NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG
getragen von:
Deutsches Krebsforschungszentrum
Universitätsklinikum Heidelberg
Thoraxklinik-Heidelberg
Deutsche Krebshilfe

Study Title

Randomized Phase-II Study of Trabectedin/Olaparib Compared to Physician's Choice in Subjects with Previously Treated Advanced or Recurrent Solid Tumors Harboring DNA Repair Deficiencies

Short Title/ Acronym: NCT-PMO-1603 (TOP-ART)

Final Study Report

(according to §42b AMG / §13(9) GCP-V)

Version Number/ Date:	V02-final, 25.07.2025
Investigational Product:	Olaparib (Lynparza®) / Trabectedin (Yondelis®)
EudraCT Number:	2017-001755-31
Protocol-Number:	NCT-2017-0417
Registry-Number:	clinicaltrials.gov NCT03127215

Sponsor:

Ruprecht-Karls-University of Heidelberg, Medical Faculty
Represented in law by Heidelberg University Hospital and its acting Commercial Director Katrin Erk
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Study Initiation and Completion Dates:

FPFV/FPI	07.11.2018
LPFV/LPI	26.06.2023
LPLV/LPO	19.12.2023
EOS	19.12.2023
DBL	19.08.2024

Signatures

The present trial study report was subject to critical review and has been approved in the present version. The information contained is consistent with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (current version), the principles of ICH-GCP and all local regulatory requirements.

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of this study.

Coordinating Investigator/ Designated Representative of Sponsor

Place, Date	Prof. Dr. Richard F. Schlenk

Synopsis

Name of Sponsor/Company:

Ruprecht-Karls-University Heidelberg, Medical Faculty
represented in law by its acting Commercial Director Katrin Erk

Im Neuenheimer Feld 672, D-69120 Heidelberg

Name of Finished Product:

(1) Lynparza®
(2) Yondelis®

Name of Active Ingredient:

(1) Olaparib
(2) Trabectedin

Title of Study:

Randomized Phase-II Study of Trabectedin/Olaparib Compared to Physician's Choice in Subjects with Previously Treated Advanced or Recurrent Solid Tumors Harboring DNA Repair Deficiencies TOP-ART, NCT-PMO-1603

Protocol versions:

Version Final 2.0, 23.07.2018 (1st submission)

Version Final 4.0, 13.11.2019 (1st substantial amendment)

Study center(s) and Principle Investigator(s):

For a detailed list of all study centers and principle investigators see appendix 1.

Publication (reference):

C.E. Heilig, D. Hübschmann, H. Kopp, K.H. Metzeler, S. Richter, B. Hermes, N. von Bubnoff, T. Kindler, J. Siveke, S. Wagner, S. Ochsenreither, H. Süße, B. Brors, A. Benner, D. Jäger, C. Von Kalle, H. Glimm, S. Gröschel, S. Fröhling, R.F. Schlenk. 1945 - Randomized Phase II Study of Trabectedin/Olaparib Compared to Physician's Choice in Subjects with Previously Treated Advanced or Recurrent Solid Tumors Harboring DNA Repair Deficiencies. Annals of Oncology (2019) 30 (suppl_5): v760-v796.

C.E. Heilig, M. Teleanu, I.A. Bhatti, S. Richter, J.T. Siveke, S. Wagner, H. Kopp, T. Kindler, L. Illert, A. Golf, K. Dormann, A. Benner, H. Süsse, A. Freitag, C. Von Kalle, H. Glimm, D. Hübschmann, S. Fröhling, R.F. Schlenk. 487P - Randomized phase II study of trabectedin/olaparib compared to physician's choice in subjects with previously treated advanced or recurrent solid tumors harboring DNA repair deficiencies. Annals of Oncology (2022) 33 (suppl_7): S197-S224.

