EUDARIO Clinical Trial
GANNET53 EUROPEAN PROJECT

A multicentre, open-label, three-arm randomised Phase II trial assessing the safety and efficacy of the HSP90 inhibitor Ganetespib in combination with Carboplatin followed by maintenance treatment with Niraparib ***versus*** Ganetespib plus Carboplatin followed by Ganetespib and Niraparib ***versus*** Carboplatin in combination with standard chemotherapy followed by Niraparib maintenance treatment in platinum-sensitive ovarian cancer patients

EUDARIO: **Eu**ropean Trial on enhanced **D**N**A** **R**epair **I**nhibition in **O**varian Cancer

A seventh framework programme (FP7) project of the European Union (Grant agreement no 602602)

EUDRACT Number: 2017-004058-40

Confidentiality statement

The information contained in this protocol, especially unpublished data, is confidential. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Independent Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from the coordinating investigator Nicole Concin and the Belgian BGOG trial centre, except to the extent necessary to obtain informed consent from those persons to whom the study drug may be administered.

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1.1 Declaration of the sponsor and the coordinating investigator

The present study protocol was subject to critical review. Its content is consistent with the current risk/benefit evaluation of the IMP as well as with the moral, ethical and scientific principles of good clinical practice, the latest version of the Declaration of Helsinki, the local laws and the regulations and the applicable regulatory requirements.

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The signatories above confirm that they have read this study protocol and agree that it contains all information required for study performance. They also agree to conduct the study as set out in this protocol. It has been understood that all documentation previously not published will be kept in strictest confidence.

Protocol authorisation – Investigator

Study title

Eudario
A multicentre, open-label, three-arm randomised Phase II trial assessing the safety and efficacy of the HSP90 inhibitor Ganetespib in combination with Carboplatin followed by maintenance treatment with Niraparib versus Ganetespib plus Carboplatin followed by Ganetespib and Niraparib versus Carboplatin in combination with standard chemotherapy followed by Niraparib maintenance treatment in platinum-sensitive ovarian cancer patients

Version: 4.0
EudraCT Number: 2017-004058-40

Principal investigator (Name in capital letters) _____

I declare that the study mentioned above will be conducted according to AMG/ICH-GCP Guidelines (ICH-E6; CPMP/135/95) and the most recent version of the Declaration of Helsinki. To ensure quality of data, study integrity, and compliance with the protocol and the various applicable regulations and guidelines, the sponsor may conduct site visits to institutions participating in this study.

I consent to co-operate fully with any quality assurance visit undertaken by third parties, including representatives from the sponsor or national and/or foreign regulatory, as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital patient charts and other study files) to these authorised individuals.
I agree to inform the sponsor immediately in case a regulatory authority inspection is scheduled.

_____ _____
SIGNATURE Principal investigator place, date

ONLY FOR GERMANY:

