MDS/AML, secondary primary malignancies (SPM) and pregnancy): see section 9
- Grip strength via dynamometer (only after 3 and 6 months of treatment)
- Episode of falling: asked by the physician
- Presence of brain metastasis, if applicable

5.1.3 End of treatment

About 4 weeks ± 7 days after last dose of Niraparib

- ECOG
- CA125 levels as collected per standard of care
- Clinical symptoms and co-morbidities (e.g. hypertension, ascites, nausea, fatigue, pain)
- Co-medication
- Physical examination as standard of care
- Complete blood count as assessed per standard of care
- Serum Biochemistry
- Glomerular filtration rate (GFR)
- Quality of life questionnaires including:
  - SF-12 questionnaire
  - FACT questionnaires: fatigue by FACT-F questionnaire
  - EORTC questionnaires: EORTC QLQ-C30, QLQ-OV28
  - Patient reported outcome with PRO CTCAE
- Changes in Niraparib dose; time, duration and reason for dose interruption, reduction(s), including new dose prescribed; time and reason for treatment termination, if patient has to stop during observation time
- Pregnancy
- Efficacy: CFI, TFST, ORR, OS and treatment duration with Niraparib

- TFI (therapy free interval)
- Adverse Events: see section 9
- Subsequent therapy, if applicable
- Episode of falling: ask by physician
- Brain metastasis, if applicable

5.1.4 Follow Up

After treatment with Niraparib patients will be followed up every 6 months until 7 years or end of study including the following:

- Efficacy: CFI, TFST, ORR, OS and treatment duration with Niraparib
- TFI (therapy free interval)
- Adverse Events: see section 9
- Pregnancy
- Subsequent therapy (type and duration), if applicable
- Episode of falling, every six months
- Presence of brain metastasis, if applicable

5.1.5 Grip strength (Weakness) via dynamometer

One of the central features of the phenotype of frailty is weakness (e.g. measured by grip strength), as one of the functions most likely dependent on energetics and speed of performance (e.g., mobility) aspects.
Evaluation of the grip strength is usually measured directly with a dynamometer. The measurement includes 3 serial tests of maximum grip strength with the dominant hand and the mean have to be calculated. Weakness is commonly defined as adjusted grip strength in the lowest 20th percentile of a community dwelling population of adults 65 years of age and older. Women fulfill this criteria with a BMI and a hand craft of the following: ≤23 und ≤17kg; 23,1-26 und ≤17,3kg; 26,1-29 und ≤18kg und >29 und ≤21kg.

Table 3: Visit schedule

Study Procedures	**Baseline**	**Treatment with Niraparib (every 3 months)**	**End of treatment (4 weeks ± 7 days after last dose of Niraparib visit)**	**Follow Up (every 6 months until 7 years or patient's death whatever comes first, ± 2 weeks)**
Patient informed consent	x			
Eligibility Criteria	x			
Demographic data (age, height, weight)[a]	x	**x**		
ECOG	x	**x**	**x**	
Medical/Family history of cancer	x			
CA-125[b]	x	x	x	
Available biomarkers at time of enrollment (among others BRCA status)	x			
Clinical symptoms and co-morbidities	x	x	x	
Co-medication	x	x	x	
Physical examination[b]	x	x	x	
Complete blood count[b]	x	x	x	
Serum biochemistry	x	x	x	
GFR	x	x	x	
Smoking and alcohol use	x			
Individual patients questionnaire[c]	x			
QoL questionnaires (SF-12, FACT-F, QLO-C 30&OV28, patient reported outcome with PRO CTCAE)	x	x	x	
General patient expectations of Niraparib[d]	x			
Niraparib dosage (start, changes, end dosis); time and reason for treatment termination		x	x	
Subsequent therapy[e]			x	x
Efficacy: CFI, TFST, ORR, TFI, OS and treatment duration with Niraparib			x	x
Adverse events (including ADR, AE, AESI, MDS/AML, SPM)	x	x	x	

Pregnancy	x	x	x	x
Grip strength	x	x[e]		
Episode of falling[f]		x	x	x
Brain metastases[g]		x	x	x

[a] weight: every time; age at baseline und Niraparib therapy start; height: only at baseline

[b] as standard of care/as per clinical practice

[c] questionnaire, see Appendix 2

[d] questionnaire, see Appendix 3; one time at therapy start

[e] if applicable

[f] only after 3 and 6 months treatment

[g] if applicable, during FU: every 6 months; asked by physician

6. SAMPLE SIZE AND DURATION OF FOLLOW-UP

300 patients (200 subjects *BRCA*-wild type (negative) and 100 subjects *BRCA*-mutant (positive) will be examined over a time period of up to 7 years (long term survival) in follow up.