M. Rübsam, M. Rheinnecker, B. Hutter, M. Fröhlich, C.E. Heilig, N. Paramasivam, M. Oleś, C. Ball, H. Glimm, M. Hlevnjak, M. Zapatka, P. Lichter, S. Fröhling, R.F. Schlenk, D. Hübschmann. 131O - A composite biomarker for evaluation of homologous recombination repair deficiency in a pan-cancer cohort. Annals of Oncology (2023) 34 (suppl_2): S233-S277

R.F. Schlenk, M. Rübsam, M. Teleanu, S. Richter, J.T. Siveke, S. Wagner, H. Kopp, T. Kindler[8], L. Illert, A.H. Golf, K. Dorman, N. Schreck, A. Benner, H. Süße, A. Freitag, C. von Kalle, H. Glimm, D. Hübschmann, S. Fröhling, C.E. Heilig. 196P - Randomized phase II study of trabectedin/olaparib compared to physician's choice in subjects with previously treated advanced or recurrent solid tumors harboring DNA repair deficiencies. Annals of Oncology (2024) 35 (suppl_2): S238-S308

Phase of Development: Phase II

Studied period (years):

Date of first enrollment (FPI): 07.11.2018

Date of last enrollment (LPI): 26.06.2023

Date of last completion (LPO): 19.12.2023

Objectives:

Primary Objective

- To assess clinical activity of combination therapy with trabectedin and olaparib in adult patients with advanced or recurrent solid tumors harboring DNA repair deficiency. Clinical efficacy is determined by disease control rate (DCR) at week 16 after five 21-days cycles of treatment in the experimental arm and either also after five 21-days cycles or alternatively four 28-days cycles in the physician's choice arm.

Secondary Objectives

- To assess progression-free survival (PFS) of combination therapy with trabectedin and olaparib in comparison to treatment as per physician's choice in adult patients with advanced or recurrent solid tumors harboring DNA repair deficiency.
- To assess overall survival (OS) of combination therapy with trabectedin and olaparib in comparison to treatment as per physician's choice in adult patients with advanced or recurrent solid tumors harboring DNA repair.
- To assess Tumor Response Rate (TRR) including CR and PR according RECIST v1.1 criteria after 16 weeks of combination therapy with trabectedin and olaparib in comparison to treatment as per physician's choice in adult patients with advanced or recurrent solid tumors harboring DNA repair deficiency.
- Patient reported outcomes including quality of life of patients treated with combination therapy with trabectedin and olaparib in comparison to treatment as per physician's choice.
- Safety/tolerability of combination therapy with trabectedin and olaparib in comparison to treatment as per physician's choice

Methodology:

The trial was designed as a multicenter randomized, open-label, phase II study to gain evidence of antitumor activity and safety of trabectedin and olaparib in adult patients with (locally) advanced or metastatic solid tumors and homologous repair deficiency compared to treatment according to current guidelines (physician's choice).

Randomisation was done either into experimental arm E or into physician's choice arm C in a 1:1 ratio considering a stratification after phenotypes of mesenchymal malignoma and epithelial malignoma.

The duration of the trial treatment for each patient was expected to be about 5 months, including 42 days safety observation and a continuous follow-up every 12 weeks until end of study (EOS). In case of clinical benefit, treatment period was longer but no longer than EOS.

Patients randomized into the standard arm C had the possibility to cross over into the experimental arm E before or at the time of disease assessment at week 16 upon disease progression, within a period of 6 months after disease assessment at week 16 and after experiencing unacceptable toxicity demanding cessation treatment while achieving no objective response.

The disease control rate DCR after five cycles of trabectedin/olaparib or corresponding amount of cycles in the physician's choice arm was assessed according to RECIST criteria Version 1.1.

Number of patients (planned and analyzed):

Planned initially:

Number of evaluable patients: n=102 (51 per treatment arm)

Total sample size: n=108 patients (considering 5% drop-out rate)

Planned after Amendment:

Number of evaluable patients: n=118 including n=102 patients without platin-refractory disease (51 per treatment arm) + n=16 patients with platin-refractory disease.

Total sample size: n=124 patients (considering 5% drop-out rate)

Platinum-refractory disease was defined in the protocol as progressive disease during or immediately after treatment with platinum-based chemotherapy (Amendment-Protocol 4.0)

Analyzed:

Registered: n=150, Randomized: n=119, Not randomized: n=31

Randomized and Treated: n=117 (n= 2 patients randomized by mistake including n= 1 patient, which was randomized twice. Those patients were not treated and thus, excluded from analysis).

