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

"COMPASS"

Statistical Analysis Plan

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Approved by

Lead coordinating investigator (LKP) according to AMG and representative of the sponsor

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Place, Date, Signature

1 Background

1.1 Trial objective

To compare QoL in patients treated with trabectedin/PLD vs. other standard combination therapy of carboplatin/ PLD, carboplatin/ gemcitabine, or carboplatin/ paclitaxel.

1.2 Trial design

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

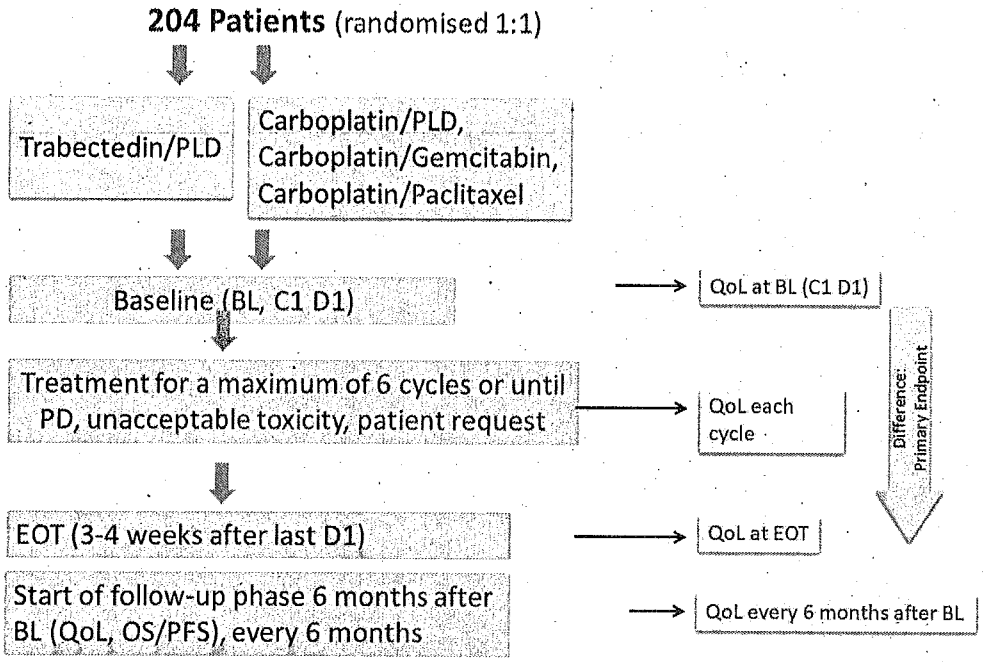
The main scope of the trial is to evaluate QoL during and after chemotherapy comparing trabectedin/PLD with other standard platinum-based chemotherapy in platinum-sensitive disease.

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, 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).



2 Analysis sets

2.1 Definitions

The following data sets for analysis are defined:

Intention-to-treat population (ITT) The intention-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 for the primary endpoint, 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.

Inclucion and Exclusion Criteria

Nr.	Inclusion Criteria	Variable	Comment
1	≥ 18 years	*age*	
2	≥ 1 prior line of chemo	Number of *emnpcomptherapie.chemoX_drug* entries	
3	eligible for platin (Inv. Decision)	-	
4	ECOG ≤ 2	*physexam_ecog*	BSL visit