7. DATA COLLECTION PROCESS

7.1 DATA MANAGEMENT

The data is entered by the staff of the study center into the data input mask of the web-based documentation system. In accordance with the data validation plan adapted for this study, the system validates online the entered data by:

- Value range checks: check for permissible values in a field
- Field type checks: check whether the entered value matches the definition of the field (e.g., numeric, alphanumeric, or date fields)
- Logical checks: check the relationship between different data fields in the sense of consistency or plausibility checks

If incomplete or incorrect entries are made, queries that are stored in the system are generated automatically. Any remaining questions are then clarified by telephone with the study physician. The discrepancies and their resolution are documented.

The input of AEs is additionally checked manually.

The validated data is transferred to the data center of the CRO via a secured internet connection (https) and stored in the database according to the database structure plan adapted for this study.

Every data entry and every data change is automatically provided with user and date (audit trail).

The participating physician is obligated to provide all necessary background information on his/her recordings upon request. This is particularly important when mistakes are assumed in the data input or transmission.

The participating physician asserts that the recorded data are true.

7.2 MONITORING

A monitor commissioned by the Sponsor can randomly check the data collection by matching the data stored in the eCRF with the medical records. Patients are informed about this aspect before participation in the non-interventional study and asked for their consent. Only patients who have given their informed consent can be observed in the non-interventional study.

The site initiation will be performed online. During the study a risk-based monitoring with one further on-site monitoring will be performed. At the end of the study the close-out visit will be on-site as well.

7.3 MONITORING, QUALITY CONTROL AND ARCHIVING

Before the first subject is recruited into the study, the local representative or delegate will:

- establish the adequacy of the facilities and the investigators capability to appropriately select the sample
- discuss with the investigator(s) (and other involved personnel involved with the study) their responsibilities with regards to protocol compliance, and the responsibilities of NOGGO or its representatives. This will be documented in a NIS Primary Agreement between NOGGO and the investigator

Contacts with the sites to:

- provide information and support to the investigator(s)
- confirm that the research team is complying with the protocol and that data are being accurately recorded in the CRFs
- ensure that the subject informed consent forms are signed and stored at the investigators site
- ensure that the CRFs are completed properly and with adequate quality.

Monitoring activities for:

- checking a sample of ICFs
- checking that subjects exist in medical records (a sample)

The extent and nature of monitoring will be decided during the study planning based on design, complexity, number of subjects, number of sites, etc. different signals (e.g., high rejection rate in a site) should be used as potential identification of low protocol compliance by investigators. If these, or any other signals occurs or if the local coordinator is suspicious of a potential non-optimal level of protocol compliance by the site investigator, specific measures should be adopted to evaluate the situation, identify the issue and implement specific action plans to correct the situation.

7.4 TRAINING OF STUDY SITE PERSONNEL

The PI will ensure that appropriate training relevant to the NIS is given to investigational staff and that any new information relevant to the performance of this NIS is forwarded to the staff involved.

7.5 ARCHIVING

The completeness and access to patient records and study-relevant examination results are to be ensured according to legal requirements over 10 years after the end of the study. The storage can also take place in digitized form.

8. STATISTICAL ANALYSIS AND OBJECTIVES

8.1 PRIMARY OBJECTIVES

- Identification of disease, patient and treatment factors associated with long term survival

8.2 SECONDARY OBJECTIVES

- Evaluation of therapy management of Niraparib with focus on long term survival (including dose, adverse events, duration of treatment, QoL)
- Identification of Niraparib specific factors associated with long-term survival (<5 vs >5 years)

8.3 STATISTICAL ANALYSIS AND SAMPLE SIZE

Due to the explorative nature of the study, the statistical analysis is not carried out in a confirmatory manner, but rather exploratively.

Statistical description and analysis method:

- Usual descriptive statistics such as mean, median, quartile, and absolute and relative frequencies

- Mann-Whitney and t-test for quantitative data, Chi-square or Fisher's test for qualitative data
- Survival analysis: Kaplan-Meier curves, Cox regression
- Prediction of long-term survivors: Selection of factors by means of stepwise multiple logistic regression, determination of a cut-off value by means of ROC analysis

A number of four interim analyses are planned in which only descriptive analyses will be conducted. The interim analyses will be conducted after 100, 150, 200 and 300 patients. A detailed Statistical Analysis Plan (SAP) will be prepared before the first interim analysis.

The sample size determination is based on the desired precision of the prediction of the long-term survivors. For a score with sensitivity of 75%, a one-sided 95% confidence interval will extend the observed proportion of 75% by only 10%, i.e. 95%CI [0.675; Inf], if 91 long-term survivors are included in the study. Since a prevalence of approximately 35% of long-term survivors in the study population is assumed, a total of 260 patients are needed. Taking into account about 15% drop-outs, the total number of cases is 300 patients. For this calculation, the test for confidence intervals for a proportion using normal approximation was used which is implemented in the software nQuery.

8.4 INTERIM ANALYSIS

Interim analysis are planned after 100 patient enrollment, 1-year follow-up from LPI, 3-years follow-up from LPI, 5-years enrollment from LPI.

