"COMPASS"

Comparison of QoL between Trabectedin / PLD and standard platinum-based therapy in patients with platinum sensitive recurrent ovarian, fallopian tube and peritoneal cancer

Intergroup-Study of NOGGO and BNGO

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I have read and checked the protocol diligently; I comply with the stated demands and requirements and agree to conduct the study according to the guidelines of Good Clinical Practice (GCP) and the requirements of the responsible authorities in regard to reconciliation of original data and to audits/inspections.

I consent to report every serious clinical adverse event to the CRO within one working day, whether it is related to study medication or not.

_____ _____

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Deputy (Print name): _____

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Place and Date Signature Deputy

If applicable: 2nd Deputy (Print name): _____

_____ _____

Place and Date Signature 2nd Deputy

1 Table of contents

List of tables

List of figures

2 Abbreviations

AE	Adverse Event
AMG	Arzneimittelgesetz (German Drug Law)
ANC	Absolute neutrophil count
AP	Alkaline Phosphatase
AST/ALT	Aspartate aminotransferase (=sGOT)/ Alanine Aminotransferase (=sGPT)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CI	Confidence Interval
CPK	Creatine phosphokinase
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computer Tomography
CTC/CTCAE	National Cancer Institute: Common Terminology Criteria for Adverse Events
DNA	Desoxyribonucleic Acid
DSUR	Developmental Safety Update Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EORTC	European Organisation for the Research and Treatment of Cancer
EOT	End Of Treatment
EP	Efficacy Population
ESMO	European Society for Medical Oncology
FPI	First Patient In
FU	Follow Up
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transpeptidase
Hb	Hemoglobin
HR	Hazard Ratio
ICH	International Conference on Harmonisation
ITT	Intent-To-Treat population
IKF	Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
i.v.	Intravenous
IWRS	Interactive Web Response System
kg	Kilogram
LKP	Leiter der Klin. Prüfung (Coordinating investigator)
LPI	Last Patient In
LVEF	Left Ventricular Ejection Fraction
MASCC	Multinational Association of Supportive Care in Cancer
MDRD	Modification of Diet in Renal Disease
mg	Milligram
m^2	Square meter
ml	Milliliter
MR	Minor Response
MRI	Magnetic Resonance Imaging
NaCl	Sodium chloride
NCI	National Cancer Institute
NRS	Nutritional Risk Screening
OS	Overall Survival
pCR	Pathol. Complete Remission
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
PLD	Pegylated Liposomal Doxorubicin
p.o.	Per os; orally
PP	Per Protocol population
PR	Partial Response
q	every
ROC	Recurrent Ovarian Cancer
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Stable Disease
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SR	Subtotal Response
SUSAR	Suspected Unexpected Serious Adverse Reaction
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
TEAE	Treatment Emergent Adverse Events
TOI-QLQ-OV	Trial Outcome Index of the EORTC QLQ-C30 and QLQ-OV28
TNM	Primary Tumor / Lymph Node / Distant Metastasis
ULN	Upper Limit of Normal
WHO	World Health Organization

3 Synopsis

Study title	Comparison of Quality of life (QoL) between trabectedin/PLD and standard platinum-based therapy in patients with platinum sensitive recurrent ovarian, fallopian tube and peritoneal cancer
Study type	Phase IV, open-label, prospective, multi centre randomized trial
Objectives	To compare QoL in patients treated with trabectedin/PLD vs. other standard combination therapy of carboplatin/ PLD, carboplatin/ gemcitabine, or carboplatin/ paclitaxel
Endpoints	Primary endpoints: Primary Endpoint is the observation of change in QoL. This is measured for every patient as the change from baseline (C1 D1) to end of treatment (EOT) visit (3-4 weeks after C6 D1 or, in case of progression/relapse, 3-4 weeks after day 1 of last treatment Cycle). The primary QoL measure is the mean score of the Trial Outcome Index (TOI). The TOI is based on selected items from the EORTC QLQ-C30 version 3.0 and QLQ-OV28 (TOI-QLQ-OV) and includes the C-30 functional scales physical and role functioning, the symptom scales constipation, diarrhea, nausea and vomiting, in addition to the first 24 items of the EORTC Ovar 28 (i.e. all items of the EORTC Ovar 28, excluding sexual functioning). The primary endpoint will be analysed by general linear models for paired samples. Secondary endpoints: • Clinical benefit rate (CR, PR, SD), or PD in patients with measurable disease • Difference in QoL for all other time points not included in primary endpoint • Progression-free survival (PFS) • Overall survival (OS) • Time to next medical intervention

Study design

This is a multicenter, randomized, controlled, open-label study including patients with recurrent, platinum-sensitive, ovarian, peritoneal or fallopian tube cancer.

The main scope of the trial is to evaluate QoL during and after chemotherapy comparing trabectedin/PLD with other standard platinum-based chemotherapy in platinum-sensitive disease.

Patients with recurrent, platinum-sensitive, ovarian, fallopian tube and peritoneal cancer will be stratified according to surgery for relapse (tumor free vs. not tumor free resection) vs. no surgery in the same setting and age (< 75 years vs. ≥ 75 years), and randomized 1:1 to receive either trabectedin/PLD (Arm A) or one of 3 platinum-based standard therapies without bevacizumab (Arm B, "other standard therapy"). In case of randomization to "other standard therapy", the investigator has the choice between carboplatin/PLD, carboplatin/gemcitabine and carboplatin/paclitaxel. Patients in both treatment arms will receive chemotherapy up for 6 cycles or until disease progression (PD), unacceptable toxicities or patient's wish to stop therapy, whichever occurs first.

Arm A (Trabectedin/PLD)

Patients randomized to Arm A will receive PLD 30 mg/m^2 i.v. as a 1-hour infusion followed by trabectedin 1.1 mg/m^2 as a 3-hour infusion immediately after the PLD infusion. Treatment is repeated every 3 weeks for 6 cycles or until disease progression.

Arm B (carboplatin/ PLD, carboplatin/gemcitabine, or carboplatin/ paclitaxel)

Patients randomized to Arm B will receive up to 6 cycles of the platinum-based therapy as mentioned above and administered according to respective SmPC.

In both of the arms, tumor assessments (CT or MRI) are performed as standard of care until progression / relapse, death or end of follow up. A CT/MRI before baseline is required, however, the timeframe in which a patient can be randomized in the trial after tumor assessment is left up to the

investigator. A change from CT into MRI in the follow up period is possible at any time.

During treatment, clinical visits (blood cell counts, detection of toxicity) occur prior to every treatment dose. Safety will be monitored continuously by careful monitoring of all adverse events (AEs) and serious adverse events (SAEs).

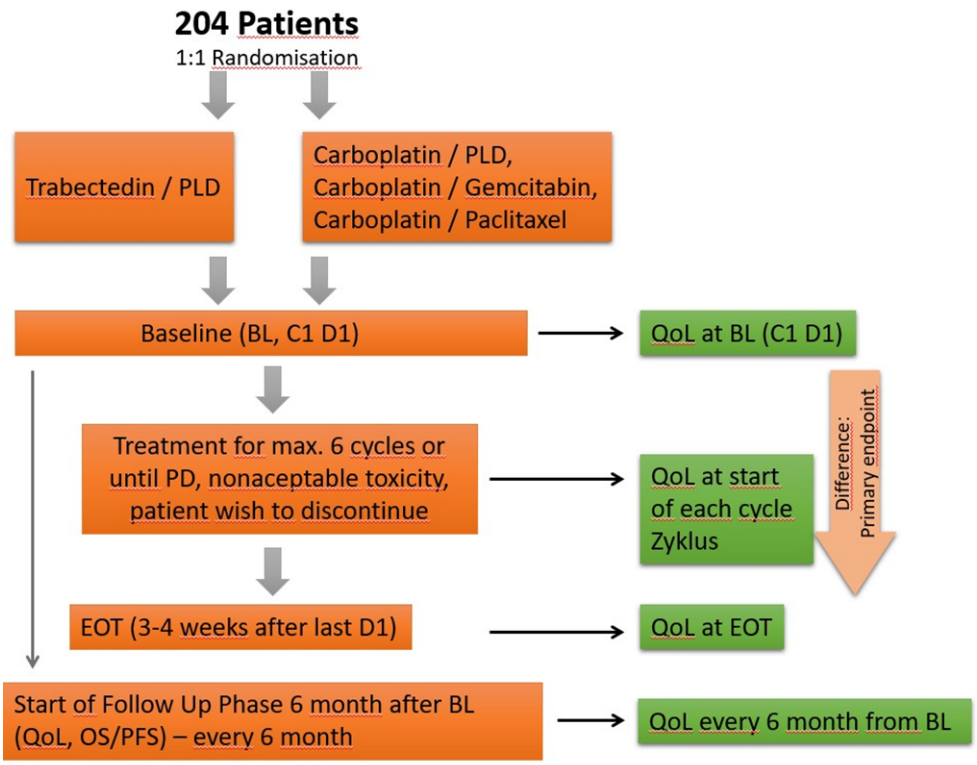

Figure 1: Study Scheme.

About 20 sites will participate in this study to recruit 204 patients in 52 months.

Rationale

Ovarian cancer remains the second-most lethal gynecologic malignancy after cervical cancer, with approximately 125,000 deaths annually worldwide [2]. Most patients with this type of cancer are initially diagnosed in already advanced stages. Surgery including maximal debulking followed by chemotherapy with carboplatin and paclitaxel has become the standard treatment [3] in first line therapy.

Although most patients achieve a complete response, the majority will suffer a relapse and eventually die from the disease. Relapses occurring ≥ 6 months after end of first line platinum-based treatment are considered platinum sensitive and are advised to be re-treated with a platinum based regimen [4]. However, this definition has been widely discussed as the type of relapse treatment is determined by various factors. The sole definition of the recurrence populations exclusively via the platinum-free therapy interval is therefore insufficient [5].

Recurrent ovarian cancer represents a major clinical challenge; few compounds have shown activity in large randomized trials, including carboplatin/cisplatin, paclitaxel, pegylated liposomal doxorubicin (PLD), gemcitabine and trabectedin [6-8].

Non-platinum monotherapy is the preferred treatment for patients who experience disease recurrence soon after completing first-line therapy (platinum-resistant disease). This so called platinum-resistant patients, represent a subgroup with a worse prognosis [9].

For platinum-sensitive patients, the standard of care in Germany (according to the current S3-Guidelines) is carboplatin combined with e.g. gemcitabine, paclitaxel or PLD. These combination chemotherapies showed an improvement of PFS and OS compared with platinum monotherapy [10]. But similarly the combination of trabectedin/PLD also showed an improvement of PFS and OS in the favorable subgroup of platinum-sensitive patients with a relapse free interval of more than 6 months after platinum-based therapy [11]. As a result, trabectedin in combination with PLD is considered an option for patients with relapsed, platinum-sensitive, ovarian cancer [12].

Because most women with recurrent ovarian cancer ultimately die of their cancer, QoL and regimen convenience are objectives that are as important as

efficacy. In palliative cancer therapy, the QoL is one of the most important objectives; besides the prolongation of OS. Platinum-based combination chemotherapy is known to be intense and toxic and can therefore, be associated with impaired QoL. Therefore, there is a strong rational to compare the platinum-free combination trabectedin/PLD with other standard platinum-based combinations in terms of their impact on QoL.

Procedures used in this study (such as the chemotherapy, the blood tests and the radiology investigations) are in line with those usually used in the treatment of patients with recurrent ovarian, peritoneal or fallopian tube cancer in routine clinical practice. In terms of the chemotherapy, carboplatin/PLD, carboplatin/gemcitabine, carboplatin/paclitaxel are recommended chemotherapy regimens by the S3 German Guideline (highest-level national guidelines in Germany) [12] for platinum-sensitive relapse, as just mentioned above.

Taken together, the risks emerging from participation in this clinical trial are acceptable and the results of the study may have an impact on future treatment of patients in the given indication.

Chemotherapy schedule

Arm A: Trabectedin/PLD:

- Dexamethasone 20 mg; PLD 30 mg/m^2 D1, Trabectedin 1.1 mg/m^2 D1; qd22

Arm B: Other standard treatment according to respective SmPC and published therapy algorithms [1]:

- Carboplatin/PLD: Carboplatin AUC5 D1, PLD 30 mg/m^2 D1; qd29
- Carboplatin/Gemcitabine: Carboplatin AUC4 D1; Gemcitabine 1.000 mg/m^2 D1, D8; qd22
- Carboplatin/Paclitaxel: Carboplatin AUC5 D1, Paclitaxel 175 mg/m^2 D1; qd22

Patients will be treated for 6 cycles (or more in case of clinical benefit, but this extended treatment will not be part of the study) or until PD,

unacceptable toxicity or patient's wish to discontinue, whichever occurs first.