_____ _____
SIGNATURE Substitute of investigator place, date

NAME in capital letters: _____

_____ _____
SIGNATURE physician place, date

NAME in capital letters: _____

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4 PROTOCOL SYNOPSIS

Title	A multicentre, open-label, three-arm randomised Phase II trial assessing the safety and efficacy of the HSP90 inhibitor Ganetespib in combination with Carboplatin followed by maintenance treatment with Niraparib versus Ganetespib plus Carboplatin followed by Ganetespib and Niraparib versus Carboplatin in combination with standard chemotherapy followed by Niraparib maintenance treatment in platinum-sensitive ovarian cancer patients
Short title	**EUDARIO**
EudraCT number	2017-004058-40
Protocol version/date	V 4.0 12Nov2020
Indication	Women with platinum-sensitive, high-grade serous, high-grade endometrioid, undifferentiated epithelial ovarian cancer, carcinosarcoma, fallopian tube or primary peritoneal cancer (proven by central histo-pathological review)
Phase/Design	This is an open-label, three-arm, randomised (1:1:1) Phase II study **Safety run in:** - For Ganetespib/Carboplatin combination (arms B and C): safety evaluation by IDMC will be performed 4 weeks after inclusion of 6 and 12 patients, respectively (without recruitment stop). - For Ganetespib/PARPi combination (arm C): safety evaluation by IDMC will be performed 4 weeks after start of maintenance therapy of 6 and 12 patients, respectively (with stop of entering maintenance treatment in arm C).
Non-investigational treatment, dosing and pharmaceutical form	Standard arm (arm A): Carboplatin (AUC5 d1, q3w i.v.) in combination with Paclitaxel (175 mg/m² d1, q3w i.v.) or Carboplatin (AUC4 d1, q3w i.v.) in combination with Gemcitabine (1000 mg/m² d1, d8, q3w i.v.) followed by maintenance therapy with Niraparib (200/ 300 mg oral daily, q4w)
Investigational treatment, dosing and pharmaceutical form	First experimental arm (arm B): Ganetespib (150 mg/m^2, d1, q3w) in combination with Carboplatin (AUC5 d1, q3w i.v.) followed by maintenance treatment with Niraparib (200/ 300 mg oral daily, q4w) Second experimental arm (arm C): Ganetespib (150 mg/m² d1, q3w i.v.) plus Carboplatin (AUC5 d1, q3w i.v.) followed by Ganetespib (100 mg/m² d1, d8, d15, d22, q4w i.v.) and Niraparib (200 mg oral daily, q4w)

	Ganetespib and Niraparib are investigational products and will be provided by Aldeyra Therapeutics and TESARO, respectively.
Planned study duration	First patient in: Nov 2018 Last patient in: Feb2020 Last patient last treatment (LPLT) with Ganetespib: May 2021 Estimated End of study: Aug 2022
Number of patients	A total of 120 patients will be randomised, 40 patients per treatment-arm
Sites / Countries	13 sites in 5 countries (Austria, Belgium, France, Germany, Italy)
Inclusion criteria	Patients must meet the following criteria to be eligible for study entry: • Signed and dated written informed consent prior to admission to the study in accordance with ICH-GCP guidelines and with the local legislation. • Female patients ≥18 years of age • High-grade serous, high-grade endometrioid, undifferentiated epithelial ovarian cancer, carcinosarcoma, fallopian tube or primary peritoneal cancer • Platinum-sensitive relapse >6months after previous platinum-based treatment (calculated from the first day of the last cycle of the last platinum-based chemotherapy until the date of progression confirmed according to RECIST 1.1 on imaging) • No limits in number of prior lines • Measurable or evaluable disease according to RECIST 1.1 • ECOG performance status 0-1 • Adequate functions of the bone marrow o Platelets ≥ 100 x 10^9/L o Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L o Hemoglobin ≥8.5 g/dl (patients may not receive a transfusion within 4 weeks prior to initiating study treatment) o • Adequate function of the organs o Creatinine clearance ≥ 30ml/min, as calculated using the Cockroft-Gault equation Total bilirubin ≤ 1.5 x upper limit of normal (≤ 2.0 in patients with known Gilberts syndrome) OR direct bilirubin ≤ 1 x ULN o SGOT/SGPT (AST/ALT) ≤ 2.5 x upper limit of normal unless liver metastases are present, in which case they must be ≤ 5 x ULN

  - Urinanalysis or urine dipstick for proteinuria less than 2+. Patients with ≥ 2+ on dipstick should undergo 24-hour urine collection and must demonstrate < 1 g of protein/24 hours; except the proteinuria is clearly related to a catheter in the urinary system.
- Adequate coagulation parameter: aPTT ≤ 1.5 x ULN (patients on heparin treatment must have an aPTT between 1.5-2.5 x ULN), or INR ≤ 1.5. (In patients receiving anticoagulants (such as warfarin) INR must be between 2.0 and 3.0 in two consecutive measurements 1-4 days apart).
- Participant receiving corticosteroids (dose < 10 mg/day methylprednisolone equivalent), including inhaled steroids, may continue as long as their dose is stable for at least 4 weeks prior to initiating protocol therapy.
- Participants must agree to not donate blood during the study or for 90 days after the last dose of study treatment
- Female participant has a negative serum pregnancy test within 7 days prior to taking study treatment if of childbearing potential and agrees to abstain from activities that could result in pregnancy from screening through 180 days after the last dose of study treatment, or is of nonchildbearing potential. Nonchildbearing potential is defined as follows (by other than medical reasons):
  - ≥ 45 years of age and has not had menses for >1 year
  - Patients who have been amenorrhoeic for < 2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range upon screening evaluation
  - Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by imaging. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must be willing to use 2 adequate barrier methods throughout the study, starting with the screening visit through 180 days after the last dose of study treatment. See below for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.
  - Birth Control: Participants of childbearing potential who are sexually active and their partners must agree to the use of a highly effective form of contraception throughout their participation beginning with time of consent, during the study treatment and for 180 days after last dose of study treatment(s):

  - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral route
    - Intravaginal route
    - Transdermal route
  - Progestogen-only hormonal contraception associated with inhibition of ovulation
    - Oral
    - Injectable
    - Implantable
  - Intrauterine device
  - Intrauterine hormone-releasing system
  - Bilateral tubal occlusion
  - Vasectomized partner
  - Sexual abstinence, if the preferred and usual lifestyle of the subject
- Participant must agree to not breastfeed (or store breast milk for use) during the study or for 180 days after the last dose of study treatment.
- Able to take oral medications
- Availability of archival ovarian cancer tissue from primary diagnosis (delivery of FFPE block or slides is prerequisite for randomisation)

Conditions for the start of maintenance therapy with Niraparib, or Ganetespib

Before start of the maintenance therapy patients must have following lab values:

- Absolute neutrophil count ≥ 1,500/µL
- Platelets ≥ 100,000/µL
- Hemoglobin ≥ 9 g/dL
- Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault equation
- Total bilirubin ≤ 1.5 x ULN (≤2.0 in patients with known Gilberts syndrome) OR direct bilirubin ≤ 1 x ULN
- Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x ULN unless liver metastases are present, in which case they must be ≤ 5 x ULN

Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Ovarian tumours with low malignant potential (i.e. borderline tumours)

- Any prior radiotherapy to the pelvis or abdomen, or any radiotherapy encompassing > 20 % of the bone marrow within 2 weeks, or any radiotherapy within 1 week prior to Day 1 of protocol therapy
- Surgery (including open biopsy and traumatic injury) within 4 weeks prior to first dose of Ganetespib, or anticipation of the need for major surgery during study treatment
- Minor surgical procedures, within 24 hours prior to the first study treatment
- Known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).
- Any serious, uncontrolled medical disorder, non-malignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, chronic obstructive pulmonary disease, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
- Current or recent (within 10 days prior to the first study drug dose) chronic daily treatment with aspirin (>325 mg/day).
- Patients with a history of diagnosis, detection or treatment of any prior malignancies ≤ 2 years prior to initiating protocol therapy, except: basal or squamous cell carcinoma of the skin and cervical cancer that has been definitively treated.
- Clinically significant gastro-intestinal (GI) tract abnormalities that may increase the risk for GI bleeding and / or perforation including but not limited to: active peptic ulcer disease, known intraluminal metastatic lesion/s with risk of bleeding; inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease), history of bowel obstruction within 1 year prior to first study treatment (excluding postoperative, i.e. within 4 weeks post surgery), other GI condition with increased risk of perforation such as recurrence deeply infiltrating into the muscularis or mucosa of the rectosigmoid or the mucosa of the bladder, or history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess
- Non-healing wound or non-healing bone fracture
- Patients with symptomatic brain or leptomeningeal metastases (patients who are asyptomatic since treatment of brain or leptomeningeal metastases, eg. after irradiation, are eligible)
- Left ventricular ejection fraction (LVEF) defined by ECHO below the institutional lower limit of normal
- Cerebrovascular accident (CVA)/ stroke or transient ischemic attack (TIA) or sub-arachnoid haemorrhage within ≤ 6 months prior to first study treatment.
- Significant cardiac disease: New York Heart Assiciation (NYHA) Class 3 or 4; myocardial infarction within the past 6 months; unstable angina; coronary angioplasty or coronary atrial or ventricular cardiac arrhythmias