8.5 FINAL MEDICAL REPORT

A written report will be prepared no later than 12 months after termination (LPO) or after a premature termination of the non-interventional study. The structure of the report is based on internationally accepted standards such as STROBE and includes among other information:

- Number of patients included in the study
- Number of participating centers

- Descriptive presentation of selected observation variables (defines in the statistical analysis plan (SAP))
- Review of representativeness of participating centers and patients
- Representation of the effect of disturbance variables and the importance for the interpretation of the results
- Assessment of the results with regard to previous treatment recommendations
- Overall assessment of the study

9. ADVERSE EVENT REPORTING

9.1. Definitions

Definition of Adverse Event (AE):
Any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with the patient's exposure to this medicinal product. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product.
AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time after the time of medicinal product exposure.
Definition of Serious Adverse Event (SAE):

Any untoward medical occurrence that, at any dose;

- results in death
- is life threatening (i.e., an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);
- requires inpatient hospitalization or prolongation of existing hospitalization*
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect; or
- is an important medical event**

*Exception: Preplanned (at time of informed consent) hospitalization for elective procedures will not be considered criteria for an SAE. The reason for the planned hospitalization should be captured in the medical history section in the eCRF. Complications experienced during these hospitalizations must be reported as AEs (or SAEs, if hospitalization is prolonged due to the AE).

**Medical and scientific judgment should be exercised in determining whether situations or events should be considered SAEs; an important medical event may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are allergic bronchospasm, blood dyscrasias, or convulsions that may require intensive treatment in an emergency room or at home but do not result in hospitalization, development of drug dependency or drug abuse, and transmission of disease associated with the administration of the Niraparib.

Definition Adverse Event of Special Interest (AESI) for Niraparib:

An Adverse Event of Special Interest is defined as any AE (serious or non-serious) that is of scientific and medical concern with the patient's exposure **to a specific** medicinal product, for which ongoing monitoring and rapid communication to [redacted] Pharmacovigilance is required.

Adverse Events of Special Interest (AESI) for niraparib include the following:

- Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)
- secondary cancers (new malignancies [other than MDS or AML])
- pneumonitis
- embryo-fetal toxicity

All AESIs should be reported as SAEs.

Definition of Adverse Drug Reactions (ADR):
An ADR is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a medicinal product, suspected to be causally related to the product. ADRs should be reported as SAEs.

9.2. Special Situations: Abuse, Misuse, Medication Errors, Overdose, and Accidental or Occupational Exposure:

- **Abuse:** is the persistent or sporadic, intentional excessive use of the medicinal product, which is accompanied by harmful physical or psychological effects.
- **Misuse:** medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.
- **Medication error:** is any preventable incident that may cause or lead to inappropriate exposure to the medicinal product, or patient harm while the

medicinal product is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

- **Overdose:** is a deliberate or accidental administration of the medicinal product, to a study patient, at a dose greater than the product label indication and/or SmPC. If an overdose with Niraparib occurs, [redacted] pharmacovigilance should be notified immediately, and the patient should be observed closely for AEs. Associated AEs should be treated and monitored by the investigator. The dosage of Niraparib administered, any associated AEs, and/or treatment provided to the patient because of the overdose, should be reported.
- **Accidental /Occupational exposure:** is the unintentional exposure to a medicinal product as a result of one's professional or non-professional occupation, or accidental exposure to a non-professional to whom exposure was not intended (i.e., study product given to wrong patient).

Reporting Special Situations: All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure associated with exposure to niraparib must be reported on a Special Situations Report Form to [redacted] Pharmacovigilance within 5 business days of awareness regardless of whether or not an AE or SAE has occurred. If the abuse, misuse, medication error, overdose, or accidental / occupational exposure is associated with an AE, an SAE Report Form must also be submitted to [redacted] Pharmacovigilance within 1 (one) business day or no more than 3 (three) calendar days during holidays of awareness for patients enrolled prospectively in an observational study.

9.3. Assessment of Adverse Events

9.3.1. Severity Assessment

All AEs will be assessed by the Investigator for severity* according to Common Terminology Criteria for Adverse Events (CTCAE) V5.0, 14 June 2010, National Institutes of Health (NIH), National Cancer Institute (NCI). The CTCAE severity Grades 1 through 5 provide unique clinical descriptions of the severity of each AE. The CTCAE V5.0 is available on the NCI/NIH website. Disease progression is an efficacy criterion and is therefore not considered an ADR or SAE (even if fatal).

Note that there is a distinction between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in section 9.1.1. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe.

9.3.2. Relationship to Study Data Collection

The Investigator must provide a causality assessment regarding the relationship of the event with the niraparib treatment prescribed to the patient for all AEs. One of the following categories should be selected based on medical judgment, considering all contributing factors:

- Related: A causal relationship between the medicinal product and AE is a reasonable possibility. For example, the occurrence of the AE cannot be explained by other causative factors. The AE, however, can be explained by pharmacological effect of the medicinal product such as a similar event having been reported previously, alteration of the dose effect, the timing or seriousness of the AE, etc. Positive rechallenge/dechallenge is supportive.
- Not related: A causal relationship between the medicinal product and AE is not a reasonable possibility. There is no temporal relationship between the medicinal product and event, or an alternative etiology is more reasonable.