Inclusion criteria

1. Women aged ≥ 18 years
2. Patients with histologically confirmed diagnosis of epithelial ovarian cancer, primary peritoneal carcinoma or fallopian tube cancer who received ≥1 prior chemotherapy
3. Patients must be eligible for platin-containing therapy; Patient is defined as platin-sensitive when considered for platin-containing therapy by the investigator. The time frame from end of prior therapy until disease progression alone is not pivotal for study participation. Patients without a platin-containing regimen in the previous line who are also eligible for platin-containing regime are also appropriate for participation
4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2
5. Adequate baseline organ function as defined as
    - Leucocytes > 3.0 x 10^9/l
    - Platelet count > 100 x 10^9/l
    - Absolute neutrophil count (ANC) ≥1500/mm^3
    - Haemoglobin ≥ 9 g/dl
    - Alkaline Phosphatase (AP) ≤ 2.5 × ULN (consider hepatic isoenzymes 5 nucleotidase or gamma glutamyl transpeptidase (GGT), if the elevation could be osseous in origin)
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN
    - Creatinine-Clearance ≥ 60 ml/min (MDRD formula or Cockroft & Gault formula)
    - Serum creatinine ≤ 1.5 mg/dl
    - Creatine phosphokinase (CPK) ≤ 2.5 × ULN
    - Total bilirubin < ULN
6. Women of childbearing potential should use contraceptives or abstain from heterosexual activity for the course of the study through 6 months after the last dose of study medication or be surgically sterile.

7. Adequate cardiac function defined as left ventricular ejection fraction (LVEF) ≥ 50% as determined by echocardiogram

   Patients must provide written informed consent prior to performance of study specific procedures or assessments, and must be willing to comply with treatment and follow up assessments and procedures.

Exclusion criteria

1. Only malignancies, which influence the prognosis
2. Any unstable or serious concurrent condition (e.g. active infection requiring systemic therapy).
3. Chemotherapy or radiation therapy or tumor embolization within 2 weeks prior to the first dose of study drug or planned during study participation.
4. Patients who have refractory disease. Refractory disease is defined if relapse occurs <4 months after beginning of platin-containing therapy.
5. Hypersensitivity to the active substance or to any of the excipients of study drug
6. Findings from ECG and/or assessment of LVEF which indicate an anthracycline-related cardiotoxic process which contradicts administration of liposomal doxorubicin or trabectedin in accordance with the requirements of the SmPCs.
7. Biological therapy, immunotherapy, hormonal therapy or treatment with an investigational agent within 14 days (for bevacizumab, 30 days) prior to the first dose of study drug.
8. Any condition that is unstable or could jeopardize the safety of the patient and their compliance in the study
9. Participation in another clinical study with experimental therapy within the 30 days before start of and during treatment. Participation in a non-interventional study should be discussed with sponsor and NC beforehand.
10. Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4)
11. Patients who are depending on the sponsor/CRO or investigational site as well as on the investigator.
12. Pregnancy or lactation period, or planning to become pregnant within 7 months after the end of treatment.

Sample size
Duration of the study (planned)

204 patients (Arm A, 102; Arm B, 102)
Enrolment start date (FPI): Q3 2017
Recruitment period: 52 months
Enrolment finish date (LPI): Q4 2022
Treatment period: up to 6 cycles administered every 3 weeks or 4 weeks (depends on therapy regimen)
Follow-up-period: starting from end of study treatment for 12 months after baseline for the last patient included.
End of Follow-up: Q2 2024

Table 1: Treatment Schedule.

	Screening (day)	**Treatment cycles 1-6[1]**	**End of study treatment**	**FU [13]**
	- 14 to 0	**D1**[5]	3-4 weeks after C6 D1 or 3-4 weeks after last D1 (progression)	Starting 6M after BL (C1 D1), every 6 months[14]
Informed consent	X			
Body height	X			
Concomitant diseases	X			
ß-HCG-Pregnancy test (for women with childbearing potential)	X			
Physical examination / ECOG	X	X	X	
Charlson Score	X		X	
ECG[11], Echocardiogram [2, 11, 6]	X		X	
Weight	X	X	X	
Randomization	X			
Calculation of medication dose[3]		X[5]		
Laboratory examinations[8] Blood count[9] (before every cycle)	X	X[12]	X	
Tumor evaluation (using always the same method), CA 125[10]	X[6]	TO BE PERFORMED AS STANDARD OF CARE		
Adverse events		X	X[7]	
Concomitant medication	X	X	X	
Quality of Life[4]: EORTC QLQ-C30 and QLQ-OV28	(X)[15]	X[15]	X	X
NRS 2002	X		X	
Documentation of Follow-up therapy, PFS and OS			X	X

[1]Therapy will continue for 6 cycles or until one of the discontinuation criteria (Section 10.4.1) applies.

[2] In case of anomalies further examinations during therapy as clinically indicated.

[3] At day 1 of each therapy application

[4] Prior to first application of each therapy cycle

[5] For gemcitabine also D8 to be documented

[6] CT and Echocardiogram to be performed as standard of care and can be older than 14 days before treatment if investigator considers this as acceptable.

[7]-AEs and SAEs to be documented until 30 days after EoT or until start of new antitumor therapy, whatever occurs first

[8] Laboratory: Serum: Creatinine, ALT, AST, AP, total bilirubin, albumin, CPK

[9] Blood count: Haemoglobin, white blood cell count with differential (total neutrophil count including lymphocyte, monocyte, eosinophil and basophil counts), platelets

[10] Evaluation of CA 125 may not be required (Investigators decision)

[11] Findings from ECG and/or assessment of LVEF which indicate an anthracycline-related cardiotoxic process which contradicts administration of PLD or trabectedin in accordance with the requirements of the SmPC is an Exclusion criteria.

[12] Trabectedin: Additional monitoring of haematological parameters bilirubin, alkaline phosphatase, aminotransferases and CPK should occur weekly during the first two cycles of therapy, and at least once between treatments in subsequent cycles.

[13] If EOT or other visits are planned 6 month (± 4 weeks) after Baseline, a separate visit for first FU is not necessary as long as all examinations and QoL assessments were performed.

[14] until 5 years after Baseline or end of study

[15] Quality of Life Assessments can be obtained up to 15 days before Baseline Visit.

4 Background and Rationale

4.1 Rationale

Ovarian cancer remains the second-most lethal gynecologic malignancy after cervical cancer, with approximately 125,000 deaths annually worldwide [2]. Most patients present with disease in advanced stage. Surgery including maximal debulking followed by chemotherapy with carboplatin and paclitaxel has become the standard treatment [3].

Although most patients achieve a complete response, the majority will suffer a relapse and eventually die from the disease. Relapses occurring ≥ 6 months after end of first line platinum-based treatment are considered platinum sensitive and are advised to be re-treated with a platinum-based regimen [4]. However, this definition has been widely discussed as the type of relapse treatment is determined by various factors. The sole definition of the recurrence populations exclusively via the platinum-free therapy interval is therefore insufficient [5].
Recurrent ovarian cancer represents a major clinical challenge; few compounds have shown activity in large randomized trials, including carboplatin/cisplatin, paclitaxel, pegylated liposomal doxorubicin (PLD), gemcitabine, and trabectedin.

Non-platinum monotherapy is the preferred treatment for patients who experience disease recurrence soon after completing first-line therapy (platinum-resistant disease). This so called platinum-resistant patients, represent a subgroup with a worse prognosis[9].

For platinum-sensitive patients, the standard of care in Germany according to the current S3-Guidelines is carboplatin combined with gemcitabine, paclitaxel or PLD. These combination chemotherapies showed an improvement of PFS and OS compared with platinum monotherapy [10]. But similarly the combination of trabectedin/PLD also showed an improvement of PFS and OS in the favorable subgroup of platinum-sensitive patients with a relapse free interval of more than 6 months after platinum-based therapy [11]. As a result, trabectedin in combination

with PLD is considered an option for patients with relapsed, platinum-sensitive, ovarian cancer[12].

As mentioned above the standard after surgical debulking at initial surgery is chemotherapy with carboplatin and paclitaxel. So, in the relapse situation, many women still suffer from persistent neuropathy from initial therapy, making re-treatment with taxanes, especially paclitaxel a difficult endeavor [13]. For instance, the ICON4/AGO-Ovar-2.2 study [14] demonstrated improved survival by adding paclitaxel to a platinum agent in patients with platinum-sensitive recurrent ovarian cancer. However, this combination was associated with significant neurotoxicity [15]. Studies have shown that patients report motor neuropathy as the most unpleasant adverse effect of treatment [16] and the development of neuropathy is a major factor impairing QoL [17], which can lead to early treatment discontinuation.

Regarding platinum backbone of the doublet chemotherapy, carboplatin and cisplatin have a similar efficacy, although carboplatin has a more favorable toxicity profile and convenient administration [7, 10, 14]. Carboplatin exhibits considerably lower nephrotoxicity than cisplatin. However, renal function must be monitored when determining dosage regimens to avoid acute toxicity, because renal clearance is the primary means by which carboplatin is cleared from the body. Carboplatin causes dose-limiting and cumulative myelo-suppression, characterized by thrombocytopenia, granulocytopenia and anemia. Thrombocytopenia following carboplatin therapy is frequent and severe [18, 19]. Although cumulative myelosuppression is the main toxicity associated with carboplatin, there is also a significant risk of neurotoxicity and hypersensitivity reactions. A study at the Cleveland Clinic Cancer Center [20] reported that hypersensitivity to carboplatin developed in 12 % of carboplatin-treated patients. Because of the possibility of fatal cross-hypersensitivity, the use of cisplatin in patients who have developed hypersensitivity to carboplatin is not recommended [21]. Though platinum-based regimens are the current standard of care in first-line therapy of ovarian cancer, their long-term toxicities represent a challenge in the treatment of patients with relapsed ovarian cancer. Patients with ovarian cancer will often be retreated with multiple courses of recurrence therapy. Caution should be used in patients who receive multiple sequential courses of chemotherapy, because they may experience excessive toxicity and may not be able to tolerate doses used for first-line therapy; thus, clinical judgment should be used when selecting doses and regimens (NCCN). For this purpose, a non-platinum-based regimen such as trabectedin/PLD could be an alternative option.

Because most women with recurrent ovarian cancer ultimately die of their cancer, QoL and regimen convenience are objectives that are as important as efficacy. In palliative cancer therapy, the QoL is one of the most important objectives, besides the prolongation of OS. Platinum-based combination chemotherapy is known to be intense and toxic and can, therefore, be associated with impaired QoL. Therefore, there is a strong rational to compare the platinum-free combination trabectedin/PLD with other standard platinum-based combinations in terms of their impact on QoL.

4.2 Pegylated liposomal doxorubicin (PLD)

Doxorubicin is an anthracycline class with broad spectrum of antineoplastic activity. PLD is doxorubicin hydrochloride encapsulated in liposomes aimed at escaping recognition and uptake by the mononuclear phagocyte system. PLD safety profile is improved over doxorubicin, with less cardiotoxicity, nausea, vomiting and alopecia.

The major toxicity is direct against the bone marrow, limiting the dose of PLD. Irreversible cumulative cardiac toxicity limits the total deliverable dose as well. Special attention must be given to the myocardial damage that may be associated with cumulative doses of doxorubicin and caution should be observed in patients who have received other anthracyclines. PLD is approved both in the United States (Doxil®) and in Europe (Caelyx®) for patients with recurrent ovarian cancer after initial standard chemotherapy. The approved dose of PLD as a single agent for the treatment of ovarian carcinoma is 50 mg/m^2 administered every 4 weeks.

4.3 Trabectedin

Trabectedin is an antineoplastic agent. It binds covalently to the minor groove of DNA, bending DNA towards the major groove, and disrupts transcription leading to G2-M cell cycle arrest and ultimately apoptosis [22].

The clinical development program was focused primarily on ovarian cancer and soft tissue sarcoma, where trabectedin demonstrated activity at very low concentrations in both preclinical models and humans.

Trabectedin received marketing authorization in the European Union (EU) in 2007 for the treatment of patients with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Also, trabectedin in combination with PLD was approved for patients with relapsed platinum-sensitive ovarian cancer by the European Medicines Agency (EMA) in 2009. Further information regarding trabectedin may be found in the Summary of Product Characteristics (SmPC).

4.4 Clinical safety and efficacy data of trabectedin/PLD

The efficacy of trabectedin in the treatment of patients with recurrent ovarian cancer is based primarily on clinical data from the phase III study ET-743-OVA-301 (OVA-301). This was an open-label, multicenter, randomized clinical trial designed to investigate the efficacy and safety of the combination of PLD 30 mg/m², followed by trabectedin 1.1 mg/m² every 3 weeks compared with the approved standard single-agent PLD 50 mg/m² every 4 weeks [11, 23]. In the primary analysis by independent radiology review, the combination resulted in a statistically significant 21% decrease in the risk of disease progression or death vs. PLD alone. For platinum sensitive patients (PFI ≥ 6 months) the median PFS was 9.2 months for trabectedin/ PLD vs. 7.5 months for PLD (HR 0.73, p= 0.017) with even a 27 % reduction of risk.

A subgroup analysis of OS by platinum sensitivity based on PFI (0 to 6 months, 6 to 12 months, and >12 months) showed greater benefit (HR <1) in OS in patients receiving trabectedin/PLD compared with PLD monotherapy. The effect was most prominent in the partially platinum-sensitive (platinum-free interval 6-12 months) group. In the partially platinum-sensitive subset of patients, trabectedin/PLD induced a significant 36 % decrease in the risk of death compared with PLD alone (HR = 0.64; 95 % CI, 0.47–0.86; P = 0.0027). Median OS was 22.4 months in the trabectedin/PLD arm versus 16.4 months in the PLD arm [24].

The results were supported further by three phase II trials in which trabectedin has been investigated as single-agent in 2nd or 3rd line therapy in patients with relapsed advanced ovarian cancer. Regimens assessed were: 0.58 mg/m² over 3-h weekly x 3 q4w, 1.3 mg/m² over 3-h q3w and 1.5 mg/m² over 24-h q3w [8, 25, 26].