6	Leucocytes >3.0x10^9/l	*wbc; wbc_unit; wbc_clinsig*	CAVE other units are possible
7	platelet count >100x10^9/l	*plat; plat_unit; plat_clinsig*	CAVE other units are possible
8	absolut neutrophil count >1500/mm^3	*neut; neut_unit; neut_clinsig*	CAVE other units are possible
9	haemoglobin ≥ 9g/dl	*hgb; hgb_unit; hgb_clinsig*	CAVE other units are possible
10	Alkaline Phosphatase (AP) ≤ 2.5 × ULN	*ap; ap_unit; ap_clinsig*	
11	Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN	*alt; alt_unit; alt_clinsig* *ast; ast_unit; ast_clinsig*	
12	Creatinine-Clearance ≥ 60 ml/min (MDRD formula or Cockroft & Gault formula)	*creatinine_clear*	
13	Serum creatinine ≤ 1.5 mg/dl	*creatinine; creatinine_unit; creatinine_clinsig*	CAVE other units are possible
14	Creatine phosphokinase (CPK) ≤ 2.5 × ULN	*creatphkinase; creatphkinase_unit; creatphkinase_clinsig*	
15	Total bilirubin < ULN	*bilirubin; bilirubin_clinsig*	
16	Women of childbearing potential should use contraceptives	-	
17	Adequate cardiac function defined as left ventricular ejection fraction (LVEF) ≥ 50% as determined by echocardiogram	*echo_result*	normal (1) abnormal (2) if (2), then *echo_abnormal* (string)
18	Patients must provide written informed consent	*infcons_dt*	
Nr.	**Exclusion Criteria**	**Variable**	**Comment**
1	Only malignancies, which influence the prognosis	-	*To be discussed with clinicians at DRM*
2	Any unstable or serious concurrent condition (e.g. active infection requiring systemic therapy).	*comorbidities*	If *yes*, then discuss *comorbidities_bsys* with clinicians
3	Chemotherapy or radiation therapy or tumor embolization within 2 weeks prior to the first dose of study drug or planned	*chemoX_stopdt* and *treat_dt_vis*	The difference between *chemoX_stopdt* and *treat_dt_vis* must be at least 14 days.

	during study participation		
4	Patients who have refractory disease. Refractory disease is defined if relapse occurs <4 months after beginning of platin-containing therapy	*chemoX_startdt* und *ct_mrt_dt*	The difference between *chemoX_start* and *ct_mrt_dt* must be at least 120 days.
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	*ekg_result*	If *außerhalb der Norm - klin. signifikant (2)* then discuss with clinicians
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	*maint_stopdt* and *treat_dt_vis*	A time difference of more than 14 days is required, if *maint_drug = 1* (Bevacizumab), a time difference of more than 30 days is required
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	-	-
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	-	-

2.2 Application

Primary analysis and all further efficacy endpoints and description of the study population will be performed in the ITT population. Sensitivity analyses may be conducted in the PP population. Safety analyses will be performed in the safety analysis set.

3 Trial centres

Site	Number of randomized patients
Charité Universitätsmedizin Berlin	12
Universitätsklinikum Carl Gustav Carus	5
Ruppiner Kliniken GmbH	2
Universitätsklinikum Freiburg	3
Universitätsklinik der Johannes Gutenberg-Universität Mainz	7
ZAGO - MVZ GynKrefeld GmbH	4
CaritasKlinikum St. Theresia	21
Praxis Krebsheilkunde für Frauen Dr. Oskay-Özcelik	1
Gynäkologisches Zentrum Bonn	6
Universitätsfrauenklinik Leipzig	9
Studien GbR Braunschweig	4
Universitätsklinikum Aachen	3
Sankt Gertrauden-Krankenhaus	4
Krankenhaus Nordwest gGmbH	1
Sana Klinikum Offenbach	3
Klinikum Südstadt Rostock	1
Christliches Klinikum Unna gGmbH	1
Onkologische Schwerpunktpraxis Dr. Illmer	2