Randomised and Analyzed: n= 117

Subset of non-platin refractory patients n=101

In the full analysis population set: 117

In the per-protocol analysis set: 117

In the safety analysis set: 117

In the subset of non-platin refractory patients: 101

Diagnosis and main criteria for inclusion:

Indication

Relapsed and metastatic solid tumors with homologous recombination DNA repair deficiency

Main Inclusion criteria

- Progressive locally advanced or metastatic malignancy as determined by local investigator.
- At least one measurable lesion that can be accurately assessed at baseline by CT or MRI and is suitable for repeated assessment
- Prior administration of at least one standard treatment for primary and/or relapsed malignancy according to current guidelines
- Identification of defective DNA repair via Homologous Recombination, as determined by molecular analysis within NCT/DKTK MASTER. Eligibility for the study is defined by the molecular tumorboard of NCT on the basis of whole-exome/genome sequencing and the presence of genomic markers for “BRCAness”
- Adequate bone marrow, renal, and hepatic function defined by laboratory tests
- After amendment-protocol 4.0: Patients with platinum-refractory disease, defined as progressive disease during or immediately after treatment with platinum-based chemotherapy

Investigational product, dose and mode of administration, batch numbers:

(1) Olaparib

Drug Code:	AZD2281
Trade Name:	Lynparza ®
ATC Code:	L01XX46
Pharmaceutical formulation:	Tablets

Route of administration:	Oral
Dose:	150 mg
Batch numbers:	L007463, L011118, L015461, 1000163408, 1000139479, BABD
(2) Trabectedin	
Drug Code:	ET-743
Trade Name:	Yondelis ®
ATC Code:	L01CX01
Pharmaceutical formulation:	Injection, Powder, Lyophilized, For Solution,1 mg vial
Route of administration:	Intravenous
Dose:	1.1 mg/m²
	reduction steps: 0.9 mg/m², 0.75 mg/m²
Batch numbers:	C18454, C20111, C20110, C20217, C19053, C21512, C23053, C23261, C23335, C18433, C19069, C19114, C19164, C19312, C20042, C20143, C20438, C21180, C21315, C21444, C21443, C22018, C22137, C22239, C22547, C23415, C23416, C19125, C19228, C19269, C19306, C19343, C19397, C20102, C22348, C22402, C22566, C23086, C23085, C23190, C23278, C23318, C23395, C18475, C18480, C20216, C21510, C23251, C23252, C19073, C19258, C19368, C20545, C21071, C21141, C21312, C21442, C21482, C22325, C22335, C22334, C23013, C23100, C23101, C23189, C23311, C19079, C19297, C19325, C20005, C20235, C20475, C19194, C19272, C19327, C22143, C23028, C18434, C18439, C19131, C19248, C19266, C21379, C22376, C23351

Reference therapy, dose and mode of administration, batch number:

Standard of care

Duration of Treatment:

The treatment duration of an individual patient was planned to be 16 weeks.

Criteria for Evaluation:

Primary efficacy analysis

The primary endpoint of the study was disease control rate (DCR) after five cycles of trabectedin/olaparib or corresponding amount of cycles in the physician's choice arm until planned evaluation at week 16. It was defined as proportion of patients with complete response (CR), partial response (PR) or stable disease (SD) according to RECIST version 1.1.

Secondary efficacy analyses

- Progression-free survival (PFS), defined as the time from randomisation to radiologically confirmed progression of disease or death from any cause, whichever occurs first
- Overall survival (OS), defined as the time from randomisation to time of death from any cause
- Tumor response rate (TRR) defined as the percentage of patients with complete remissions (CR) and partial remissions (PR) according to RECIST version 1.1
- Patient reported outcomes (PRO), assessed by using of questionnaires of the European Organization for Research and Treatment of Cancer (EORTC)

Safety Analysis:

– All AEs, their severity, SAEs, the relation of AEs to the study treatment, dose modifications for toxicity and discontinuation of study treatment. Toxic effects were graded according to CTCAE v5.0.