- History of prolonged QT syndrome, or family member with prolonged QT syndrome
- QTc interval > 470 msec when 3 consecutive ECG values are averaged
- Ventricular tachycardia or a supraventricular tachycardia that requires treatment with a Class Ia antiarrhythmic drug (e.g. sotalol, amiodarone, dofetilide). Use of other antiarrhythmic drugs is permitted
- Second- or third-degree atrioventricular (AV) block, except: treated with a permanent pacemaker
- Complete left bundle branch block (LBBB)
- Concomitant use of drugs which prolong QTc interval and have a known risk to cause Torsade de Pointes (see appendix F for a non-exhaustive list)
- History of evidence of haemorrhagic disorders, patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorders, coagulopathy or tumour involving major vessels.
- Participation in another clinical study with experimental therapy within 28 days or five half-lives (whichever is shorter) of experimental therapy before start of treatment.
- Participant must not be simultaneously enrolled in any interventional clinical trial.
- Women who are pregnant or are lactating
- Patients unable to be regularly followed for any reason (geographic, familiar, social, psychologic, housed in an institution eg. prison because of a court agreement or administrative order)
- Subjects that are dependent on the sponsor/CRO or investigational site as well as on the investigator.
- History of known hypersensibility against any medication used in the study
- Intolerance / Hypersensitivity reactions to components and exipients of study drugs
- Peripheral neuropathy of grade >2 per NCI CTCAE, version 5.0, within 4 weeks prior to randomization
- Administration of a live, attenuated vaccine within 30 days prior to Cycle1 Day 1 or anticipation that such a live attenuated vaccine will be required during the study. Examples of live vaccines include but are not limited to: measles, mumps, rubella, varicella zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), typhoid and intranasal influenza vaccines (eg. Flumist®). Inactivated influenza vaccinations can be administered during the flu season.
- Any other condition that, in the opinion of the investigator, may compromise the safety, compliance of the patient, or would preclude the patient from successful completion of the study

Endpoints

Primary endpoint:
Progression-free survival (PFS) by RECIST 1.1

Secondary endpoints:
PFS according to pre-defined subgroups
Post-progression PFS (PFS2)
Time to First Subsequent Therapy (TFST)
Time to Second Subsequent Therapy (TSST)
Safety: Adverse events (AEs), measure according to NCI CTCAE, version 5.0
Objective response rate (ORR)
Patient-reported outcome (PRO)
Overall survival (OS)

Experimental endpoints:
Biomarker analysis on DNA, RNA and protein level (e.g. free circulating tumour DNA, circulating tumour cells etc.)