The most common haematological toxicity observed during the study OVA-301 was neutropenia. The incidence of grade 3/4 neutropenia cases evaluated as drug-related adverse events was higher in the trabectedin/PLD arm compared with PLD alone although this neutropenia was reversible and non-cumulative. Grade 3/4 ALT elevations were also more common with the combination but were transient and non-cumulative. Hand-foot syndrome and mucositis were less frequent with trabectedin/PLD than with PLD alone.

Trabectedin, as a single-agent or combined with PLD, does not usually show the symptomatic clinical toxicity (e.g., neurotoxicity, renal toxicity or skin/nail toxicity) associated with other chemotherapeutic agents of common use.

Thus, these results of the most recent studies have shown that trabectedin, in combination with PLD, is effective for the treatment of patients with platinum-sensitive relapsed ovarian cancer

without substantially increased toxicity compared with PLD alone. Especially patients in long-term treatment, having received 6 or more cycles, show a good tolerability, since the observed toxicities were transient and not cumulative [27].

4.5 Quality of Life: EORTC QLQ-C30 and QLQ-OV28

The European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) is an integrated system for assessing the health-related QoL of cancer patients participating in international clinical trials. The core questionnaire, the EORTC QLQ-C30 [28] is a 30-item questionnaire composed of multi-item scales and single items that reflect the multidimensionality of the quality-of-life construct [29]. It incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality-of-life scale. The remaining single items assess additional symptoms commonly reported by cancer patients (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea), as well as the perceived financial impact of the disease and treatment.

Following its general release in 1993, the QLQ-C30 has been used in a wide range of cancer clinical trials, by a large number of research groups. The EORTC group has developed a modular approach to the assessment of QoL. A number of modules specific to e.g. tumor site or treatment modality have been developed to be administered in addition to the QLQ-C30. A module is defined as a set of items assessing QoL issues not (sufficiently) covered by the QLQ-C30 and considered to be relevant for the target population and the research question on hand.

Such a module is the ovarian cancer module (EORTC QLQ-OV28). It was developed to supplement the EORTC QLQ-C30 for issues of relevance to the QoL of patients with ovarian cancer. The QLQ-OV28 module assesses abdominal/gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side-effects, hormonal/menopausal symptoms, body image, attitude to disease/treatment and sexual functioning [30].

The primary objective of this study is to evaluate the overall burden of the therapy. Based on experience from our study HECTOR (AGO Ovar 2.12 [31]), a score called “Trial Outcome Index” (TOI) was created. We wanted to develop a score similar to the FACIT TOI [32], which consists for the FACIT TOI in Physical Well-Being (PWB), Functional Well-Being (FWB), and "additional concerns" subscales.

For this trial the primary outcome is the mean TOI of items from the EORTC QLQ-C30 version 3.0 and QLQ-OV28. This new score we called TOI-QLQ-OV. It is based on items from the C-30 functional scales physical and role functioning, the symptom scales constipation, diarrhea, nausea and vomiting, in addition to the first 24 items of the QLQ-OV28 (i.e. all items of the EORTC QLQ-OV28 excluding sexual functioning). The sexual functioning items are excluded as those will not be answered by all patients. The new scale ranges from 0 (high level of functioning / no symptomatology) to 100 (low level of functioning / high symptomatology).

This TOI-QLQ-OV was tested with patient data from the HECTOR study of the standard treatment arm. Reliability was tested for all time points with good results (Chronbach's alpha >0.9, N=550 assessments including EOT and Follow up). A change of 3.9 points from Baseline to about 24 weeks (including a range from 20 to 27 weeks) resulted in a standard deviation of 14.2 within 72 patients (see Table 2 for the assessments at different time points and Table 3 for the differences to Baseline values).

Table 2: TOI-QLQ-OV with data from HECTOR study.

Time point	mean	SD	N
Baseline	32.7	17.6	232
At 12 weeks	36.4	15.0	152
At 24 weeks	40.7	16.5	14

Table 3: TOI-QLQ-OV changes to different time points with data from HECTOR study-

Change from Baseline to…	mean	SD	N
12 weeks	4.5	12.6	135
24 weeks	5.9	11.8	13
24 weeks or end of therapy (20 to 27 weeks)	3.9	14.2	72

4.6 Justification for the selection of the control arm

Carboplatin and paclitaxel therapy for patients with advanced ovarian carcinoma relapsing after six months of previous platinum-based chemotherapy has been evaluated in the ICON4/0VAR 2.2 study [14], in which the addition of a taxane led to a longer PFS (hazard ratio [HR] 0.76, p= .0004) and OS (HR 0.82, p=.02) over a conventional platinum-based chemotherapy in patients with platinum-sensitive, recurrent ovarian cancer.

In another randomized study, Pfisterer et al. [7] confirmed that combination therapy, in this case carboplatin/gemcitabine, prolongs PFS over a platinum single agent. With a median follow-up of 17 months, median PFS was 8.6 months for gemcitabine plus carboplatin vs. 5.8 months for carboplatin alone, HR 0.72, p=.0031. No survival differences were found in this trial.

Also, PLD was proven to be an active agent in second-line therapy for ovarian carcinoma which obtained regulatory approval in both platinum-resistant and platinum-sensitive recurrent ovarian cancer [33]. The combination of PLD plus carboplatin was shown to be safe and active in a phase II trial [34]. A large phase III trial (CALYPSO), comparing carboplatin/PLD vs. carboplatin/paclitaxel showed non inferior PFS results (HR 0.82; median 11.3 months for carboplatin/PLD vs. 9.4 months for carboplatin/paclitaxel) [35] . With a median follow-up of 49 months, also no statistically significant difference was observed between arms in OS (HR = 0.99 (95% confidence interval 0.85, 1.16); log-rank P = 0.94). Median survival times were 30.7 months (carboplatin/PLD) and 33.0 months (carboplatin/paclitaxel) [36].

Therefore, according to the current German S3 Guidelines for treating ovarian cancer, the upon mentioned combination chemotherapies are regarded the standard of care in platinum-sensitive recurrent ovarian carcinomas [12].

4.7 The relevance of this study to current care and benefit-risk assessment

This trial investigates the QoL between trabectedin/PLD vs. the other standard of a carboplatin-based chemotherapy in recurrent ovarian, fallopian tube or primary peritoneal platinum-sensitive cancer. Although platinum-based combination therapies are considered the current standards of care in this setting, long-term toxicities represent huge challenges in platinum-pretreated patients with relapsed cancer. Because most women with recurrent ovarian cancer ultimately die of their cancer, QoL and regimen convenience are as important as efficacy in assessing the role of a treatment combination.

If the concept proves to be effective, this could potentially lead to a new standard of care and patients in the prognostically favorable situation of platinum-sensitive cancer will no further need burdening platinum-based therapy. In palliative cancer therapy, the QoL is one of the most important objectives, besides the prolongation of OS.

Procedures used in this study (such as the chemotherapy, the blood tests and the radiology investigations) are in line with those usually used in the treatment of patients with recurrent ovarian, peritoneal or fallopian tube cancer in routine clinical practice. In terms of the chemotherapy, carboplatin/PLD, carboplatin/gemcitabine, carboplatin/paclitaxel are

recommended chemotherapy regimens by the S3 German Guidelines (highest-level national guidelines in Germany) [12] for platinum-sensitive relapse, as just mentioned above.
Taken together, the risks emerging from participation in this clinical trial are acceptable and the impact of the study results on the future treatment of patients in the given indication.

5 Endpoints

5.1 Efficacy objectives

Primary Endpoint is the observation of change in QoL. This is measured for every patient as the change from Baseline to EOT (3-4 weeks after C6 D1 or, in case of progression, after last D1). The primary QoL measure is the mean score of the previously defined TOI-QLQ-OV (see Section 4.5) between the treatment arms.

The main secondary efficacy objectives are as follows:

- Clinical benefit rate (CR, PR, SD), or PD in patients with measurable disease
- Difference in QoL for all other time points not included in primary endpoint
- Progression-free survival (PFS) defined as the time from randomization to the first occurrence of progression or recurrence, as determined by the investigator using CT criteria, or death from any cause
- Overall survival (OS), defined as the time from randomization to death from any cause
- Time to next medical intervention (e.g. chemotherapy, immunotherapy)

5.2 Safety objectives

The safety objective is to evaluate the safety and tolerability of trabectedin/PLD in patients with platinum sensitive recurrent ovarian, fallopian tube and peritoneal cancer, focusing on adverse events and serious adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

6 Patient Selection

6.1 Inclusion Criteria

1. Women aged ≥ 18 years
2. Patients with histologically confirmed diagnosis of epithelial ovarian cancer, primary peritoneal carcinoma or fallopian tube cancer who received ≥1 prior chemotherapy
3. Patients must be eligible for platin-containing therapy; Patient is defined as platin-sensitive when considered for platin-containing therapy by the investigator. The time frame from end of prior therapy until disease progression alone is not pivotal for study participation. Patients without a platin-containing regimen in the previous line who are also eligible for platin-containing regime are also appropriate for participation
4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2
5. Adequate baseline organ function as defined as
6. Leucocytes > 3.0 x 10^9/l
7. platelet count > 100 x 10^9/l
8. Absolute neutrophil count (ANC) ≥1500/mm^3
9. Haemoglobin ≥ 9 g/dl
10. Alkaline Phosphatase (AP) ≤ 2.5 × ULN (consider hepatic isoenzymes 5 nucleotidase or gamma glutamyl transpeptidase (GGT), if the elevation could be osseous in origin)
11. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN
12. Creatinine-Clearance ≥ 60 ml/min (MDRD formula or Cockroft & Gault formula)
13. Serum creatinine ≤ 1.5 mg/dl
14. Creatine phosphokinase (CPK) ≤ 2.5 × ULN
15. Total bilirubin < ULN
16. Women of childbearing potential should use contraceptives or abstain from heterosexual activity for the course of the study through 6 months after the last dose of study medication or be surgically sterile.
17. Adequate cardiac function defined as left ventricular ejection fraction (LVEF) ≥ 50% as determined by echocardiogram
18. Patients must provide written informed consent prior to performance of study specific procedures or assessments, and must be willing to comply with treatment and follow up assessments and procedures.

6.2 Exclusion Criteria

1. Only malignancies, which influence the prognosis
2. Any unstable or serious concurrent condition (e.g. active infection requiring systemic therapy).
3. Chemotherapy or radiation therapy or tumor embolization within 2 weeks prior to the first dose of study drug or planned during study participation.
4. Patients who have refractory disease. Refractory disease is defined if relapse occurs <4 months after beginning of platin-containing therapy.
5. Hypersensitivity to the active substance or to any of the excipients of study drug
6. Findings from ECG and/or assessment of LVEF which indicate an anthracycline-related cardiotoxic process which contradicts administration of liposomal doxorubicin or trabectedin in accordance with the requirements of the SmPCs.
7. Biological therapy, immunotherapy, hormonal therapy or treatment with an investigational agent within 14 days (for bevacizumab, 30 days) prior to the first dose of study drug.
8. Any condition that is unstable or could jeopardize the safety of the patient and their compliance in the study
9. Participation in another clinical study with experimental therapy within the 30 days before start of and during treatment. Participation in a non-interventional study should be discussed with sponsor and NC beforehand.
10. Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4)
11. Patients who are depending on the sponsor/CRO or investigational site as well as on the investigator.
12. Pregnancy or lactation period, or planning to become pregnant within 7 months after the end of treatment.

7 Patient Recruitment and Randomization

Investigators will recruit patients directly during regular clinical consultation visits in the respective center. All study related investigations and enrolment of patients will only be performed after written consent was collected using the ethics committee approved patient information and consent form (see also chapter 15.4).

Patients fulfilling the inclusion-/exclusion criteria (see Chapter 6 Patient Selection) will be captured online in the eCRF as screening patients to obtain a screening number which is used for identification during the central evaluation process.

Stratification and randomization is performed online in the EDC-System after capturing all necessary data. Only after complete registration of a patient and following randomization sites can start with study therapy.

8 Therapy schema

Patients will receive the following treatment regimen in the study:

Arm A: Trabectedin / PLD:

Dexamethasone 20 mg i.v. 30 minutes before PLD; D1

PLD (30 mg/m^2) in 250 ml G5% i.v. for 1h; D1

Trabectedin (1.1 mg/m^2) in 500 ml NaCl 0.9% i.v for 3h (administration after PLD); D1

The use of central venous access is strongly recommended. To minimize the risk of PLD infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent PLD infusions may be administered over a 1 hour period (see PLD SmPC for specific administration advice).

Repeated every three weeks (qd22), following the treatment schedule.

Arm B: Other standard treatment according to respective SmPC and current literature [1]:

Carboplatin/PLD:

Carboplatin AUC5 in 250 ml G5% i.v. for 1h, D1

PLD (30 mg/m^2) in 250 ml G5% i.v. for 1h, D1

To minimize the risk of PLD infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent PLD infusions may be administered over a 1 hour period (see PLD SmPC for specific administration advice).

Repeated every four weeks (qd29), following the treatment schedule.