Statistical methods:

Definition of study populations:

- Full analysis population (FAP): all randomized patients with treatment groups assigned in accordance with the randomisation, regardless of the treatment actually received. Patients who were randomized but did not subsequently receive treatment are included in the full analysis population (n=117)
- Per protocol (PP) population: the subset of ITT population who had no important protocol deviations that could affect response to treatment (n=101).
- Safety population**:** all randomized patients with a signed informed consent who received at least one dose of any study drug (n=117).

General analysis principles:

- The statistical tests of the primary endpoint were controlled by a one-sided significance level α of 0.025. All secondary and safety analysis was two-sided with a significance level of 5%.
- For patients with incomplete follow-up, time to last follow- up date was used as the censoring time in the analysis of time-to-event data.

Demographic and other Baseline Characteristics:

Categorical characteristics like sex, performance status (ECOG), previous anticancer treatment, tumor staging according to UICC (TNM), were summarized by counts and percentages.

Continuous variables like age, weight and laboratory values were summarized by the number of subjects with available data, mean, standard deviation, minimum value, maximum value as well as median and interquartile range.

Treatment exposure and compliance:

- Summary statistics are presented for the dosage of trabectedin/olaparib received at each cycle, dose modifications for toxicity, discontinuation and withdrawal from study treatment, as well as drop-out from the follow-up during the post-study phase.
- The number of cycles administered, actual and total doses administered, dose modifications for toxicity, discontinuation and withdrawal from study treatment as well as drop-out from the follow-up during the post-study phase are described.

Analysis of the primary endpoint:

- The primary endpoint of the study was the disease control rate (DCR). The score test of the difference in proportions was used to test the null hypothesis H0: DCRe − DCRc ≤ 0 against the alternative H1: DCRe − DCRc > 0. In addition, the confidence interval for differences in proportions as proposed by Agresti and Caffo was computed.
- To consider uncertainties about treatment effects, an interim analysis for futility was conducted after 30 patients are evaluable for the primary objective (i.e. 30% of the total number of 102 patients; equally randomized to each treatment arm). The conditional power based on the proportions according to the study design results in a conditional power of 0.3313, which was above the predefined condition of >0.3. Therefore, recruitment was continued.

Analysis of secondary endpoints:

Descriptive statistics and patient data listing are used for the presentation of response data:

- Tumor response: defined as CR or PR according to RECIST v1 .1 criteria and assessed at 8 and 16 weeks, as well as every 12 weeks during the extended treatment period.
- Survival Analysis (PFS- and OS):
  PFS defined as the time from randomisation to progression of disease or death from any cause, whichever occurs first. Patients without event were censored at the date of

last response evaluation. OS defined as the time from the date of randomization to the date of death due to any cause. For patients who were still alive and patients who were lost to follow up, OS was censored at the date they were last known to be alive.

The method of Kaplan and Meier was used to estimate the distributions of PFS and OS in total and in both treatment arms. Cox proportional hazards regression was used to examine the influence of covariates on PFS/OS if deemed clinically relevant.

Safety Analysis:

- The assessment of safety was based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges and/or show prominent worsening from baseline during the study phase.
- Adverse events were summarized by presenting the number and percentage of patients having any adverse events or serious adverse events, and having each individual adverse event, and by determining and summarizing the maximum individual toxicity grade (over all forms of toxicity) for each treatment cycle during the study phase. The most common AEs (those occurring in at least 10% of the treatment group) were determined.
- Laboratory data were summarized by presenting summary statistics of raw data. Incidence rates are summarized.

Patient Reported Outcomes Analysis:

- Patient reported outcomes were scored descriptively by use of EORTC Quality of Live (QoL) scales before treatment start, at week 8 and week 16. Only a small number of patients participated in the surveys, so no statistical analysis was conducted.

Software:

All analyses were performed using SAS, version 9.4 (www.sas.com), and R, version 3.6.1 or higher (www.rproject.org).