5 SCHEMATIC DIAGRAM OF THE STUDY DESIGN

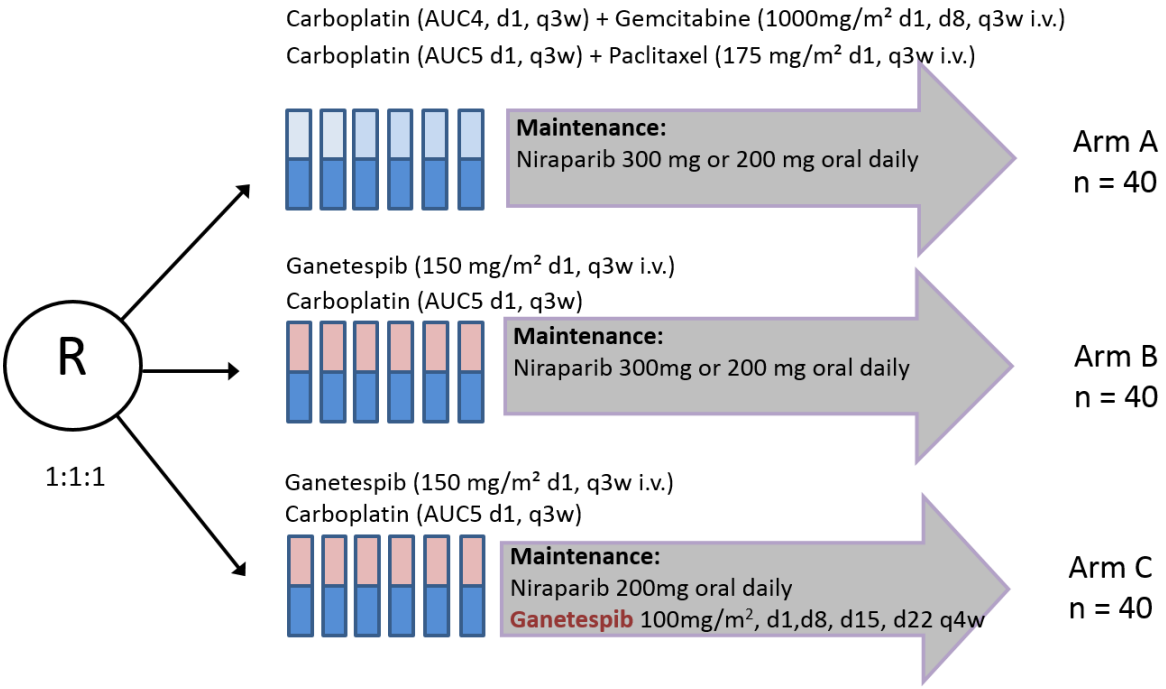

Figure 1: Schematic diagram of the study design

6 ABBREVATIONS AND DEFINITIONS

AE	adverse events
AGO	Arbeitsgemeinschaft Gynäkologische Onkologie
Akt	protein kinase B
ALT (SGPT)	alanine-aminotransferase
ALK	anaplastic lymphoma kinase
AMG	Arzneimittelgesetz (Austrian Drug Law, German Drug Law)
AML	Acute Myeloid Leukemia
ANC	absolute neutrophil count
AP	alkaline phosphatase
AST (SGOT)	aspartate-aminotransferase
ATPase	adenosine triphosphatase
AUC	area under the curve
bcr-abl	fusion gene
BP	Blood pressure
BRAF	v-raf murine sarcoma viral oncogene homolog B
BRCA	Breast Cancer Gene
BSA	body surface area
B-Raf	proto-oncogene
CA	Competent Authority
CA-125	carbohydrate antigen 125
CBC	complete cell count
CDK4	cyclin-dependent kinase 4
C_{max}	maximum drug concentration
c-MET	proto-oncogene
CRF	case report form
CRO	clinical research organisation
c-Src	proto-oncogene tyrosine-protein kinase Src
CR	complete response
CT	computed tomography
CTC	circulating tumour cells
CTCAE	common terminology criteria for adverse events
CTNNB1	catenin (cadherin-associated protein), beta 1
CYP	cytochrome protein
DEHP	Di-Ethylhexyl Phthalate
DLT	dose-limiting toxicity
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ECG	electrocardiography
ECOG PS	Eastern Co-Operative Oncology Group performance status
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
EORTC	European Organisation for Research and Treatment of Cancer

EOS	end of study
EOT	end of treatment
EPO	Erythropoietin
ESF	Eligibility Screening Form
FDA	Food & Drug Administration
FFPE	formalin-fixed paraffin-embedded
FPI	first patient in
GCIG	Gynaecologic Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GFR	glomerular filtration rates
GI	gastrointestinal
GIP	Gastrointestinal perfusion
HDPE	high-density polyethylene
HER2	human epidermal growth factor receptor 2
HGS	high-grade serous
HR	hazard ratio
HR	Hard rate
Hsp90	heat shock protein 90
Hsp90i	Hsp90 inhibitor
IB	Investigator Brochure
ICH	International Conference of Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IMP	investigational medical product
IRB	institutional review board
ISF	Investigator Site File
IST	investigator-sponsored clinical trial
ITT	intention-to-treat
iv	intravenous
KIT	signalling protein
KRAS	v-ki-ras2 kirsten rat sarcoma viral oncogene homolog
LCK	lymphocyte-specific protein tyrosine kinase
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
M	month
MDS	Myelodysplastic Syndromes
MTD	Maximum Tolerated Dose
MRI	magnetic resonance imaging
mutp53	mutant p53
NCI	National Cancer Institute
NYHA	New York Heart Association
OC	Ovarian cancer
ORR	objective response rate
OS	overall survival
p53	tumour protein