–or-

Carboplatin/Gemcitabine:

Carboplatin AUC4 in 250 ml G5% i.v. for 1h, D1;

Gemcitabine 1.000mg/m^2 in 500 ml NaCl 0.9% i.v. as a 30min infusion D1, D8

Repeated every three weeks (qd22), following the treatment schedule.

–or-

Carboplatin/ Paclitaxel:

Carboplatin AUC5 in 250 ml G5% i.v. for 1h; D1

Paclitaxel 175mg/ m^2 in 500 ml NaCl 0.9% i.v for 3h D1

Repeated every three weeks (qd22), following the treatment schedule.

In both arms patients will be treated for 6 cycles (or more in case of clinical benefit, but this extended treatment will not be part of the study) or until PD, unacceptable toxicities or patients wish, whichever occurs first.

Note: The specifications regarding dilutions and used dilutions media mentioned in the therapy scheme are not mandatory to be followed and can be adjusted to local standard of care at sites. The dose of active substances must be observed in order to maintain comparability between sites. The sequence of medication administration in Arm A is binding but for Arm B it can be considered as suggestion.

9 Concomitant Therapy

The current chemotherapy regimens in the protocol are standard regimens, thus the investigators may administer antiemetic therapy according to local guidelines, SmPCs and the most recent MASCC/ESMO antiemetic Guideline. The administration of all types of pain killers and allergic reaction preventing drugs according local guidelines is also permitted.

All patients in Arm A must receive corticosteroids e.g. 20 mg of dexamethasone intravenously 30 minutes prior to PLD; not only as antiemetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional antiemetics (i.e.: 5-HT3-inhibitors) may be administered as needed, but avoid aprepitant, as potent CYP3A4 inhibitor. Intravenous administration through a central venous line is strongly recommended. Caution should be taken if medicinal products associated with rhabdomyolysis (e.g. statins), are administered concomitantly with trabectedin, since the risk of rhabdomyolysis may be increased. For more information about concomitant therapy and trabectedin, please see Section 4.4 (Special warnings and precautions for use) of the SmPC of trabectedin.

10 Criteria for continuation, dose adjustment, overall duration, and termination

10.1 General remarks

Toxicity will be graded according to NCI CTCAE, version 4.0. The dose modification described below is performed according to this grading system. Toxicities of severity grade 1 only will not lead to any dose reduction or cycle delay. The same holds for adverse reactions without any potential of serious or life-threatening complications according to the judgment of the physician (e.g. alopecia). In case of toxicities requiring dose modification, the dose modification should reflect the causal relationship to the respective drug(s). E.g., if the toxicity is unequivocally caused by only one drug, a dose modification of the other drug is not required. If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification. If a dose reduction is performed, the reduced dose level is usually kept throughout the rest of the study without re-escalation. However, investigators can deviate from this

procedure and increase the dose to the previous level if they feel i) that this is in the best interest of the patient and if they ii) do not expect the toxicity to reoccur.

Study treatment will be administered in a clinical treatment setting with emergency equipment and staff who are trained to monitor for and respond to medical emergencies. In case of acute allergic reactions of grade 3 or 4, the causative agent should be discontinued permanently. In case of grade 1 or 2, it is up to the physician to continue treatment without dose modification, if this is in the best interest of the patient.

The study teams will document all actions of dose modifications or treatment delays in the eCRF, including the reason for each action.

10.2 Requirements for chemotherapy administration

Patients will remain on treatment for 6 cycles in the absence of confirmed progression or unacceptable toxicity that is not resolved after applying the appropriate dose reductions. Patients with clinical benefit may continue therapy beyond 6 cycles.

In order to be treated on Day 1 of a new cycle, patients will have to fulfill these entry criteria:

- Leucocytes > 3.0 x 10^9/l
- Platelet count > 100 x 10^9/l
- Absolute neutrophil count (ANC) ≥1500/mm^3
- Haemoglobin ≥ 9 g/dl
- Alkaline Phosphatase (AP) ≤ 2.5 × ULN (consider hepatic isoenzymes 5 nucleotidase or gamma glutamyl transpeptidase (GGT), if the elevation could be osseous in origin)
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN
- Creatinine-Clearance ≥ 60 ml/min (MDRD formula or Cockroft & Gault formula)
- Serum creatinine ≤ 1.5 mg/dl
- Creatine phosphokinase (CPK) ≤ 2.5 × ULN
- Total bilirubin < ULN

If these criteria are not met on Day 1 of a new cycle, treatment administration may be delayed for a maximum of the respective cycle length and reevaluated weekly. The new cycle will start upon recovery of these parameters, according to the same criteria.

A maximum delay of one cycle length is allowed for recovery from drug-related AEs. If toxicities have not recovered within the allowed timeframe, the patient should discontinue treatment. In the event of obvious clinical benefit, the patient may remain on treatment upon agreement with the Sponsor, provided that all parameters have recovered according to the aforementioned criteria.

10.3 Chemotherapy dose adjustment

Dose reductions will be based on the worst drug-related toxicity that occurred since the last dose administration. The criteria for dose delay/reduction in Arm A are defined in Table 4. For Arm B please refer to the respective SmPC. Once a dose has been reduced because of toxicity, there will be no dose re-escalation in subsequent cycles. A maximum of two dose reductions are allowed regardless of the type of toxicity. Study treatment will be permanently discontinued for any patient who requires a third dose reduction.

Arm A: Trabectedin/PLD

Prior to re-treatment, patients must fulfil the criteria defined above. If any of the following events occur at any time between cycles, the dose must be reduced one level, according to Table 4 below, for subsequent cycles:

- Neutropenia: Neutrophile count < 0.5 x 10^9/l lasting for more than 5 days or associated with fever or infections
- Thrombocytopenia: Platelet count < 25 x 10^9/l
- Increase of Bilirubin > ULN and/or alkaline Phosphatase > 2.5 x ULN
- Increase of Aminotransferase (AST or ALT) > 5 x ULN, which has not recovered by D21
- Any other grade 3 or 4 adverse reactions (such as nausea, vomiting, fatigue)

Once a dose has been reduced because of toxicity, dose escalation in the subsequent cycles is not recommended. If any of these toxicities reappear in subsequent cycles in a patient exhibiting clinical benefit, the dose may be further reduced.

Table 4: Arm A dose reduction due to toxicity

Dosing step	PLD	Trabectedin
Dose Level 0 (Starting dose)	30 mg/m^2	1.1 mg/ m^2
Dose Level -1	25 mg/m^2	0.9 mg/ m^2
Dose Level -2	20 mg/m^2	0.75 mg/ m^2

In case of recurrent toxicity after two dose reductions of one of the agents, the other non-reduced compound may be continued for patients with clinical benefit or stop the whole treatment (see section 10.4.3). Upon occurrence of hematologic toxicities as e.g. febrile neutropenia or infection during neutropenia, all center-specific therapeutic and prophylactic actions (e.g. administration of antibiotics and growth factors) should be applied.

In case of acute allergic reactions of grade 3 or 4, the causative agent should be discontinued permanently. In case of grade 1 or 2, it is up to the physician to continue treatment without dose modification, if this is in the best interest of the patient. The study teams will document all actions of dose modifications or treatment delays in the eCRF, including the reason for each action.

Each of the chemotherapeutic agents administered in the course of this study are market approved in Germany and all participating investigators will have broad experience with these medications. Therefore, investigators are permitted to deviate from the recommendations given above in reasonable cases.

10.4 Criteria for study termination

10.4.1 Individual criteria for treatment termination

The reason for treatment termination has to be documented as follows (criteria for termination):

- Treatment completed after 6 cycles
- Progression or relapse of the disease during treatment
- Unacceptable side effects (a maximum delay of one cycle length is allowed for recovery from drug-related AEs)
- Patient’s decision/wish
- Occurrence of other diseases which interfere with study participation (e.g. secondary malignant neoplasms)
- Pregnancy
- Post-operative nutritional problems or post-operative complications

- Other reasons*

* Details will be documented in the eCRF

10.4.2 General criteria for premature termination of the trial

- Unexpected severe toxicity of the study medication
- More effective therapies become available
- Insufficient patient enrollment

10.4.3 Handling premature treatment (whole treatment) termination

If chemotherapy is prematurely discontinued, the patient will be removed from the active study part and will enter the follow-up until 5 years after baseline or end of study.

11 Study drugs

This section provides an overview on the study medication used. It is not intended to replace the careful reading of the summary of product characteristics (SmPC) for each component, which contains details on drug characteristics, storage, application, mode of action and adverse reactions. All substances are market approved in Germany for at least one kind of tumor. Moreover, the used regimens in both arms are standard of care for patients with ovarian recurrent cancer in Germany. Therefore, the protocol requires limited documentation of concomitant medication in the study. If patients receive concomitant medication, the product characteristics need to be checked by the investigator with respect to potential drug interactions. In case of any doubt, the lead principal investigator shall be consulted. The investigator or the pharmaceutical expert in delegation is responsible for the safe storage, preparation, release, and documentation of the study medication with respect to standard procedures and national guidelines. All medication shall be distributed according to the prescription of the investigator.

11.1 Pegylated Liposomal Doxorubicin (PLD)

Commercially available PLD (Caelix®) will be utilized in this study. See the Caelix® Package Insert and SmPC, for more details.

11.2 Trabectedin

Commercially available trabectedin (Yondelis®) will be utilized in this study. Trabectedin is available as a sterile lyophilized product in vials containing 1.0 mg of trabectedin (Yondelis®).

Before lyophilization, sufficient quantities of monopotassium phosphate and phosphoric acid were added to the process solution for pH adjustment. See the Yondelis® Package Insert and SmPC, for more details.

11.3 Carboplatin

Commercially available carboplatin will be utilized in this study, all available products are allowed. Carboplatin will be administered according to the directions of the prescribing information. Dose will be calculated according to Calvert's formula (14) to obtain an AUC = 5 mg/ml*min for Group A. For more details see the carboplatin Package Insert and http://www.drugs.com/pro/carboplatin.html.

11.4 Gemcitabine

Commercially available gemcitabine will be utilized in this study, all available products are allowed. See the gemcitabine Package Insert, for more details.

11.5 Paclitaxel

Commercially available paclitaxel will be utilized in this study, all available products are allowed. See the paclitaxel Package Insert, for more details.

12 Treatment schedule and schedule of assessments

Table 4: Treatment Schedule.

	Screening (day)	**Treatment cycles 1-6[1]**	**End of study treatment**	**FU-1 [13]**
	- 14 to 0	**D1**[5]	3-4 weeks after C6 D1 or 3-4 weeks after last D1 (progression)	Starting 6M after BL (C1 D1), every 6 months[14]
Informed consent	X			
Body height	X			
Concomitant diseases	X			
ß-HCG-Pregnancy test (for women with childbearing potential)	X			
Physical examination /ECOG	X	X	X	
Charlson Score	X		X	
ECG[11], Echocardiogram [2, 11, 6]	X		X	
Weight	X	X	X	
Randomization	X			
Calculation of medication dose[3]		X[5]		
Laboratory examinations[8] Blood count[9] (before every cycle)	X	X[12]	X	
Tumor evaluation (using always the same method), CA 125[10,]	X[6]	TO BE PERFORMED AS STANDARD OF CARE		
Adverse events		X	X[7]	
Concomitant medication	X	X	X	
Quality of Life[4]: EORTC QLQ-C30 and QLQ-OV28	(X)[15]	X[15]	X	X
NRS 2002	X		X	
Documentation of Follow-up therapy, PFS and OS if applicable			X	X

[1]Therapy will continue for 6 cycles or until one of the discontinuation criteria (Section 10.4.1) applies.

[2] In case of anomalies further examinations during therapy as clinically indicated.

[3] At day 1 of each therapy application

[4] Prior to first application of each therapy cycle

[5] For gemcitabine also D8 to be documented

[6] CT and Echocardiogram to be performed as standard of care and can be older than 14 days before treatment if investigator considers this as acceptable.

[7] AEs and SAEs to be documented until 30days after EoT or until start of new antitumor therapy, whatever occurs first

[8] Laboratory: Serum: Creatinine, ALT, AST, AP, total bilirubin, albumin, CPK

[9] Blood count: Haemoglobin, white blood cell count with differential (total neutrophil count including lymphocyte, monocyte, eosinophil and basophil counts), platelets

[10] Evaluation of CA 125 may not be required (Investigators decision)

[11] Findings from ECG and/or assessment of LVEF which indicate an anthracycline-related cardiotoxic process which contradicts administration of PLD or trabectedin in accordance with the requirements of the SmPCs is an Exclusion criteria.

[12] Trabectedin: Additional monitoring of haematological parameters bilirubin, alkaline phosphatase, aminotransferases and CPK should occur weekly during the first two cycles of therapy, and at least once between treatments in subsequent cycles.

[13] If EOT or other visits are planned 6 month (± 4 weeks) after Baseline, a separate visit for first FU is not necessary as long as all examinations and QOL assessments were performed.

[14] until 5 years after Baseline or end of study

[15] Quality of Life Assessments can be obtained up to 15 days before Baseline Visit.