9.4. Collecting and Recording Adverse Events

AEs may be volunteered spontaneously by the study patient or discovered by the study staff during physical examinations or by asking an open, nonleading question such as, “How have you been feeling since your last study visit?” The Investigator will document the nature of the AE, date of onset of the AE (and time, if known), date of outcome of the AE (and time, if known), severity of the AE, action taken as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE.

AEs, including laboratory abnormalities that are assessed as clinically significant or require intervention, should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

All AEs/SAEs are collected from the signing of the ICF for this study up to the end of treatment visit or the patient’s death for any cause, whichever comes first. AEs/SAEs that occur after end of treatment visit will follow the guidelines for spontaneous safety reporting.

9.4.1. Follow-Up of Adverse Events

All AEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normal levels, until stabilized with a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

If an Investigator becomes aware of an SAE after the treatment with Niraparib , the Investigator should report the SAE to [redacted] according to timelines for reporting SAEs described in section 9.4.

9.5. Reporting

Each AE will be assessed by the investigator for severity, for a causal relationship with the treatment drug and for expectedness. Events that occur after signing of informed consent, but prior to initiation of Niraparib, should be recorded in the eCRF. Any AE that occurs after first dose of Niraparib will be recorded on the AE eCRF. Disease progression is an efficacy criteria and is therefore not considered an ADR or SAE (even if fatal).

All SAEs, AEs, AESI and Special Situations will be recorded in the eCFR. It is the responsibility of the Investigator to report SAEs and ADRs in accordance with all regulations and requirements. **All SAEs, AEs, AESI and Special Situations will be reported by the sub-contracted Investigator(s) to [redacted] Pharmacovigilance (see email below).** SAEs and all follow-up information must be reported within 1 to 3 calendar days of becoming aware of the initial event or follow-up information. AEs that are not serious and that are not in the list of excluded AEs will have to be reported to [redacted] within 90 days:

- Nausea
- Fatigue
- Constipation
- Vomiting
- Headache
- Decreased appetite
- Insomnia
- Abdominal pain
- Dyspnoea
- Dizziness
- Asthenia
- Back pain
- Anthralgia
- Dyspepsia
- Nasopharyngitis
- Urinary tract infection
- Dysgeusia
- Myalgia
- Abdominal distension

In addition, signs and symptoms associated with progression of the underlying OC do not need to be reported as TEARs.

Each (S)AE and AESI should be recorded with the following information:

- Diagnosis (description of adverse event)
- Start date
- Stop date
- Concomitant drug therapy
- Maximum intensity (mild, moderate, severe)
- Action taken on Niraparib (none, dose reduction, temporarily stopped, stopped),
- outcome (recovered, not yet recovered, permanent disability, death, unknown)
- Causality / relationship to Niraparib (yes, no)
- Seriousness (yes, no), reason for seriousness

Reporting method: The CRF/eCRF page is emailed to [redacted]

It is the responsibility of Investigator to review source documentation and describe pertinent information on the reporting system. If supporting documentation is requested (eg, hospital reports, consultant reports, death certificates, autopsy reports, etc.), the Investigator should highlight all relevant and pertinent information within such documents, ensure that any patient's personal identifiers (including medical record number) are removed, and submit the documents to [redacted]. [redacted] (or designee) will return a confirmation of receipt within 1 business day. If no acknowledgment of receipt is received, the Sponsor or Investigator or designee should re-submit the query [redacted] to confirm reporting route and resubmit the report.

After receipt of the initial report, [redacted] (or designee) will review the information and, if necessary, contact the Sponsor or Investigator to obtain further information. The Sponsor or Investigator must promptly respond to queries from [redacted]

Collection of secondary data will not require reporting of any AEs or SAEs as it will be assumed that this was done during the treatment of the patient when these events occurred.

9.5.1. Submission and Distribution of Serious Adverse Reaction Reports

If an event is assessed as a suspected unexpected serious adverse reaction (SUSAR the following reporting modalities:

[redacted] Pharmacovigilance will perform all expedited reporting of events to Regulatory Authorities according to applicable regulations. Sponsor will inform all participating sites in the trial.

9.5.2. Pregnancy

The Investigator must report all pregnancies and the outcomes to [redacted] and has the responsibility to monitor the outcome of all pregnancies reported during the clinical study.

While the details of the pregnancy or other associated event e.g. elective abortion should be captured and reported using the same system chosen for SAEs and AEs, pregnancy is not an AE and therefore does not need to be reported as an AE unless there is a suspicion that Niraparib may have interfered with the effectiveness of a contraceptive medication. The Sponsor or Investigator must follow up all pregnancies, document the course and the outcome, and report this information to [redacted] within 1-3 days of becoming aware–even if the patient was withdrawn from the study or the study has finished.