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Primary efficacy results (n=117)

The null hypothesis H0: DCRe − DCRc ≤ 0 is tested against the alternative H1: DCRe − DCRc > 0 at a one-sided significance level of α = 2.5%, where DCRe denotes the disease control rate in the experimental arm and DCRc the disease control rate in the control arm. We obtain a difference in proportions (rates) of -0.1044 (-0.2745, 0.0708) which implies that the observed DCR in the control arm is higher than in the experimental arm, and hence the observed DCR does not go into the direction of the alternative. Using a stratified score test we obtain a p-value of 0.2477 (unstratified 0.2477), indicating that we cannot reject H0 at the pre- specified significance threshold, and we remain with H0 indicating that the disease control rate in the control arm is larger than or equal to that in the experimental arm. Hence, superior clinical efficacy of the experimental treatment could not be shown.

Primary efficacy results excluding platin refractory patients (n=101)

The null hypothesis H0: DCRe - DCRc ≤ 0 is tested against the alternative H1: DCRe - DCRc > 0 at a one-sided significance level of *a* = 2.5%, where DCRe denotes the disease control rate in the experimental arm and DCRc the disease control rate in the control arm. We obtain a difference in proportions (rates) of -0.0761 (-0.260546, 0.1142) which implies that the control arm performs superior. We obtain a p-value of 0.4442, indicating that we cannot reject H0 at the pre-specified significance threshold and we remain with H0 indicating that the rate in the control arm is larger than or equal to that in the experimental arm. Hence, superior clinical efficacy of the experimental treatment could not be shown.

Secondary efficacy results (n=117)

- TRR:
  The difference in proportions of the TRR at week 16 is -0.0202 (-0.1246, 0.0775) The stratified score test for differences leads to a p-value of of 0.7086 (unstratified 0.6481). Hence, we have the same interpretation for the TRR as for the DCR.
- PFS:
  Stratified Cox proportional hazards regression leads to a conditional hazard ratio HR (E versus C) of 1.132 of treatment on PFS with a p-value of 0.5453.
- OS:
  Stratified Cox proportional hazards regression leads to a conditional hazard ratio (HR) in the ITT population of 0.896 of treatment (E versus C) on OS with a p-value of 0.6573.

Secondary efficacy results excluding platin refractory patients (n=101)

- TRR:
  The difference in proportions of the TRR at week 16 is -0.0157 (-0.1306, 0.0998) The score test for differences leads to a p-value of 0.7930. Hence, we have the same interpretation for the TRR as for the DCR.
- PFS:
  Cox proportional hazards regression leads to a conditional hazard ratio HR (E versus C) of 1.289 of treatment on PFS with a p-value of 0.2645.
- OS:
  Stratified Cox proportional hazards regression leads to a conditional hazard ratio (HR) in the ITT population of 1.194 of treatment (E versus C) on OS with a p-value of 0.5312.

SAFETY RESULTS:

We observed 1904 adverse events in 117 patients. In Arm E we observed in total 905 adverse events and according to SOC category ordered according to decreasing frequency adverse events with a frequency above 10% were investigations (29.1%), Blood and lymphatic system disorders (20.3%), Gastrointestinal disorders (15.7%), General disorders and administration site conditions (10.8%). In Arm C we observed 570 and 429 adverse events in patients before or without cross over and after cross over, respectively, and according to SOC category ordered according to decreasing frequency adverse events with a frequency above 10% were investigations (27.4% and 40.6%, respectively), Blood and lymphatic system disorders (9.8% and 16.8%, respectively) and general disorders and administration site conditions (10.4% and 8.4%, respectively). We observed 450 Adverse events graded >= grade III in 117 patients. In Arm E we observed in total 212 adverse events graded ≥3 and according to SOC category ordered according to decreasing frequency with a frequency above 10% were investigations (36.8%) and Blood and lymphatic system disorders (30.7%). In Arm C we observed 110 and 128 adverse events in patients before or without cross over and after cross over, respectively, and according to SOC category ordered according to decreasing frequency with a frequency above 10% were investigations (40.9% and 54.7%, respectively) and Blood and lymphatic system disorders (16.4% and 17.2%, respectively).