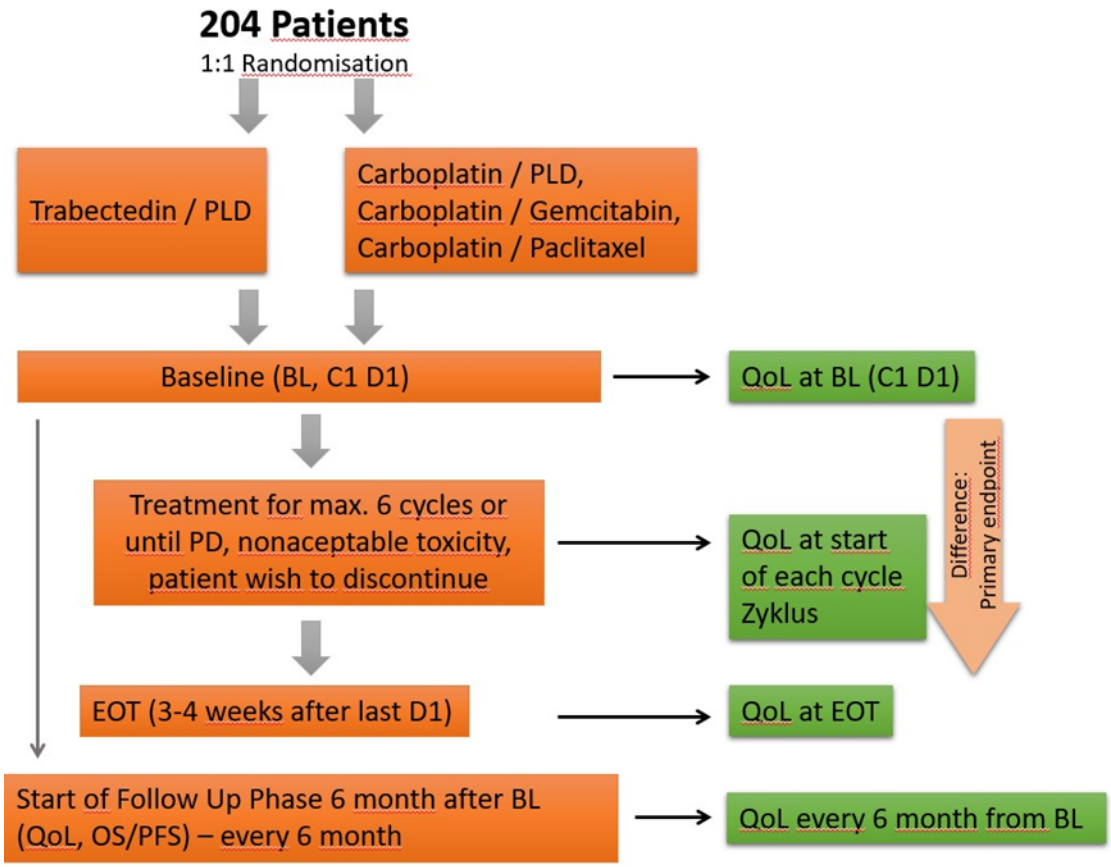

Figure 1: Study Scheme.

12.1 Screening/baseline examinations and randomization

Upon reception of patients' informed consent the following parameters have to be performed:

Within a maximum timeframe of 14 days before start of therapy
(Timeframe of echocardiogram and CT/MRI can be prolonged as per investigator decision)

- Informed consent, must be signed before any trial specific assessments take place
- Medical history, body height (height can be older), concomitant diseases, preexisting toxicities or symptoms
- Charlson score (Appendix 21.1)
- Tumor evaluation
    - Mandatory: Tumor assessment/staging (CT/MRI scan of Chest and Abdomen including pelvic region)
    - Recommended: CA 125
    - Histological type
    - BRCA-mutation status
- ß-HCG-Pregnancy test (for women with childbearing potential)
- ECOG (see table in section 21.1) and Physical examination , in case of anomalies further examinations during therapy as clinically indicated
- EKG (Electrocardiography) and Echocardiogram, in case of anomalies further examinations during therapy as clinically indicated. Findings from ECG and/or assessment of LVEF which indicate an anthracycline-related cardiotoxic process which contradicts administration of liposomal doxorubicin or trabectedin in accordance with the requirements of the SmPCs is an Exclusion criteria.
- Weight
- Calculation of medication dose, at day 1 of each therapy application
- Laboratory examinations (before every cycle): Serum: Creatinine, ALT, AST, AP, total bilirubin, albumin, CPK
- Blood count (before every cycle): Haemoglobin, white blood cell count with differential (absolute neutrophil count including lymphocyte, monocyte, eosinophil and basophil counts), platelets
- Concomitant medication
- Quality of Life: EORTC QLQ-C30 and QLQ-OV 28 as baseline assessments; those can be obtained up to 14 days before first treatment (Baseline), as this is a requirement for randomization
- NRS 2002 (see table in section 21.3)

- Check of in-/exclusion criteria

Important note: All examinations of CT or MRI are part of routine clinical practice. It is important to note that the study protocol does not limit the examinations to these mentioned above. The investigator shall perform all other/additional routine or center-specific examinations relevant for the safety of the patient or for any other planned procedures.

Patients will be stratified according to surgery for relapse (tumor free vs. not tumor free resection) vs. no surgery in the same setting, and age (< 75 years vs. ≥ 75 years).

12.2 Treatment in Arm A (Trabectedin/PLD)

Patients in Arm A receive 6 3-week cycles of trabectedin/PLD as described in Chapter 8.

12.3 Treatment in Arm B (Carboplatin/PLD, carboplatin/gemcitabine, carboplatin/paclitaxel)

Patients in Arm B receive 6 cycles of carboplatin/PLD, carboplatin/gemcitabine, or carboplatin/paclitaxel as given in respective SmPC.

12.4 General examinations before start of a new chemotherapy cycle (cycle 1*-6)

- ECOG and Physical examination (incl. blood pressure)
- Weight
- Calculation of medication dose, at day 1 of each therapy application
- Laboratory examinations (before every cycle): Serum: Creatinine, ALT, AST, AP, total bilirubin, albumin, CPK
- Blood count (before every cycle): Haemoglobin, white blood cell count with differential (total neutrophil count including lymphocyte, monocyte, eosinophil and basophil counts), platelets

  For Trabectedin additional monitoring of haematological parameters bilirubin, alkaline phosphatase, aminotransferases and CPK should occur weekly during the first two cycles of therapy, and at least once between treatments in subsequent cycles.
- Concomitant medication
- Quality of Life: EORTC QLQ-C30 and QLQ-OV 28
- Adverse Events: Assessment of toxicities and symptoms
- Tumor evaluation:
  - CT /MRI as standard of care
  - Recommended: CA 125

Important note: These examinations are required by study protocol. All examinations are part of routine clinical practice. It is important to note that the study protocol does not limit the examinations to these mentioned above. The investigator shall perform all other/additional routine or center-specific examinations relevant for the safety of the patient or for any other planned procedures.

* Assessments already performed for Screening do not have to be repeated for Cycle 1 D1 if not longer than 7 days ago.

12.5 End of study treatment (EOT)

Regular end of study treatment (EOT) is 3-4 weeks after day 1 of Cycle 6 or, in case of progression/relapse, 3-4 weeks after day 1 of last treatment Cycle. EOT means end of the active part of the trial. Follow-up for QoL and PFS/OS should continue.

- Tumor evaluation:
    - CT /MRI as standard of care
    - Recommended: CA 125
- ECOG and Physical examination
- ECG (Electrocardiography) and Echocardiogram, in case of anomalies further examinations during therapy as clinically indicated
- Weight
- Laboratory examinations: Serum: Creatinine, ALT, AST, AP, total bilirubin, albumin, CPK
- Blood count: Haemoglobin, white blood cell count with differential (total neutrophil count including lymphocyte, monocyte, eosinophil and basophil counts), platelets
- Adverse Events: Assessment of toxicities and symptoms. Serious adverse events (SAE) reporting has to be maintained until 4 weeks after EOT!
- Concomitant medication
- Quality of Life: EORTC QLQ-C30 and QLQ-OV28
- Charlson score (Appendix 21.1)
- NRS 2002 (see tables in section 21.3)
- Documentation of the follow-up therapy, PFS and OS if applicable

NOTE: Tumor assessment using CT/MRI are not a mandatory part of the EOT. The frequency of the CT or MRI is a recommendation of the protocol experts but sites can follow their local standard of care. A change from CT into MRI in the follow up period is possible at any time.

12.6 Follow-up

- Centers will perform follow-up starting 6 months after baseline. If EOT or other visits are planned 6 month (± 4 weeks) after Baseline, a separate visit for first FU is not necessary as long as all examinations and QOL assessments were performed. This phase ends 5 years after Baseline or when the study will be terminated, which is defined as the time point when the last patient has completed the mandatory 1 year follow-up. Follow-up will be performed every 6 months and includes the following parameters:
- Tumor evaluation (until progression / relapse):
    - CT /MRI as standard of care
    - Recommended: CA 125
- Quality of Life: EORTC QLQ-C30 and QLQ-OV28
- Documentation of the follow-up therapy, PFS (until progression/relapse) and OS, if applicable
- Adverse Events (until progression/relapse): Assessment of toxicities and symptoms. Serious adverse events (SAE) reporting has to be maintained until 4 weeks after EOT!

This phase ends 5 years after Baseline or when the study will be terminated, which is defined as the time point when the last patient has completed 1year follow-up.

<u>After progression/relapse of the disease:</u>
Progression/Relapse should be confirmed by radiological imaging, such as magnetic resonance imaging (MRI), computed tomography (CT) scan; CA 125 rise not supported by radiological evidence of disease is not accepted as criteria for defining progression.
After Progression/Relapse patient will enter into the follow-up phase, if she is not already in this phase. Further PFS documentation after this progression is not necessary. Quality of Life assessments, follow-up therapy and OS will be continued.

After progression/relapse information about disease status, survival and for QoL assessments may be requested from the treating physician via telephone every 6 months, if the patient gives her consent to this procedure. This can be performed by any means possible (e.g. patient visit,

telephone contact, and mail for QoL assessments). AEs and SAEs to be documented until 30 days after end of study treatment or until start of new antitumor therapy, whatever occurs first.

12.7 Patient's care after end of study

After the end of the study, instructions of Section 10.4.3 apply. The investigators of the study are experienced gynecological or medical oncologists who treat patients in routine clinical practice. Therefore, the investigators are responsible for the further treatment of the patient after the end of the study for disease progression. The investigators shall support and advice the patient and – if required – help to organize appointments with other specialized physicians.

13 Safety

13.1 Definitions

13.1.1 Adverse event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment [Dir 2001/20/EC Art 2(m)]. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following special situations also should be considered AE, but only when they lead to an adverse drug reaction:

- Drug overdose
- Drug abuse
- Drug misuse
- Drug interactions
- Drug dependency
- Exposure in uterus

Any event involving adverse drug reactions, illnesses with onset during the study or exacerbations of pre-existing illnesses should be recorded including but not limited to clinically significant changes in physical examination findings and abnormal objective test findings (e.g., CT, ECG). The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- The test result is associated with clinically significant symptoms, and/or

- The test result leads to a change in the study dosing or discontinuation from the clinical trial, significant additional concomitant drug treatment or other therapy, and/or
- The test result leads to any of the outcomes included in the definition of a SAE, and/or
- The test result is considered to be an AE by the investigator.

13.1.2 Serious adverse event (SAE)

A serious adverse event is any adverse experience occurring at any dose that suggests a significant hazard to the patient and includes any event that:

- is fatal
- is life-threatening (see clarification below)
- requires or prolongs hospitalization
- results in persistent or significant disability or incapacity
- is a congenital abnormality/birth defect
- is medically significant representing an important medical event (see clarification below)

In contrast to routine safety assessments, SAE are monitored continuously.

Life-threatening in this context refers to an adverse 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.

Adverse events reported from clinical trials associated with **hospitalization** or prolongation of hospitalization are considered serious and must be reported as a SAE unless exempted from SAE reporting (see section 13.5.2). Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the medical floor to an intensive care unit, medical floor to an infectious disease unit, etc).

Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the initial admission, as determined by the Investigator or treating physician.

Hospitalizations that do not meet criteria for SAE reporting are:

a) Reasons described in protocol [e.g., investigational medicinal product (IMP) administration, protocol-required intervention/investigations, etc]. However, events

requiring hospitalizations or prolongation of hospitalization as a result of a complication of therapy administration or clinical trial procedures will be reported as SAEs.

b) Hospitalization or prolonged hospitalization for technical, administrative, practical or social reasons, in absence of an AE.
c) Pre-planned hospitalizations: Any pre-planned surgery or procedure must be documented in the source documentation. Only if the pre-planned surgery needs to be performed earlier due to a worsening of the condition, should this event (worsened condition) be reported as a SAE.
d) An emergency visit due to an accident where the patient is treated and discharged.
e) When the patient is held 24 hours for observation and finally is not admitted.
f) Planned treatments at sites not associated to a hospital and generally considered as minor surgical procedures (i.e., laser eye surgery, arthroscopy, etc).

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

Disability means a substantial disruption of a person´s ability to conduct normal life´s functions.

A **medically significant** event: Any adverse event may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition. As guidance for determination of important medical events refer to the "WHO Adverse Reaction Terminology – Critical Terms List". These terms either refer to or might be indicative of a serious disease state. In this study protocol, the definition of medically significant event explicitly includes the suspected transmission via a medicinal product of an infectious agent. Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious adverse events, such as important medical events that might not be

immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.