An elective abortion without complications should not be regarded as an AE; however, it should be reported as the outcome to the pregnancy. Therapeutic abortions should be reported as a treatment procedure; the reason for the therapeutic abortion should be reported as a pregnancy outcome and as an AE. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

10. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

10.1. Ethics Review

The final study plan, including the final version of the informed consent form (ICF), must be approved or given a favorable opinion in writing by an Institutional Review Boards (IRB) or International Ethic Committee (IEC), as appropriate. The investigator must submit written approval to the Sponsor before he or she can enroll any patient into the study.
The Principal Investigator (PI) is responsible for informing the IRB or IEC of any amendment to the study plan in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The study plan must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.
The PI is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the PI.
Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

10.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation and Good Clinical Practice standards as well as any applicable regulatory requirements.

10.3. Written Informed Consent

The PI(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent (PIC) must be obtained before conducting any study procedures.

The PI(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

11. DISCONTINUATION FROM STUDY

Specific reasons for discontinuing from the study include the following:

- Withdrawal of consent
- Loss to follow-up (For participants who are thought to be lost to follow-up, at least 3 documented attempts, including 1 via certified mail, should be made to contact the participant before the participant is deemed lost to follow-up)
- Death from any cause
- Termination of the study
- Patients are not willing or able to take Niraparib
- Investigators decision e.g. because of SAEs/Toxicities

11.1. Procedure for Discontinuation

The reason for discontinuation will be recorded in the eCRF. Patients who discontinue voluntary should be ask about the reason(s) for discontinuation. Patients who elect to discontinue study observation will be encouraged to continue in the study so follow-up information on disease progression and survival status may be obtained.

12. DATA HANDLING AND RECORD KEEPING

12.1. Study Approval and Amendment

The study and all the possible amendments will be approved by Ethical Committee (EC) before starting any data collection procedure.

12.2. Investigator Responsibilities

Data collection, cleaning and statistical analysis will be under the responsibility of the investigator. Patients' safety surveillance and compliance to study plan will be investigators responsibility.

12.3. Data Collection and Quality Assurance

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The study CRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRFs, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

The investigator/institution should maintain trial documents and they should take measures to prevent accidental or premature destruction of these documents.

12.4. Data security

For client/server communication via the internet only encrypted transmissions are applied. State of the art encryption technology is used exclusively. In addition, the server identifies itself to the client workstation by means of a digital server certificate issued by an authorized certification authority. By this, it is ensured that data are sent only to the server of the by Sponsor authorized institution.

Data are protected from potential virtual attacks and physical damage. Views on data or reports as well as edit or read rights are controlled with individual passwords. Access authorization to the CRF databases is granted individually to investigators and program personnel by means of user accounts. Furthermore, a back-up is performed according to the following scheme:

- Daily back-up over a period of 7 days
- Weekly back-up over a period of 5 weeks
- Monthly back-up over a period of continuance of the clinical trial
- Responsible investigators will get a CD-rome after the end of the trial containing the data of the patients they have documented for archiving.

Data will be entered in the Web-based Data Capture (WBDC) system at the investigator's site. The investigator will be responsible for entering data into the WBDC system and according to

the eCRF manual. The eCRF manual will also provide the site with data entry instructions. As soon as data are entered into the EDC system, all changes and user information will be saved in an audit trail. Electronic edit checks (eChecks) are performed automatically and directly when entering data in the eCRF. Here, the user is pointed out on missing entries or implausibilities. This is done by warning and error messages, whereby the latter prevents to save the eCRF form, until the error is corrected by the user.
In addition to the eChecks there are manual checks by personnel of data management of the by Sponsor authorized institution. Manual checks are made, whenever electronic checks cannot be performed. They serve to verify the entered data validity and plausibility. These relate notably to plausibility or cross-checks to verify the correctness and completeness of the data, as well as to protocol violations and inclusion/exclusion criteria. In addition, free text entries will be checked on plausibility or any "hidden" information (e.g. the existence of an AE/SAE) or "prohibited" information (such as patients full name or documented data after withdrawal of consent). Queries will be entered into the form of the eCRF directly by data management. Timeframes are defined in which the sites must answer all queries. When data have been entered, reviewed and edited, the investigator will be notified to sign the eCRF electronically as per agreed project process and data will be locked to prevent further editing.

12.5. Subject Confidentiality and Data Protection

Confidentiality standards should be maintained by coding each patient enrolled in the study through assignment of a unique patient identification number so that patient names are not included in datasets that are transmitted.
Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the IC form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.
Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare or for treatment purposes.
Data generated by this study must be available for inspection(s) upon request by representatives of national or local health authorities, marketing authorization holder monitors, representatives, collaborators, or the EC for each study site, as appropriate.

12.6. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification (SDV). The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the study plan, GCP-guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

12.7. Retention of Records

The PI must maintain all documentations relating to the study for a period of two (2) years after the last marketing application approval or, if not approved, two (2) years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the investigator must permit access to such records.

13. PUBLICATION POLICY

The NOGGO will prepare a NIS report within twelve (12) months after completion of the last subject.

- The coordinating investigator will be the signatory of the report.
- Investigators will be provided with the summary of the final Non-Interventional Study Report on request.