We have a total number of 148 serious adverse events in 117 patients, 53 in Arm E, 57 and 38 in Arm C in patients before or without cross over and after cross over, respectively. Assessment of safety in cycle 1 revealed in Arm E 343 and 15 as well as in Arm C 226 and 18 adverse and serious adverse events, respectively. Clinically relevant higher rates according to SOC classification were identified in Arm E in Blood and lymphatic system disorders mainly driven by neutropenia/leukopenia, Gastrointestinal Disorders mainly driven by nausea, General disorders and administration site conditions mainly driven by Fatigue, whereas the contrary was observed with higher rates in Arm C in Skin and subcutaneous tissue disorders.

CONCLUSION:

From 11/2018 till 06/2023, 117 patients have been randomized (Arm E, n=60; Arm C, n=57). Various entities were included (sarcoma, n=52; cholangiocarcinoma, n=7; pancreatic cancer, n=6; gynecologic cancer, n=13 (breast n=9, uterus n=3, ovar n=1); uveal melanoma, n=5; other, n=35); prior treatment was balanced between arms. A median of 3 treatment cycles were applied; progressive disease was the main cause of treatment termination.

The disease control rate as primary endpoint of the study in Arm C was larger than or equal to that in the Arm E in all patients and the subgroup of non-platin refractory patients. Hence, superior clinical efficacy of the experimental treatment could not be shown. The same was true for the secondary endpoints TRR, PFS and OS. The overall conclusion is that the combination of Trabectedin and Olaparib was not superior to treatment of physician's choice in this cross- entity patient population, no new safety signals occurred and treatment of the combination therapy of Trabectedin and Olaparib was feasible and tolerable overall and in the subgroups of epithelial and mesenchymal neoplasms.

Substantial amendments / interruptions or early termination:

- One substantial amendment was implemented:
  Protocol Version Final 4.0, 13.11.2019 (protocol version 3.0: not applicable)
- The clinical trial was not interrupted.

Date of the report:

25.07.2025

Appendices:

Appendix 1: List of Study centers
Appendix 2: CONSORT Flow Diagram

Appendix 1: List of study centers and Principle Investigators

No.	Name of Principle Investigator	Study center
01	Prof. Dr. med. Richard F. Schlenk	Nationales Centrum für Tumorerkrankungen Im Neuenheimer Feld 460 69120 Heidelberg
03	Dr. Stephan Richter	Universitätsklinikum Dresden Medizinische Klinik und Poliklinik I Fetscherstraße 74 01307 Dresden
05	Prof. Dr. med. Jens Siveke	Universitätsklinikum Essen Innere Klinik (Tumorforschung) Westdeutsches Tumorzentrum Hufelandstr. 55 45147 Essen
06	PD Dr. med. Thomas Kindler	Universitätsmedizin der Johannes Gutenberg-Universität Mainz III. Medizinische Klinik und Poliklinik Langenbeckstraße 1 55131 Mainz
07	Dr. med. David Zurmeyer	Universitätsklinikum Frankfurt Medizinische Klinik II Theodor-Stern-Kai 7 60590 Frankfurt
08	Prof. Dr. Hans-Georg Kopp	Robert-Bosch-Krankenhaus - Klinik Schillerhöhe Abteilung für Hämatologie, Onkologie und Palliativmedizin Auerbachstr. 110 70376 Stuttgart
09	Dr. med. Alexander Golf	Universitätsklinikum Tübingen Innere Medizin VIII Otfried-Müller-Str. 10 72076 Tübingen
10	PD Dr. med. Anna Lena Illert	Universitätsklinikum Freiburg Medizin 1, Hämatologie/Onkologie Hugstetter Str. 55 79106 Freiburg
11	PD Dr. med. Tobias Herold	Medizinische Klinik und Poliklinik III Klinikum der Universität München - Großhadern Marchioninistraße 15 81377 München

Appendix 2: CONSORT Flow Diagram