13.2 Relationship of an adverse event to the study drug(s)

The causal relationship to study drug is determined by the investigators and should be used to assess all adverse events (AE). The causal relationship can be one of the following definitions:

> **Related:** There is a reasonable causal relationship between study drug administration and the AE.
>
> **Not related:** There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

In case of a missing causality assessment in the CRF or SAE reporting form, the event will be regarded as "probably related" unless further specified.

A serious ADR (SADR) is an adverse drug reaction that meets the definition of a serious event (provided above).

13.3 Severity of an adverse event

The severity of an adverse event will be assessed according to the National Cancer Institute CTC scale (version 4.0).

The following definitions will be used for adverse events that are not specified in the CTC scale:

- Mild (grade 1):
  The adverse event is noticeable to the patient; it does not require discontinuation of the dose of the study agent but may require additional therapy.
- Moderate (grade 2):
  The adverse event interferes with the patient's daily activities; it may require additional therapy or reduction of the dose of the study agent, but does not require discontinuation of the study agent.
- Severe (grade 3):
  The adverse event is intolerable and necessitates additional therapy or discontinuing the dose of the study agent.

- Life-threatening (grade 4):

  The patient is at immediate risk of death from the adverse event.

- Fatal (grade 5):

  The adverse event resulted in death of the patient.

13.4 Unexpected adverse event / SUSAR

An unexpected adverse event is any adverse drug event, the specificity or severity of which is not consistent with the current versions of the SmPCs of PLD and the standard platinum based therapy (see Table 5), respectively. Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected adverse events. An event more specific or more severe than described in the respective SmPC would be considered "unexpected".

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction, the nature, or severity of which is not consistent with the current SmPC. All suspected adverse reactions related to the IMP which occur in this trial and are both unexpected and serious (SUSARs) are subject to expedited reporting.

SAEs which are "related" and "unexpected" meet the criteria for SUSAR.

Table 5: SmPCs of reference products

Drug	Reference product(s*)
PLD	Caelyx
Trabectedin	Yondelis
Carboplatin	e.g. Carboplatin onkovis; Carboplatin Hexal; Ribocarb- L; Neocarbo; Carboplatin Bendalis; Carboplatin Kabi; Carboplatin – GRY
Gemcitabine	e.g. Gemcitabin–GRY; Gemcitabin Kabi; Gemcitabin Oncovis; Gemcitabine–HAEMATO; Gemzar; Gemedac; Gemcitabin Hexal; Gemci Cell
Paclitaxel	e.g. Paclitaxel Hospira; Paclitaxel Haematom; Paclitaxel oncovis; Paclitaxel stragen; Paclitaxel-GRY; Celltaxel; Neotaxan; Paclitaxel Hexal; Ribotax; Taxomedac

* If several generic products are available only for the underlined product the most recent SmPC will be made available to sites.

13.5 Reporting procedures

13.5.1 Reporting of Adverse Events (serious and non-serious)

All adverse events occurring during the study must be recorded in the patient's electronic case report form (eCRF).

The Sponsor will collect AEs from the date of first administration of a study drug/IMP and until 30 days after administration of the last dose of study drug/IMP or until the start of a new antitumor therapy, whichever occurs first. All AEs suspected to be related to study drug/IMP must be followed after the time of therapy discontinuation until the event or its sequelae resolve or until symptoms stabilization.

All adverse events must be recorded using medical terminology. Whenever possible the Investigator will record the main diagnosis instead of the signs and symptoms normally included in the diagnoses.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and fatal OR grades 1 – 5, will be used.

The occurrence of adverse events should be evaluated by non-directive questioning of the patient at each visit during the study. Adverse events may also be identified when patients referencing to them during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- the grade of severity according to CTCAE version 4.0 (grade 1 – 5)
- its duration (start and end dates or if ongoing at final exam)
- its relationship to the study drug(s) (see section 13.6)
- the action taken (study drug dosage not changed; study drug dosage reduced; study drug temporarily interrupted; study drug permanently withdrawn due to this adverse event*; concomitant medication given*; non-drug therapy given*; hospitalization/ prolonged hospitalization*; not applicable*; unknown)
- the outcome (fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, deteriorating, unknown)
- whether it is a serious adverse event (SAE) (see chapter 13.1.2)

***** Will be collected for serious adverse events only.

13.5.2 Reporting of Serious Adverse Events

All **serious** adverse events (SAEs, irrespective of suspected causal relationship), including deaths, which occur after the patient has given written informed consent and up to 30 days after

the last dose of study treatment was administered, or until the start of a new antitumor therapy, whichever occurs first, must be reported in writing to the Institut für Klinische Krebsforschung IKF GmbH (IKF) for review/re-evaluation within 24 hours of Investigator and/or study center receiving notification of any "serious" adverse event experienced by a patient, using the study "Serious Adverse Event" form. The IKF will notify the sponsor / other persons involved.
Beyond this period of time, only those SAEs suspected to be related to the IMP will be collected. Nonetheless, the Sponsor will evaluate any safety information related to the clinical trial that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

All SAEs suspected to be related to the study medication/IMP must be followed until the event or its sequelae resolve or until symptoms stabilization.

Tumor progression or appearance of new tumor lesions MUST NOT be reported as a SAE. Events of "disease progression" (including signs and symptoms of progression) even if they fulfill any seriousness criterion (i.e., fatal, requiring hospitalization, etc) are exempted from reporting and will only be reported in the applicable section of the CRF.
Death, as such, is the outcome of a SAE and should not be reported as the SAE term itself. Instead the cause of death should be recorded as the SAE term. When available, the autopsy report will be provided to the Sponsor.

Reports have to be sent via fax or eMail to:

Institut für Klinische Krebsforschung IKF GmbHam Krankenhaus Nordwest Steinbacher Hohl 2-26
60488 Frankfurt
Germany

Fax: +49 69 / 7601-3655
eMail: SAE@ikf-khnw.de

The study´s medical expert will perform review and second assessment of every SAE within three calendar days. Serious adverse events with at least possible relation to the study drug(s) and assessed unexpected based on the information contained in the relevant SmPC(s) (Fachinformation) are reported as Suspected Unexpected Serious Adverse Reaction (SUSAR) to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements.
An annual safety report (DSUR, developmental safety update report) will be submitted by the

Sponsor to the competent IRB and to the competent authority (BfArM).
Patients experiencing adverse events should be followed up carefully until the condition resolves, and every effort should be made to clarify the underlying cause. Follow-up information related to serious adverse events and reportable deaths must be submitted to the sponsor by telephone, fax, or e-mail as soon as relevant data become available.

13.6 Reporting Pregnancy Cases Occurred within the Clinical Trial

Pregnancy and suspected pregnancy (including a positive pregnancy test regardless of age or diseases state) of a female patient occurring while the patient is on study drug, or within three months from the patient´s discontinuation visit, are considered immediately reportable events.

The Investigator will report the following events immediately and always within 24 hours from first knowledge using the study specific Pregnancy Report Form:

- Any occurrence of a pregnancy where any kind of exposure to the study medication/IMP is suspected.
- Possible exposure of a pregnant woman (this could involve a pregnant female who came in contact with the clinical trial study medication/IMP).
- All reports of elevated/questionable or indeterminate beta human chorionic gonadotropins (β-hCGs).

Immediately after detecting a case of suspected pregnancy in a female clinical trial patient, the decision on her continued participation in the clinical trial will be jointly taken by the trial patient, the Investigator and the Sponsor, with the patient´s best interest in mind. A decision to continue the pregnancy will require immediate withdrawal from the trial.

Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Institut für Klinische Krebsforschung IKF GmbH (IKF) immediately by e-mail or facsimile using the Pregnancy Report Form.

The Investigator will follow the pregnancy until its outcome, and should follow the newborn up to 2 years after the delivery, and must notify the Institut für Klinische Krebsforschung IKF GmbH (IKF) (of the outcome of the pregnancy and of the newborn) within 24 hours of first knowledge as a follow-up to the initial report.

For any event during the pregnancy which meets a seriousness criterion (including fetal or neonatal death or congenital anomaly) the Investigator will also follow the procedures for reporting SAEs.

All neonatal deaths that occur within 30 days of birth should be reported, regardless to the causality, as SAEs. In addition, any infant death at any time thereafter that the Investigator suspects is related to the exposure to the study drug/IMP should also be reported to the Institut für Klinische Krebsforschung IKF GmbH (IKF) by e-mail or facsimile within 24 hours of the Investigators´ knowledge of the event.

14 Quality control and quality assurance

14.1 Quality assurance

The Standard Operating Procedures (SOPs) of the CRO are used for the delegated processes. For all other processes, SOPs of the Sponsor apply.

14.2 Standardization and randomization

The evaluation criteria of study endpoints are identical for all participating centers. Each center has to file its normal ranges for hematology and blood chemistry in the investigator site file (ISF). The respective laboratory institutions have participated in an appropriate quality assurance program. All certificates for these inter-laboratory comparisons in ring trials (German „Ringversuchzertifikate“) have to be filed in the ISF during the duration of the trial.

Toxicity is recorded in a standardized way according to the NCI CTC criteria version 4.0 for categorization and grading.

Patients will be stratified by two parameters: Patients will be stratified by surgery for relapse (tumor free vs. not tumor free resection) vs. no surgery in the same setting, and age (< 75 years vs. ≥ 75 years) and will be randomized 1:1 into one of the study arms. The randomization plan will be generated by a validated SAS program and underlies strict access control. The allocation of the patient numbers and treatment groups will be coordinated by IWRS system integrated in the eCRF.

14.3 Audits / inspections

In case of an audit by the sponsor or an appropriate authority, the investigator will make all relevant documents available. If an audit visit by a regional authority is announced, the respective center should inform the sponsor, CRO and coordinating investigator as early as possible in order to allow for an appropriate preparation and support.

14.4 Monitoring

It is understood that an outside monitor and other authorized personnel may contact and visit the investigator, and that they will be allowed direct access to source data/documents for trial-related monitoring, audits, IRB review, and regulatory inspection. Direct access is defined as permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. All reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and Sponsor's proprietary information will be exercised (Guideline for Good Clinical Practice, ICH Harmonized Tripartite Guideline, adopted July 1996: Chapter 5.15.1 and 1.21, respectively).

It is the monitor's responsibility to inspect the case report forms at regular intervals throughout the trial to verify adherence to the protocol: the completeness, accuracy, and consistency of the data; and adherence to Good Clinical Practice guidelines. The monitor should have access to patient charts, laboratory reports, and other patient records needed to verify the entries on the case report forms. Where local rules do not allow direct access to the source data, the monitor will verify entries in the case report form by asking direct questions of a person or persons with authorized access to the source data. The Investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

A monitoring plan with relevant details is issued prior to the trial.

14.5 Plausibility check, data cleaning and coding

Qualified members of the CRO regularly perform plausibility checks and data cleaning according to the data-cleaning plan. Some of the raw data of the eCRF also needs coding (e.g. toxicities) according to the data-coding plan. Before data base closure, data cleaning and manual plausibility checks have to be performed for the relevant contents (defined by the data-cleaning plan), and all open questions have to be resolved.

14.6 Data management

Data collection and capture, as well as creation of queries will be performed under the responsibility of the CRO. Data analysis will be performed by the responsible study biostatistician. Good Clinical Practice (GCP)-compliant handling of the data is secured by adequate SOPs. Archiving of data and results electronically recorded will be at least 10 years after the end of this study (according to legal guidelines).

14.7 Information on study drugs to trial investigators

Each of the drugs administered in the course of this study are market approved in Germany and all participating investigators will have broad experience with these medications. Therefore, investigators will be provided with all relevant and up-to-date clinical and pre-clinical information (SmPC / Fachinformation) on one example product for each component of the chemotherapeutic regimen. It is the responsibility of the investigator to have at hand the most recent information on the specific medicinal product used during local routine at the respective study site.

If additional data on the study drugs with major relevance for the conduct of the study become evident, they will be distributed to the investigators.

15 Regulatory and ethical obligations

15.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the AMG (Arzneimittelgesetz), the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki from 1996.

Before recruitment into the clinical trial, each patient will be informed that participation in the study is completely voluntary, and that she may withdraw her participation in the trial at any time without any declaration of reasons. This will not lead to any disadvantage for the respective patient. If the withdrawal is caused by an adverse drug event, the patient should inform the investigator about this fact.

15.2 Registration and request for authorization of the trial

According to GCP-V, the trial has to be submitted to and to be authorized/approved by the competent authority (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) and the competent ethics committee responsible for the trial (“federführende Ethikkommission”). Additionally, all local ethics committees responsible for individual trial sites have to give their opinion to the competent ethics committee. The respective local authorities will be informed about the trial and the participation by the individual trial sites.

The competent authority and the competent ethics committee will be informed on the course of the study with respect to safety aspects to be announced as well as on the termination of the trial and the trial results according to GCP-V.

15.3 Institutional review board / ethics committee

Prior to start of the trial the study protocol and all additionally relevant documents will be sent to the competent ethics committee by the sponsor or its delegate in order to receive the committee's opinion. The trial is only allowed to start after a positive vote of the ethics committee has been received. During the course of the study the Sponsor will inform the ethical committee about all amendments to the study protocol as well as on all SUSARs emerging from the trial according to GCP-V. In addition, the competent ethical committee will receive a DSUR once a year.

All subsequent protocol amendments and amendments to the informed consent form will be submitted to the competent ethics committee to obtain an updated vote before implementation of the changes. Serious or unexpected adverse events occurring during the trial likely to affect the safety of the subjects or the conduct of the trial will also be reported to the ethics committee.