The NOGGO is obliged to analyze all NIS data as described in the protocol. In accordance with the Declaration of Helsinki, both authors and publishers have ethical obligations. In publication of the results of the NIS, the authors are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. The NOGGO endeavors to publish the results of NIS and is committed to ensure that the data are reported in a responsible and coherent manner.
NOGGO seeks to ensure that publication in biomedical journals follow the guidelines established by the International Committee of Medical Journal Editors (ICMJE) and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals.
NOGGO is committed to ensure that authorship for all publications should comply with the criteria defined by the ICMJE. These state that: “Each author should have participated sufficiently in the work to take public responsibility for the content.”
NOGGO believes that participation solely in the collection of data or drafting the manuscript does not justify authorship. These conditions apply equally to external investigators and to NOGGO employees.

14. STUDY MANAGEMENT

14.1. NIS start and end of study

Before the first subject is enrolled in the NIS and any NIS-related procedures are undertaken the following should be fulfilled

- written approval of the NIS by the EC, according to local regulations
- proper agreements between NOGGO and the investigator/institution is signed

Should NOGGO decide to discontinue the study prior to what was established in this protocol, the investigator and relevant authorities should receive written notice describing the reasons why the study was terminated at an earlier date. The investigator will immediately notify the subjects taking part in the study; they will continue to receive their treatment according to usual clinical practice.

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APPENDIX 1. PERFORMANCE STATUS

Some examples of performance status scales are included below; these can be removed if not relevant to your study plan.

ECOG PS
0—Fully active, able to carry on all pre-disease performance without restriction
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5—Dead

Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *Journal of Chronic Diseases*; 1960:11:7-33.
Available at: http://ecog-acrin.org/resources/ecog-performance-status

APPENDIX 2. INDIVIDUAL QUESTIONNAIRE

Study-specific patient questionnaire

1. **Wie beurteilen Sie Ihren derzeitigen Gesundheitszustand auf einer Skala von 1 bis 5?**

   1 (sehr schlecht) 2 3 4 5 (sehr gut)

2. **Haben Sie aktuelle Beschwerden?**

   □ Ja
   □ Nein

   Bitte spezifizieren Sie auf einer Skala von 1 (minimal) bis 5 (maximal) Ihre Beschwerden:

   Schwäche
   □ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

   Luftnot
   □ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

   Schmerzen
   □ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

   Lymphödem
   □ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

   Taubheitsgefühl bzw. Kribbeln in Fingern u./o. Zehen (Polyneuropathie)
   □ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

   Hautveränderungen
   □ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

   Übelkeit bzw. Erbrechen
   □ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

   Appetitverlust
   □ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

Verstopfung
□ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

Durchfälle
□ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

Gewichtsverlust
□ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

Gewichtszunahme
□ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

Blähungen
□ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

Völlegefühl
□ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

Konzentrationsstörungen bzw. Gedächtnisprobleme
□ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

Luftnot unter körperlicher Belastung, auch bei leichten Tätigkeiten
□ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

Luftnot in Ruhe
□ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

Ich kann nicht längere Zeit flach liegen, weil mir die Luft knapp wird
□ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

Ich habe manchmal Luftknappheit nachts
□ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

Ich huste nachts vermehrt
□ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

Ich leide unter vermehrter Müdigkeit und eingeschränkter körperlicher Belastbarkeit
□ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

Ich muss nachts Wasserlassen

□ 1 □ 2 □ 3 □ 4 □ 5 □ keine Beschwerden

3. **Wie viele Tabletten nehmen Sie täglich ein? _____**

Nehmen Sie eines bzw. einige der folgenden Medikamente ein?

□ Beta-Blocker (z.B. Metoprolol, Bisoprolol)
□ ACE-Hemmer (z.B. Ramipril)
□ ASS
□ Statin (z.B. Simvastatin)
□ Heparin (z.B. Fraxiparin, Clexane)
□ Insulin
□ Metformin
□ Nahrungsergänzungsmittel

4. Welche der folgenden Erkrankungen haben Sie?

	Vor Erstdiagnose	Nach Erstdiagnose
a. Herz-Kreislauf-Erkrankungen	□	□
b. Bluthochdruck	□	□
c. Herzinsuffizienz	□	□
d. Koronare Herzkrankheit	□	□
e. Herzinfarkt	□	□
f. Schlaganfall	□	□
g. Polyneuropathie	□	□
h. Konzentrations-/Gedächtnisstörung	□	□
i. COPD	□	□
j. Asthma	□	□
k. Diabetes	□	□
l. Depression	□	□
m. Niereninsuffizienz	□	□
n. Gelenkbeschwerden	□	□
o. Fettstoffwechselstörung	□	□
p. andere Krebserkrankung	□	□
q. Sonstiges _____	□	□

5. Welche der Erkrankungen hat auf Ihre Lebensqualität den größten Einfluss? (Bitte geben Sie eine Erkrankung bzw. den zugeordneten Buschstaben aus Frage 4 an.)