PARP	Poly(adenosine diphosphate-ribose) polymerase
PCR	polymerase chain reaction
PD	partial response
PET	positron emission tomography
PFI	Platinum-free interval
PFS	progression-free survival
PICCS	peripherally-inserted central catheters
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PK	pharmacokinetics
PLA	proximity ligation assay
PLD	pegylated liposomal doxorubicin
PLT	Platelet
PROC	platinum-resistant ovarian cancer
PRO	patient-reported outcome
PTEN	phosphatase and tensin homolog
Pt-R	platinum-resistant
PVC	Polyvinyl Chloride
QT	interval between Q wave and T wave in the hearts electrical cycle
RBC	red blood cells
RECIST	response evaluation criteria in solid tumours
RNA	Ribonucleic Acid
SAE	serious adverse event
SAHA	suberoylanilide hydroxamic acid
SD	stable disease
SOP	standard operating procedures
SGOT	serum glutamate-oxaloacetate-transaminase
SGPT	serum glutamate-pyruvate-transaminase
SUSAR	suspected unexpected serious adverse reaction
T	Temperature
TCGA	Cancer Genome Atlas Research Network
TdP	Torsades de Pointes
TEAE	Treatment-Emergent Adverse Event
TMG	Trial Management Group
UGT	uridine diphosphate-glucuronosyltransferase
ULN	upper limit of normal
VAD	vascular access devices
VEGFR	vascular endothelial growth factor receptors
WBC	white blood cells
WHO	World Health Organization
WOCBP	women of childbearing potential
wtp53	wild type p53

Definitions

Women of childbearing potential (WOCBP): is defined as premenopausal women or less than 12 months of amenorrhoea post-menopause, and women who have not undergone surgical sterilisation or hysterectomy or bilateral salpingo-oophorectomy.

7 BACKGROUND AND STUDY RATIONALE

7.1 Ovarian cancer

Epithelial ovarian cancer (EOC) is the most lethal gynaecological malignancy. Recent data from the EUROCARE database showed a 5-year relative survival for European women diagnosed with EOC of only 38 % (range 31-41 % by European region; (1)). Across Europe 66,700 women are diagnosed with ovarian cancer and 41,900 die of the disease every year. This high mortality rate is due to the predominance of late-stage diagnoses, a high relapse rate after primary therapy and poor response of metastatic platinum-resistant tumours to current regimens. 70 % of EOC patients present with metastasised disease at the time of primary diagnosis (peritoneal carcinosis).

The current standard of primary therapy is cytoreductive surgery and adjuvant platinum-based chemotherapy. The addition of bevacizumab has been shown recently to improve progression-free survival in women with ovarian cancer (2). Initial response rates to primary therapy are high, but *inevitably* the vast majority of patients will relapse within a short period of time and ultimately die of the disease.

Treatment strategy for **recurrent ovarian cancer** depends on the platinum-free interval, which is the time between the last platinum-based therapy and the detection of relapse. If the progression of the disease is more than 6 months after the last platinum-based therapy, the tumour is considered to be platinum-sensitive and can be retreated with Carboplatin in different combinations such as with Paclitaxel, Gemcitabine or pegylated liposomal Doxorubicine (PLD).

Recent data on Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor (PARPi) treatment have led to approval of Lynparza in the maintenance treatment of relapsed, platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer with mutations in the BRCA1 or 2 genes in Europe (3). PARPi interfere with the repair mechanism of single strand DNA breaks, which allows DNA damage to progress and to result in double strand breaks. PARPi treatment of tumour cells with homologous recombination deficiency, for instance BRCA1/2 mutation, results in synthetic lethality. Furthermore, recently patients receiving Niraparib, a PARP1/2 inhibitor, as maintenance therapy, showed a significant longer progression free survival in the recently published NOVA study (4). This effect was independent of BRCA mutation status.

7.2 Study Rationale

In this study we will evaluate the therapeutic benefit of broad DNA repair pathway inhibition after induction of DNA damage.