In addition, the competent ethical committee will be informed on the course of the study with respect to the termination of the trial and the trial results.

15.4 Informed consent

It is the investigator's responsibility to obtain witnessed written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any study drug is administered. The patient should be given a copy of the informed consent documentation. The wet ink copy of the signed and dated informed consent must be retained in the institution's records, and is subject to inspection by representatives of the Sponsor or representatives from regulatory agencies.

15.5 Insurance

A clinical trials insurance will be contracted before submission of the study to the relevant authorities. A copy of the confirmation and the conditions of the insurance will be handed out to every study participant together with the informed consent form.

15.6 Patient confidentiality

The investigator must ensure that the patient's privacy is maintained. A patient should only be described by her year of birth and patient number on the case report forms and on other documents submitted to the Sponsor (pseudonymization). The investigator should keep documents that are not submitted to the Sponsor (e.g. signed informed consent form) in a strictly confidential file.

The investigator shall permit the Sponsor and authorized representatives of regulatory agencies to review the portion of the patient's medical record that is directly related to the study. The patient must be informed that his or her records will be reviewed in this manner as a part of the informed consent form.

16 Statistical design

16.1 General considerations

The present trial is designed as a prospective, multi-centre randomized phase IV study which aims at assessing the difference in QoL in patients treated with trabectedin/PLD vs. standard platinum-based combination therapies. QoL will be measured by TOI-QLQ-OV as an indicator of the overall burden of chemotherapy. In addition, several indicators of therapeutic efficacy will be summarized and the safety will be reviewed.

16.2 Sample size calculation

The primary objective of this study is to evaluate the overall burden of the therapy. Based on experience from our study HECTOR (NOGGO-R9, AGO Ovar 2.12 [31]) the TOI-QLQ-OV can be used as an indicator of the overall burden with a good reliability (Chronbach´s alpha >0.9). A relevant between-arm difference of the mean TOI-QLQ-OV-change per patient score should be at least 8 points (assuming a standard deviation of 14.2 points). 68 evaluable patients are needed in each treatment arm in order to be able to detect an 8 points difference in QoL with a two-sided significance level of 5 % and a statistical power of 90 %, based on the assumption that the standard deviation of the response variable is 14.2. Assuming a dropout rate of one third, a total of 204 patients have to be randomized.

16.3 Study Duration

The recruitment is planned to last 52 months (204 patients in 20 German sites), expecting approx. 3 patients per site and year. First patient in will be around Q3 2017.

The treatment period per patient is 18-24 weeks with a follow-up of 1 year after last patient in or 5 years after BL, whichever occurs first. This will be reflected in the patient's informed consent.

16.4 Efficacy parameters

QoL will be measured by the TOI-QLQ-OV. For the primary endpoint the difference of the changes from Baseline (assessed up to 14 days before Baseline visit) to EOT (3-4 weeks after

C6 D1 or, in case of progression/relapse, 3-4 weeks after day 1 of last treatment Cycle) will be used. The differences of changes from Baseline to other time points will be secondary outcomes.

Other secondary outcomes are OS, which will be measured as time from randomization to death of any cause. PFS will be measured as time from randomization until disease progression, disease recurrence after surgery or death of any cause.

Survival and survival rates for the different time points will be determined using the Kaplan-Meier analysis of OS and PFS. Adverse events will be recorded and graded according to version 4.0 of National Cancer Institute Common Toxicity Criteria (NCI-CTC). Peripheral sensitive neuropathy is graded according to a platinum-specific scale. Percentages of toxic effects, serious adverse events and complications will be compared between arms using the Fisher´s exact test.

16.5 Analysis

Prior to final analysis, we will perform data verification with respect to completeness and plausibility (data cleaning). Inconsistencies and mistakes will be clarified with the study centers and will be removed. The data cleaning process starts soon after first patients are enrolled and monitored. Major protocol violations and special cases will be listed. Finally, a conference with coordinating investigator, statistician, and other involved persons of the study will discuss and define the statistical analysis plan and the handling of special cases and major violations. In this conference also those violations will be defined, which will result in the exclusion of the Per protocol-population or even from the Efficacy population (see following section). During the discussion of protocol violations, the cases were blinded with respect to the therapy arm of each case to the members of the above-mentioned committees.

The primary efficacy analysis will include all randomized patients with at least a QoL Score at baseline and EOT, with patients grouped according to the treatment assigned at randomization.

16.5.1 Study populations for the analysis

The following data sets for analysis are defined:

Efficacy Population (EP)

The efficacy population (EP) includes all patients who were randomized and have evaluable QoL assessments at baseline and EOT. Treatment assignment is based on the randomized treatment (primary population). The EP is used for the primary efficacy analysis on QoL.

Intent-to-treat population (ITT)

The intent-to-treat (ITT) population includes all patients who were randomized. Treatment assignment is based on the randomized treatment (primary population).

The ITT population is the primary population for the analysis of the patient's characteristics, and all other efficacy endpoints such as PFS, OS and objective response.

Per protocol (PP) population

This population will include all randomized patients who fulfill major inclusion and exclusion criteria and receive at least one cycle of the treatment. Treatment assignment is based on the treatment actually received.

Safety analysis set

The safety population for chemotherapy related toxicity comprises all patients who received at least one cycle of any component of carboplatin or trabectedin.

Several subgroup analyses including but not limited to BRCA-mutation (yes/no), surgery performed (yes/no), tumor rest (yes/no), age and line of chemotherapy are planned. Further details will be specified in the statistical analysis plan (SAP).

16.5.2 Statistical methods for the analysis

The primary endpoint will be analysed by general linear models for paired samples.

All secondary endpoints, such as baseline and therapy-related data, will be evaluated in an explorative or descriptive manner, providing means, medians, ranges, standard deviations and/or confidence intervals. If p values are calculated (e.g. in subgroup comparisons or across treatment arms), they will be interpreted exploratory. Usually, no error adjustment for multiple testing will be performed. Thus the p values will reflect the comparison-wise error and not the experiment-wise error. All p values will be two-sided if not stated otherwise. The statistical

methods described in this section are suited for the data and distributions usually expected in this type of trials. The suitability will be checked after data entry. If necessary, the statistical method will be modified accordingly.

Efficacy, toxicity and other event rates are calculated, providing confidence intervals. In case of comparison between patient groups, these rates will be analyzed by Fisher's exact test or chi^2 test, respectively.

Event related data like PFS, time to progression, duration of response and OS time will be estimated by the Kaplan Meier product limit method and compared using the logrank test. For the median values of PFS or OS the 95 % confidence interval will be calculated. Multivariate analyses may be performed by suitable regression models (proportional hazard regression model, logistic regression).

The statistical tests, except where otherwise stated, are carried out with a two-sided significance level of 5 %. The analyses are carried out using current versions of IBM SPSS Statistics or R.

Further details of the planned procedure and specific analyses will be defined in the statistical analysis plan, latest prior to locking the database.

16.6 Methods against bias

Patients will be randomly assigned to one of the treatment arms and stratified by important prognostic factors. Multivariate analyses will be applied whenever appropriate to evaluate the effect of confounding factors. The analysis will be performed according to the EP, but we will perform diverse additional sensitivity analyses, specified in the final SAP.

17 Data management

17.1 Data collection

Designated investigator staff will enter the data required by the protocol into the electronic case report forms (eCRF). These persons will not be given access to the EDC (electronic data capture) system until they have been adequately trained. Automatic validation during data entry will check for data discrepancies and, by generating appropriate error messages, allow these data to be confirmed or corrected. The investigator must certify that the data entered into the eCRF are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the study site.

In case of technical problems a paper CRF is available. All forms must be identified with patient pseudonym, date of the observation, and center number. Paper forms will be completed using a black ballpoint pen, and entries must be legible. Errors should be crossed by a single line but

not obliterated, the correction inserted, and the change initialed and dated by the investigator or an authorized member of the study staff.

17.2 Confidentiality

All patient-related data are recorded in a pseudonymized way. Each patient is unequivocally identified by a trial subject number, attributed at recruitment into the study. The investigator has to keep a patient identification log, including the full name and address of the subject and eventually additional relevant personal data.

17.3 Investigator site file

Each participating trial site will file relevant documents (protocol, CVs, approvals of the authorities etc.) and trial related correspondence in the investigator site file (ISF).

18 Funding of the study and responsibilities

18.1 Financing

This study is an investigator-initiated trial (IIT). It is based on the idea and conception of the lead coordinating investigator (LKP). PharmaMar has provided a research grant supporting the conduct of the study. There will be a remuneration of the investigators for an enrolled and fully documented patient. The breakdown of this sum will be explained in the investigator´s contract. No study medication will be provided.

18.2 Responsibilities

The NOGGO e.V. Augustenburger Platz 1, 13353 Berlin is the Sponsor of the study according to German Law (AMG) and represents therefore the legal entity behind the study. Lead coordinating investigator (LKP according to AMG) is Prof. Sehouli. Responsible for the conduct of the study is the Sponsor who delegate several processes related to the study conduct to a Contract Research Organisation (CRO): Institut für Klinische Krebsforschung IKF GmbH f(IKF). The CRO is responsible for quality assurance related to the processes under its responsibility. For all other processes, responsibility for quality assurance remains with the Sponsor. The Sponsor as well as the CRO might designate experienced personnel to observe the GCP conformity of the study conduct. All organizational, formal, and content-related changes of the protocol or the logistics require consent of the Sponsor.

Essential decisions with respect to the study conduct such as content related protocol changes will be communicated to the LKP, Sponsor, CRO, steering committee and or the statistician in charge. All these members agree that this communication can be done by phone or e-mail. For interim (if applicable) and final analyses safety data such as toxicity, early termination, deaths,

SUSARs etc., will be presented to the sponsor listed in tables and commented by the lead coordinating investigator.

19 Administrative and legal obligations

19.1 Protocol amendments

Any modification to the protocol impacting on the conduct of the study, the potential benefit of the study, or which may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol.

Any amendment to the protocol will be agreed upon by the lead coordinating investigator (LKP) and the Sponsor. Updated versions of the study documents will be submitted to the competent authority and the responsible ethical committee prior to implementation (according to §10, Abs. 2 to 4 GCP-V).

Administrative or technical changes of the protocol (minor corrections and/or clarifications) that do not affect study conduct, nor change the risk-benefit-assessment, will be agreed upon by the lead coordinating investigator (LKP), the Sponsor and the CRO and will be documented in a memorandum to the protocol. The responsible ethical committee will be informed about such changes at the discretion of the Sponsor/lead coordinating investigator. The Sponsor/lead coordinating investigator will assure that all documents related to protocol amendments have been included in the investigator site file at all participating study centers.

19.2 Trial termination

This clinical trial may be completed regularly as planned or may be prematurely discontinued by the Sponsor. If the trial is completed regularly, the Sponsor will notify the competent authority as well as the competent ethics committee in writing. If the trial is prematurely terminated or suspended, the Sponsor will inform the competent authority as well as the competent ethics committee of the termination or suspension and the reason(s) for the termination or suspension within 15 days in accordance with national regulations.

19.3 Trial documentation and data storage

The investigator must ensure that all records pertaining to the conduct of the clinical study, including signed (e)CRFs, informed consent forms, drug accountability records, source documents, and other study documentation are adequately stored for the required time period

to allow for review and reconstruction of the study. This documentation must be retained for 10 years following completion of the study or for the length of time requested by the Sponsor.

19.4 Publication and registration of the study

The results of this study will be published by the lead coordinating after final analysis has been performed. Publication will be independent of the nature of the results obtained (whether they were positive or negative). The manuscript written for publication, together with the materials provided by the statistician can be accepted as the final study report.

This clinical trial is registered at www.clinicaltrials.gov.

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21 Appendices

21.1 Charlson Score

Table 6: Charlson Score with age points [37, 38]

Assigned weights for diseases	Conditions
1	Myocardial infarct Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2	Hemiplegia Moderate or severe renal disease Diabetes with end organ damage Any tumor Leukemia Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor AIDS
Assigned weights for each condition that a patient has. The total equals the score. Example: chronic pulmonary (1) and lymphoma (2) = total score (3). Additionally, each decade of age ≥50 years is equivalent to a 1-point increase in comorbidity (ie, 50–59 years=1 point; 60–69 years=2 points).	

21.2 ECOG-Classification

Table 7: ECOG Performance Status as developed by the Eastern Cooperative Oncology Group.

Grade	ECOG Performance Status
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

21.3 NRS

Screening auf Mangelernährung im Krankenhaus

Nutritional Risk Screening (NRS 2002)

nach Kondrup J et al., Clinical Nutrition 2003; 22: 415-421

Empfohlen von der Europäischen Gesellschaft für Klinische Ernährung und Stoffwechsel (ESPEN)

Vorscreening:

- Ist der Body Mass Index < 20,5 kg/m² ? □ ja □ nein
- Hat der Patient in den vergangenen 3 Monaten an Gewicht verloren? □ ja □ nein
- War die Nahrungszufuhr in der vergangenen Woche vermindert? □ ja □ nein
- Ist der Patient schwer erkrankt? (z.B. Intensivtherapie) □ ja □ nein

⇒ Wird eine dieser Fragen mit **„Ja"** beantwortet, wird mit dem Hauptscreening fortgefahren

⇒ Werden alle Fragen mit **„Nein"** beantwortet, wird der Patient wöchentlich neu gescreent.