_____

6. Ist bei Ihnen das Brustkrebsgen BRCA untersucht worden?

□ Ja
□ Nein
□ weiß nicht

Wenn ja, was war das Ergebnis?

□ BRCA 1 bzw. 2 positiv
□ negativ
□weiß nicht

7. Ist eine der folgenden Nebenwirkungen im Laufe Ihrer bisherigen Behandlung aufgetreten?

□ Herzschädigungen
□ Veränderungen des Blutbildes
□ Haarausfall
□ schwere Müdigkeit bzw. Erschöpfung
□ Schmerzen
□ Übelkeit bzw. Erbrechen
□ Taubheitsgefühl bzw. Kribbeln in Zehen u./o. Fingern (Polyneuropathie)
□ Gedächtnis- und Konzentrationsstörungen
□ Sonstiges

8. Welche der Nebenwirkungen hat Sie am meisten belastet?

□ Polyneuropathie
□ Übelkeit/Erbrechen
□ Fatigue
□ Haarausfall
□ Magen-/Darm-Probleme
□ Hautveränderungen
□ Knochenschmerzen
□ Konzentrationsschwierigkeiten
□ Vergesslichkeit
□ Gedächtnisprobleme
□ Sonstiges

9. Welche der Nebenwirkungen Ihrer Behandlung belastet Sie noch heute?

□ Polyneuropathie
□ Übelkeit/Erbrechen
□ Fatigue
□ Haarausfall
□ Magen-/Darm-Probleme
□ Hautveränderungen
□ Knochenschmerzen
□ Konzentrationsschwierigkeiten
□ Vergesslichkeit
□ Gedächtnisprobleme
□ Sonstiges

10. Distress Thermometer

Anleitung:

ERSTENS: Bitte kreisen Sie am Thermometer rechts die Zahl ein (0-10) die am besten beschreibt, wie belastet Sie sich in der letzten Woche einschließlich heute gefühlt haben.

ZWEITENS: Bitte geben Sie an, ob Sie in einem der nachfolgenden Bereiche in der letzten Woche einschließlich heute Probleme hatten. Kreuzen Sie für jeden Bereich JA oder NEIN an.

JA	NEIN		JA	NEIN	
		Praktische Probleme			**Körperliche Probleme**
O	O	Wohnsituation	O	O	Schmerzen
O	O	Versicherung	O	O	Übelkeit
O	O	Arbeit/Schule	O	O	Erschöpfung
O	O	Beförderung (Transport)	O	O	Schlaf
O	O	Kinderbetreuung	O	O	Bewegung/Mobilität
			O	O	Waschen, Ankleiden
		Familiäre Probleme	O	O	Äußeres Erscheinungsbild
O	O	Im Umgang mit dem Partner	O	O	Atmung
O	O	Im Umgang mit den Kindern	O	O	Entzündungen im Mundbereich
			O	O	Essen/Ernährung
		Emotionale Probleme	O	O	Verdauungsstörungen
O	O	Sorgen	O	O	Verstopfung
O	O	Ängste	O	O	Durchfall
O	O	Traurigkeit	O	O	Veränderungen beim Wasser lassen
O	O	Depression	O	O	Fieber
O	O	Nervosität	O	O	Trockene/juckende Haut
O	O	Verlust des Interesses an alltäglichen Aktivitäten	O	O	Trockene/verstopfte Nase
			O	O	Kribbeln in Händen/Füßen
			O	O	Angeschwollen/aufgedunsen fühlen
		Spirituelle/religiöse Belange	O	O	Gedächtnis/Konzentration
O	O	In Bezug auf Gott	O	O	Sexuelle Probleme
O	O	Verlust des Glaubens			

Sonstige Probleme: _____

11. Wie oft treiben Sie Sport bzw. sind Sie körperlich aktiv?

□ keine sportliche Betätigung
□ weniger als 1 Stunde in der Woche
□ regelmäßig, 1-2 Stunden in der Woche
□ regelmäßig, 2-4 Stunden in der Woche
□ regelmäßig, mehr als 4 Stunden in der Woche

12. Halten Sie aktuell eine bestimmte Diät oder Ernährungsform ein?

□ ja
□ nein
□ vegetarisch
□ vegan
□ koscher
□ halal

□ kohlenhydratarm
□ andere:

Wenn ja, warum halten Sie diese Ernährungsform ein?

□ Glaube
□ Lebensqualität
□ Empfehlung Arzt
□ Empfehlung alternative Medizin
□ Glaube an Prognoseverbesserung
□ andere: _____

13. Hat sich Ihre Ernährung seit der Diagnose verändert?

□ ja
□ nein

Inwiefern? Essen Sie seitdem:

□ mehr Obst und Gemüse
□ regelmäßiger am Tag
□ weniger Zucker
□ weniger Farbstoffe
□ weniger Alkohol
□ weniger Fette
□ Sonstiges

14. Sind Sie in der letzten Woche gefallen (gestürzt)?

□ ja
□ nein

Wenn ja, wie oft?