4 Analysis variables

4.1 Demography and baseline characteristics

Characteristic	variable name and instructions
Age	age
ECOG	physexam_ecog
FIGO	figo_primary
BRCA mutation	brca_eot and brca_type_eot
BMI	weight_demog, height
localisation of primary tumor	loc_prim
Histological type	hist_prim_seroes, hist_prim_muzinoes, hist_prim_endomet, hist_prim_klarz, hist_prim_uroth, hist_prim_mueller
histopathological Grading	nuclgrade
histopathological Grading low/high	nuclgrade1
Chemotherapy-free interval	must be calculated as interval from end of last platinum-based therapy mnpcomppretherapies.chemo1_stopdt or mnpcomppretherapies.chemo2_stoptdt, whichever occurred last, to start of COMPASS-therapy emnpcomptherapie.chemo1_starttdt or emnpcomptherapie.chemo2_starttdt, whichever occurred first
Platin-free interval	must be calculated as interval from end of last platinum-based therapy mnpcomppretherapies.chemo1_stopdt or mnpcomppretherapies.chemo2_stoptdt (depending on which was platinum-based), if platinum == "Plating-haltige Therapie", to start of COMPASS-therapy emnpcomptherapie.chemo1_starttdt or emnpcomptherapie.chemo2_starttdt, whichever occurred first
previous Chemotherapy	emnpcomptherapie.chemo1_drug, emnpcomptherapie.chemo2_drug
Result primary surgery	surgery_prim_result
Result relapse surgery	surgery_rezidiv_res
maintenance therapy previous treatment	emnpcomptherapie.maint_drug
number of previous lines of chemotherapy	Number of emnpcomptherapie:chemo1_drug entries
Charlsen score comorbidities and charlson score	• charlson_myoc_yn • charlson_heart_yn • charlson_pervasc_yn • charlson_zervasc_yn • charlson_dement_yn • charlson_lung_yn • charlson_tissue_yn • charlson_ulcus_yn • charlson_mildliv_yn • charlson_diab_yn • charlson_hemi_yn • charlson_kidney_yn • charlson_sevdiab_yn • charlson_leuc_yn • charlson_lymph_yn • charlson_sevliv_yn • charlson_mettum_yn • charlson_aids_yn • charlson_tum_yn • charlson_cscore
Hb-value	hgb, hgb_unit, hgb_clinsig
Creatinine	creatinine, creatinine_unit, creatinine_clinsig

Albumin	albumin, albumin_unit, albumin_clinsig
Lymph node metastases • **Number of locations per patient** • **frequency of each location**	two versions: lloc_prim_iinterna, lloc_prim_icom, lloc_prim_iext, lloc_prim_lakt, lloc_prim_sakral, lloc_prim_paraort, lloc_prim_inguinal, loc_prim_other, and: lloc_icommunis, lloc_iexterna, lloc_lakteraal, lloc_sakral, lloc_paraaort, lloc_inguinal, loc_other
distant metastases / M-Stadium	mstage, mstage_loc_visc, mstage_loc_pleural, mstage_loc_lymph
CA125 Baseline	also if „Bestimmung bei Rezidiv" (ca125_result, ca125_clinsig, ca125_result_anam, ca125_clinsig_anam)
NRS Baseline	nrs_screen1

4.2 Primary variable

QoL will be measured by the TOI-QLQ-OV. The difference of the changes from Baseline (assessed up to 14 days before Baseline visit) to EOT (3-4 weeks after C6 D1) will be used as primary endpoint. In case of missing assessment at EOT, an assessment +/- 6 weeks before/after EOT is also eligible.

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).

Thus, the primary variable TOI-QLQ-OV is defined as the mean of the following subscores:

- QLQ-C30 functional scale "physical function" (qol_c30_i101, qol_c30_i102, qol_c30_i103, qol_c30_i104, qol_c30_i105)
- QLQ-C30 functional scale "role function" (qol_c30_i106, qol_c30_i107)
- QLQ-C30 symptom scale Constipation (qol_c30_i116),
- QLQ-C30 symptom scale Diarrhea (qol_c30_i117),
- QLQ-C30 symptom scale Nausea and vomiting (qol_c30_i114, qol_c30_i115)
- QLQ-OV28 symptom scale abdominal/GI (qol_ov28_i101 to qol_ov28_i106)
- QLQ-OV28 symptom scale peripheral neuropathy (qol_ov28_i111 and qol_ov28_i112)
- QLQ-OV28 symptom scale hormonal (qol_ov28_i118 and qol_ov28_i119)
- QLQ-OV28 symptom scale body image (qol_ov28_i120 and qol_ov28_i121)
- QLQ-OV28 symptom scale attitude to disease/treatment (qol_ov28_i122, qol_ov28_i123 and qol_ov28_i124)
- QLQ-OV28 symptom scale chemotherapy side effects (qol_ov28_i113 to qol_ov28_i117)
- QLQ-OV28 symptom scale other single items (qol_ov28_i107 to qol_ov28_i110)