⇒ Wenn für den Patienten z.B. eine große Operation geplant ist, sollte ein präventiver Ernährungsplan verfolgt werden, um dem assoziierte Risiko vorzubeugen.

Hauptscreening:

Störung des Ernährungszustands	Punkte
Keine	**0**
Mild Gewichtsverlust > 5%/ 3 Mo. oder Nahrungszufuhr < 50-75% des Bedarfes in der vergangenen Woche	**1**
Mäßig Gewichtsverlust > 5%/ 2 Mo. oder BMI 18,5-20,5 kg/m² und reduzierter Allgemeinzustand (AZ) oder Nahrungszufuhr 25-50% des Bedarfes in der vergangenen Woche	**2**
Schwer Gewichtsverlust> 5% /1 Mo. (>15% / 3 Mo.) oder BMI <18,5 kg/m² und reduzierter Allgemeinzustand oder Nahrungszufuhr 0-25% des Bedarfes in der vergangenen Woche	**3**

+

Krankheitsschwere	Punkte
Keine	**0**
Mild z.B. Schenkelhalsfraktur, chronische Erkrankungen besonders mit Komplikationen: Leberzirrhose, chronisch obstruktive Lungenerkrankung, chronische Hämodialyse, Diabetes, Krebsleiden	**1**
Mäßig z.B. große Bauchchirurgie, Schlaganfall, schwere Pneumonie, hämatologische Krebserkrankung	**2**
Schwer z.B. Kopfverletzung, Knochenmarktransplantation, intensivpflichtige Patienten (APACHE-II >10)	**3**

\+ **1** Punkt, wenn Alter ≥ 70 Jahre

≥ 3 Punkte	Ernährungsrisiko liegt vor, Erstellung eines Ernährungsplanes
< 3 Punkte	wöchentlich wiederholtes Screening. Wenn für den Patienten z.B. eine große Operation geplant ist, sollte ein präventiver Ernährungsplan verfolgt werden, um das assoziierte Risiko zu vermeiden

T. Schütz, L. Valentini, M. Plauth. Screening auf Mangelernährung nach den ESPEN-Leitlinien 2002. Aktuel Ernaehr Med 2005; 30: 99-103.

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Nutritional Risk Screening (NRS 2002) - English Version

If the answer to any question is **YES,** Final Screening is performed.
If the answer is **NO** to all questions, the patient is re-screened at weekly intervals. If, for example, the patient is scheduled for a major operation, a preventative nutritional care plan is considered to avoid the associated risk status.

1. Is BMI < 20.5?
2. Has the patient lost weight within the last 3 months?
3. Has the patient had a reduced dietary intake in the last week?
4. Is the patient severely ill (e.g. in intensive therapy)?

Final Screening			
	Impaired nutritional status	**Severity of disease (= increase in requirements)**	
Absent **Score 0**	Normal nutritional requirements	Absent **Score 0**	Normal nutritional requirements
Mild **Score 1**	Wt loss > 5% in 3 months, or food intake below 50-75% of normal requirement in preceding week	Mild **Score 1**	Hip fracture, chronic patients, in par ticular, with acute complications: *cirrhosis, COPD, chronic hemodialysis, diabetes, oncology*
Moderate **Score 2**	Wt loss > 5% in 2 months, or BMI 18.5-20.5 + impaired general condition, or food intake of 20-60% of normal requirement in preceding week	Moderate **Score 2**	Major abdominal surgery, stroke, *s evere pneumonia, hematologic malignancy*
Severe **Score 3**	Wt loss > 5% in 1 month (> 15% in 3 months), or BMI < 18.5 + impaired general condition, or food intake of 0-25% of normal requirement in preceding week	Severe **Score 3**	Head injury, bone marrow transplantation, *intensive care patients (APACHE > 10)*
Score:	+	**Score:**	**= Total score:**
Age	if ≥ 70 years: add 1 to total score above		= **Age-adjusted total score**
Score ≥ 3: the patient is nutritionally at risk, and a nutritional care plan is initiated. **Score < 3:** Weekly rescreening of the patient. If the patient, for example, is scheduled for a major operation, a preventative nutritional care plan is considered to avoid the associated risk status.			

Prototypes for Severity of Disease

Score=1: a patient with chronic disease, admitted to hospital due to complications. The patient is weak, but out of bed regularly. Protein requirement is increased, but can be covered by oral diet or supplements in most cases.

Score=2: a patient confined to bed due to illness, e.g. following major abdominal surgery. Protein requirement is substantially increased, but can be covered, although artificial feeding is required in many cases.

Score=3: a patient in intensive care with assisted ventilation etc. Protein requirement is increased, and cannot be covered, even by artificial feeding. Protein breakdown and nitrogen loss can be significantly attenuated.

21.4 EORTC QLQ-C30 version 3.0 (German Version)

GERMAN

EORTC QLQ-C30 (Version 3)

Wir sind an einigen Angaben interessiert, die Sie und Ihre Gesundheit betreffen. Bitte beantworten Sie die folgenden Fragen selbst, indem Sie die Zahl einkreisen, die am besten auf Sie zutrifft. Es gibt keine „richtigen" oder „falschen" Antworten. Ihre Angaben werden streng vertraulich behandelt.

		Überhaupt nicht	Wenig	Mäßig	Sehr
1.	Bereitet es Ihnen Schwierigkeiten, sich körperlich anzustrengen (z. B. eine schwere Einkaufstasche oder einen Koffer zu tragen)?	1	2	3	4
2.	Bereitet es Ihnen Schwierigkeiten, einen längeren Spaziergang zu machen?	1	2	3	4
3.	Bereitet es Ihnen Schwierigkeiten, eine kurze Strecke außer Haus zu gehen?	1	2	3	4
4.	Müssen Sie tagsüber im Bett liegen oder in einem Sessel sitzen?	1	2	3	4
5.	Brauchen Sie Hilfe beim Essen, Anziehen, Waschen oder Benutzen der Toilette?	1	2	3	4

Während der letzten Woche:		Überhaupt nicht	Wenig	Mäßig	Sehr
6.	Waren Sie bei Ihrer Arbeit oder bei anderen tagtäglichen Beschäftigungen eingeschränkt?	1	2	3	4
7.	Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt?	1	2	3	4
8.	Waren Sie kurzatmig?	1	2	3	4
9.	Hatten Sie Schmerzen?	1	2	3	4
10.	Mussten Sie sich ausruhen?	1	2	3	4
11.	Hatten Sie Schlafstörungen?	1	2	3	4
12.	Fühlten Sie sich schwach?	1	2	3	4
13.	Hatten Sie Appetitmangel?	1	2	3	4
14.	War Ihnen übel?	1	2	3	4
15.	Haben Sie erbrochen?	1	2	3	4
16.	Hatten Sie Verstopfung?	1	2	3	4

Bitte wenden

GERMAN

Während der letzten Woche:	**Überhaupt nicht**	**Wenig**	**Mäßig**	**Sehr**
16. Hatten Sie Verstopfung?	1	2	3	4
17. Hatten Sie Durchfall?	1	2	3	4
18. Waren Sie müde?	1	2	3	4
19. Fühlten Sie sich durch Schmerzen in Ihrem alltäglichen Leben beeinträchtigt?	1	2	3	4
20. Hatten Sie Schwierigkeiten sich auf etwas zu konzentrieren, z.B. auf das Zeitunglesen oder das Fernsehen?	1	2	3	4
21. Fühlten Sie sich angespannt?	1	2	3	4
22. Haben Sie sich Sorgen gemacht?	1	2	3	4
23. Waren Sie reizbar?	1	2	3	4
24. Fühlten Sie sich niedergeschlagen?	1	2	3	4
25. Hatten Sie Schwierigkeiten, sich an Dinge zu erinnern?	1	2	3	4
26. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Familienleben beeinträchtigt?	1	2	3	4
27. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Zusammensein oder Ihre gemeinsamen Unternehmungen mit anderen Menschen beeinträchtigt?	1	2	3	4
28. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung für Sie finanzielle Schwierigkeiten mit sich gebracht?	1	2	3	4

Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 1 und 7 an, die am besten auf Sie zutrifft

29. Wie würden Sie insgesamt Ihren Gesundheitszustand während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

30. Wie würden Sie insgesamt Ihre Lebensqualität während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

21.5 EORTC QLQ-OV28 (German Version)

GERMAN

EORTC QLQ – OV28

Patientinnen berichten manchmal die nachfolgend beschriebenen Symptome oder Probleme. Bitte beschreiben Sie, wie stark Sie diese Symptome oder Probleme während der letzten Woche empfunden haben.

Während der letzten Woche:	**Überhaupt nicht**	**Wenig**	**Mäßig**	**Sehr**
31. Hatten Sie Bauchschmerzen?	1	2	3	4
32. Hatten Sie ein aufgeblähtes Gefühl in Ihrem Bauch/Magen?	1	2	3	4
33. Hatten Sie das Problem, dass Sie sich durch Ihre Kleidung beengt fühlten?	1	2	3	4
34. Haben Sie als Folge Ihrer Erkrankung oder Behandlung Veränderungen Ihrer Stuhlgewohnheiten erlebt?	1	2	3	4
35. Wurden Sie durch abgehende Winde belastet?	1	2	3	4
36. Hatten Sie schnell ein Völlegefühl, unmittelbar nachdem Sie zu essen begonnen hatten?	1	2	3	4
37. Hatten Sie Verdauungsstörungen oder Sodbrennen?	1	2	3	4
38. Hatten Sie Haarausfall?	1	2	3	4
39. Nur bei Haarausfall ausfüllen:Hat Sie der Haarausfall belastet?	1	2	3	4
40. War Ihr Geschmacksempfinden beim Essen oder Trinken verändert?	1	2	3	4
41. Hatten Sie kribbelnde Hände oder Füsse?	1	2	3	4
42. Hatten Sie ein Taubheitsgefühl in Ihren Fingern und Zehen?	1	2	3	4
43. Fühlten Sie sich in Ihren Armen und Beinen schwach?	1	2	3	4
44. Hatten Sie Muskel- und Gelenkschmerzen?	1	2	3	4
45. Hatten Sie Hörprobleme?	1	2	3	4
46. Mussten Sie häufig urinieren?	1	2	3	4
47. Hatten Sie Hautprobleme (z.B.: Jucken, Trockenheit)?	1	2	3	4
48. Hatten Sie Hitzewallungen?	1	2	3	4
49. Hatten Sie nächtliche Schweissausbrüche?	1	2	3	4

Bitte wenden

GERMAN

Während der letzten Woche:	**Überhaupt nicht**	**Wenig**	**Mäßig**	**Sehr**
50. Fühlten Sie sich als Folge Ihrer Krankheit oder Behandlung körperlich weniger anziehend?	1	2	3	4
51. Waren Sie mit Ihrem Körper unzufrieden?	1	2	3	4
52. Wie sehr hat Sie Ihre Krankheit belastet?	1	2	3	4
53. Wie sehr hat Sie Ihre Behandlung belastet?	1	2	3	4
54. Waren Sie wegen Ihres künftigen Gesundheitszustandes besorgt?	1	2	3	4

Während der letzten vier Wochen:	**Überhaupt nicht**	**Wenig**	**Mäßig**	**Sehr**
55. Wie sehr waren Sie an Sex interessiert?	1	2	3	4
56. Wie sehr waren Sie sexuell aktiv?	1	2	3	4
Nur ausfüllen, wenn Sie sexuell aktiv waren:				
57. Wie weit hatten Sie Freude am Sex?	1	2	3	4
58. Hatten Sie eine trockene Scheide während Sie sexuell aktiv waren?	1	2	3	4

EORTC QLQ - OV28

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have abdominal pain?	1	2	3	4
32. Did you have a bloated feeling in your abdomen / stomach?	1	2	3	4
33. Did you have problems with your clothes feeling too tight?	1	2	3	4
34. Did you experience any change in bowel habit as a result of your disease or treatment?	1	2	3	4
35. Were you troubled by passing wind / gas / flatulence?	1	2	3	4
36. Have you felt full too quickly after beginning to eat?	1	2	3	4
37. Have you had indigestion or heartburn?	1	2	3	4
38. Have you lost any hair?	1	2	3	4
39. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
40. Did food and drink taste different from usual?	1	2	3	4
41. Have you had tingling hands or feet?	1	2	3	4
42. Have you had numbness in your fingers or toes?	1	2	3	4
43. Have you felt weak in your arms or legs?	1	2	3	4
44. Did you have aches or pains in your muscles or joints?	1	2	3	4
45. Did you have problems with hearing?	1	2	3	4
46. Did you urinate frequently?	1	2	3	4
47. Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
48. Did you have hot flushes?	1	2	3	4
49. Did you have night sweats?	1	2	3	4

Please go on to next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
50. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
51. Have you been dissatisfied with your body?	1	2	3	4
52. How much has your disease been a burden to you?	1	2	3	4
53. How much has your treatment been a burden to you?	1	2	3	4
54. Were you worried about your future health?	1	2	3	4

During the past 4 weeks:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
55. To what extent were you interested in sex?	1	2	3	4
56. To what extent were you sexually active?	1	2	3	4

Answer the following two questions only if you were sexually active:

57. To what extent was sex enjoyable for you?	1	2	3	4
58. Did you have a dry vagina during sexual activity?	1	2	3	4