□ 1 Mal
□ 2 Mal
□ 3 Mal
□ 4 Mal
□ 5 Mal
□ >5 Mal

APPENDIX 3. PATIENTS EXPECTATION NIRAPARIB TREATAMENT

Umfrage – Erwartung zur Niraparib Therapie

1. Wie beurteilen Sie Ihren derzeitigen Gesundheitszustand auf einer Skala von 1 bis 5?

□1 □2 □3 □4 □5
sehr schlecht sehr gut

2. Nehmen Sie regelmäßig Tabletten?

O ja

O nein

Wenn ja, gegen welche Erkrankung?

Wie viele Tabletten nehmen Sie?

3. Haben Sie Probleme, Tabletten einzunehmen oder gibt es Gründe, warum Sie keine Tabletten einnehmen oder einnehmen möchten?

O ja

O nein

Wenn ja, benennen Sie bitte die Gründe:

O Einnahme vergessen
O ich glaube nicht an die Effekte
O Tabletten sind zu groß
O Einnahme von zu großer Anzahl an Tabletten
O Sonstiges

4. Haben Sie schon einmal was von einer Erhaltungstherapie gehört?

O ja

O nein (bitte lesen Sie die Erklärung dazu und fahren Sie mit Frage 5 fort)

Wenn ja von wem:

O Arzt
O anderer Patient
O Verwandte
O Internet
O Fernsehen
O pharmazeutische Broschüre
O Sonstiges

Eine Erhaltungstherapie zu bekommen bedeutet, dass Sie eine zusätzliche Anti-Krebs-Therapie nach Ihrer Chemotherapie erhalten. Diese Therapie zielt darauf ab, ein weiteres Fortschreiten des Tumors zu verzögern. Die Verzögerung des Tumorwachstums bedeutet eine Stabilisierung der Erkrankung und kein aggressives Tumorwachstum für die angegebene Zeit, allerdings ohne bisherige wissenschaftliche Beweise für eine allgemeine Verlängerung der Lebenserwartung.

5. Erhalten Sie eine Erhaltungstherapie?

O ja

O nein

6. Was ist oder was wäre ihr persönliches Ziel eine Erhaltungstherapie zu wählen? (Mehrfachantworten möglich)

O Verkleinerung des Tumors
O Abnahme des Tumormarkers CA 125
O Verzögerung des Tumorwachstums
O Heilungschancen vergrößern
O keine Verschlechterung der Lebensqualität
O Verbesserung der Lebensqualität
O Sonstiges

7. Was ist ihr wichtigstes persönliches Ziel einer Erhaltungstherapie? (Maximal 1 Antwort möglich)

O Verkleinerung des Tumors
O Abnahme des Tumormarkers CA 125
O Verzögerung des Tumorwachstums
O Heilungschancen vergrößern
O keine Verschlechterung der Lebensqualität
O Verbesserung der Lebensqualität
O Sonstiges

8. Was ist die maximale Dauer der Therapie, die Sie bereit wären zu nehmen, wenn Sie die Behandlung gut vertragen?

O 6–12 Monate
O 12–18 Monate
O 18–24 Monate
O 24–36 Monate
O 48–60 Monate
O bis zum erneuten Tumorwachstum

9. Wie groß sollte eine Verzögerung des Tumorwachstums für Sie sein, um eine gut verträgliche Erhaltungstherapie durchzuführen / einzunehmen?

Ich würde eine bis zu 24 Monate andauernde Erhaltungstherapie nehmen, wenn sie zu einer Verzögerung des Tumorwachstums führt von:

O 3 Monaten
O 4 Monaten
O 5 Monaten
O 6 Monaten
O mehr als 6 Monate
O ich möchte eine so lange Therapie nicht

10. Welche Art der Verabreichung von Medikamenten bevorzugen Sie bei der Erhaltungstherapie?

O in Tablettenform (oral)
O direkt ins Blut (intravenös)
O ich habe keine Vorliebe

Bitte geben Sie einen Grund für Ihre Antwort an:

---

11. Wie bevorzugen Sie die zeitliche Einnahme der Medikamente?

O zweimal am Tag (oral)
O einmal täglich (oral)
O zweimal die Woche (oral)
O einmal wöchentlich (intravenös)
O alle drei Wochen (intravenös)

12. Welche Nebenwirkungen würden Sie am meisten stören, wenn Sie eine Erhaltungstherapie erhalten würden? (Maximal 3 Antworten möglich)

O hoher Blutdruck
O erhöhtes Infektionsrisiko
O erhöhtes Blutungsrisiko
O Polyneuropathie (Polyneuropathie ist eine Krankheit der peripheren Nerven, in deren Verlauf es zu Schmerzen, Kribbeln, Brennen oder zu Taubheitsgefühlen in den Armen und Beinen kommen kann)
O Ödeme (Wassereinlagerungen)
O Übelkeit
O Erbrechen
O Erschöpfung
O Hautauschlag oder Infektionen der Haut
O gestörte Wundheilung

O Durchfall
O Verstopfung
O Blutarmut
O Bauchschmerzen
O Haarausfall