For functional and symptom scales, the score is calculated as: $score = \frac{RS-1}{range} \times 100$, where *RS* is the arithmetic mean of the component items and *range* is the difference between the possible maximum and the minimum response to individual items, which is 3 for all considered items. Note that according to the EORTC QLQ-C30 manual, functional scales are calculated such that high values correspond to high functionality and symptoms such that high values represent high level of problems. Since the TOI is calculated as the mean of functional and symptom scales, the functional scale is reversed for this calculation.

4.3 Secondary variables

- Clinical benefit rate (CR, PR, SD), or PD in patients with measurable disease (ct_mrt_result)
- Difference from baseline in TOI-QLQ-OV 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 (start date: randdt, event (one of: still progression-free survivor, progression, death, lost to follow-up): patient_status, time to event: patient_status_dt and in case of progression patient_status_prdt, in case of death patient_status_ddt)
- Overall survival (OS), defined as the time from randomization to death from any cause (start date: randdt, event (one of: still progression-free survivor, progression, death, lost to follow-up): patient_status, time to event: patient_status_dt, in case of death patient_status_ddt)
- Time to next medical intervention (e.g. chemotherapy, immunotherapy) (start date: randdt, event (yes/no) fu_therapy, time to event fu_therapy_startdt)
- maintenance therapy in FU (fu_therapy_type)

4.4 Exploratory endpoints

- Change in Charlson Score from Screening to EOT
- Change in NRS from Screening to EoT)
- ECOG at each visit (physexam_ecog)
- All subscores of QLQ-C30 and QLQ-OV28 at each visit

4.5 Safety/Tolerability

- Number of each reason for EoT (eot_reason)
- Number of completed cycles per patient (maximal mnpvisno in mnpcomptreat_arm_a and mnpcomptreat_arm_b).
- Number of early stops, i.e., end of treatment before completion of 6 cycles (number maximal mnpvisno in mnpcomptreat_arm_a and mnpcomptreat_arm_b below 6).
- Number of dose reductions (doseadj_vis) and reason (doseadj_reason_vis), if AE then more details regarding each therapy are provided:
    - Trabectedin (action_trab)
    - PLD (action_pld)
    - Carboplatin (action_platin)
    - Gemcitabin (action_gemcit)
    - Paclitaxel (action_paclitax)
- Number of AEs (mnpcompae)
- Number of SAEs (mnpcompsae)
- Number of all hematological toxicities (either AE or SAE) ≥ Grade 3 (information about grade of AE contained in grade, for SAEs contained in sae_ctcgrade, information whether hematological must be discussed with clinical team and a new variable must be defined)
- Number of all non-hematological toxicities (either AE or SAE) ≥ Grade 3 (information about grade of AE contained in grade, for SAEs contained in sae_ctcgrade, information whether non-hematological must be discussed with clinical team and a new variable must be defined)
- Polypharmacy: ≥ 5 CMs at Baseline (concmed_startdt muss "älter sein als randdt bzw. concmed_stopdt muss nach eot_dt)

NOTE: all variables related to adverse events may be reported repeatedly per patient if the grade of the AE has changed (instruction in eCRF: Report only one grade of each toxicity. If grade changes, enter a stop date here and begin a new AE with same date but changed grade.). Start date is stored in aestart_dt and end date in aestop_dt.

5 Handling of missing values and outliers

5.1 Missing values

Missing values on the primary variable will be handled differently, depending on the sensitivity analysis. In the predefined primary analysis, missing values may be replaced with TOI-QLQ-OV assessments 6 weeks before or after EOT. In case these are missing as well, the primary analysis will be discarding these patients.

As sensitivity analyses, an imputation approach using last-observation-carried forward should be implemented.

As additional sensitivity analysis, two other modeling approaches will be taken. A mixed model will be implemented to take into account all measurements of TOI-QLQ-OV, therefore enabling to include all patients with at least one measurement available. Additionally, a joint model will be implemented to evaluate the impact of the assumptions of informative dropouts.

5.2 Outliers

In case of potentially problematic analysis, sensitivity analyses with and without the outliers will be performed to assess the impact of the outliers on the results and their interpretation.

6 Sample size

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 [1]) 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). 77 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 206 patients have to be randomized.

7 Statistical analyses / methods

7.1 Demography and baseline characteristics

All analyses will be reported for the total population and split up by treatment arm. The information about the treatment arm is contained in the file casenodes_comp in the variable mnp_rando_gr. No statistical test will be performed to compare baseline characteristics between randomized treatment arms.

7.2 Primary analysis

As primary analysis, a mixed effects model will be used with QoL at the end of treatment as outcome variable, and treatment arm and QoL at baseline as explanatory variables, and a random intercept for study site. The null hypothesis is that there is no difference between the treatment arms regarding change of QoL. The p-value of the coefficient of treatment arm will be used as decision criterion: a p-value < 0.05 will be considered as significant. Study sites with small number of patients may be aggregated into one "Other" site to avoid computational problems.

Two analyses will be performed as sensitivity analyses. A mixed model will additionally take into account all

other measurements of QoL by adding a time variable and a random intercept and random slope of time for the patient.

Additionally, both described mixed models will also be implemented in a joint model with a time-to-dropout component, to take into account potential informative dropouts. Joint models have been reported recently as a suitable method to avoid bias due to informative dropouts in QoL analysis [2].

Only if all models consistently lead to a positive (or negative) conclusion about the treatment effect, the results will be considered robust.

7.3 Secondary analyses

7.3.1 Secondary endpoints

Difference from baseline in TOI-QLQ-OV for all other timepoints not included in primary analysis will be analyzed analogously to the primary analysis.

The secondary variables clinical benefit rate and maintenance therapy in FU are proportions, so Boschloo's test, Fisher's exact test or Chi-squared test will be applied.

The analysis of the time-to-event endpoints 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.

7.3.2 Safety / Tolerabiltiy

The analysis of all safety variables is performed descriptively, thus frequencies by treatment arm and in total will be reported. Comparisons between treatment arms will be performed with Boschloo's test, Fisher's exact test or Chi-squared test.

7.4 Planned subgroup analyses

Subgroup are planned for following groups: BRCA-mutation (yes/no), surgery performed (yes/no), tumor rest (yes/no), age (<70 vs. >=70), first relapse vs. second or later, and number of previous lines of chemotherapy.

8 Interpretation of results

The primary endpoint quality of life requires particular care with regard to interpretation of the study's results. First, data is likely to be missing not at random, therefore several analysis strategies are applied to check the sensitivity of the analysis with regard to model assumptions. Results should only be considered robust and interpreted accordingly, if all sensitivity analyses suggest similar conclusions. Second, a related aspect is that quality of life should not be interpreted with taking into account the overall survival. Third, the clinical relevance of a potential difference in quality of life is important for the interpretation of the results. When planning the trial, a difference of at least 8 points in the mean TOI-QLQ-OV-change was defined as clinically relevant.

9 Software

R (version 4.0 or later) will be used. For mixed models, the R packages lme4 and nlme will be considered. For joint models, the package JM will be used.

10 References

[1] Sehouli, J., et al. Topotecan plus carboplatin versus standard therapy with paclitaxel plus carboplatin (PC) or gemcitabin plus carboplatin (GC) or carboplatin plus pegylated doxorubicin (PLDC): A randomized phase III trial of the NOGGO-AGO-Germany-AGO Austria and GEICOGCIG intergroup study (HECTOR). in ASCO Annual Meeting Proceedings. 2012.

[2] Touraine, Célia, et al. "When a joint model should be preferred over a linear mixed model for analysis of longitudinal health-related quality of life data in cancer clinical trials." BMC Medical Research Methodology 23.1 (2023): 1-15.