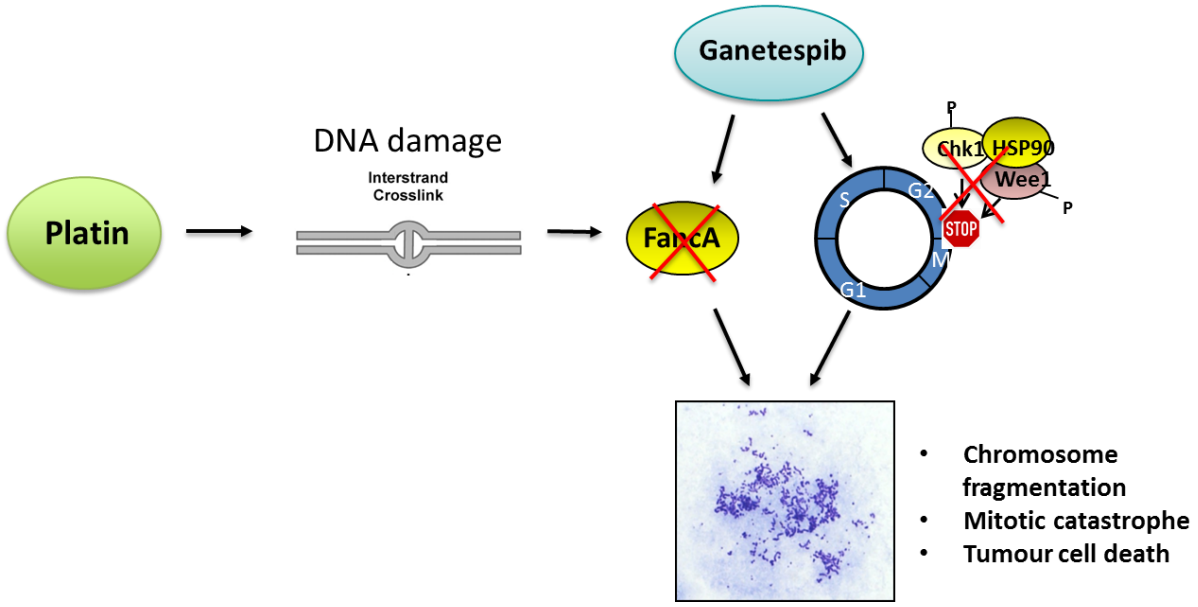

Figure 2: Hypothesized mechanism of action in Eudario Trial (5)

This is achieved by combining 1) standard induction platinum-based chemotherapy with an HSP90 inhibitor on one hand and 2) maintenance PARP inhibitor treatment combined with an HSP90 inhibitor on the other hand. We use the clinically most advanced HSP90 inhibitor, Ganetespib. Our approach of broad DNA repair inhibition is applied in tumours with a mutant p53 background (corresponding to specific histological subtypes) to maximize potential therapeutic effects.

7.2.1 Rationale for Combination of Carboplatin with Ganetespib

HSP90 inhibitors destabilise a number of HSP90 client proteins, such as those governing the Fanconi Anemia DNA repair pathway (e.g. FancA) and the G2/M checkpoint (e.g. Chk1 and Wee1). This raises the possibility for using HSP90 inhibitors in combination with DNA damaging chemotherapeutics to induce massive chromosome fragmentation followed by cell death.
Carboplatin is used as first line therapy in ovarian cancer patients as well as in the platinum-sensitive relapsed situation. It mainly acts by forming interstrand crosslinks (ICL) within the DNA double helix, which can only be removed by the Fanconi Anemia pathway. Since key proteins of the Fanconi Anemia pathway are HSP90 clients (e.g. FancA), HSP90 inhibitor Ganetespib virtually eliminates a functional Fanconi Anemia DNA repair complex, thereby preventing the repair of DNA interstrand crosslinks. In parallel, Ganetespib abrogates Chk1 and Wee1 expression thereby circumventing a G2/M arrest of DNA-damaged tumour cells. Consequently, cells with unrepaired DNA damage rush into mitosis, thereby inducing massive tumour cell death.

Importantly, untransformed cells are protected against Carboplatin/Ganetespib induced cell death due to an intact G1 checkpoint triggering a transient cell cycle arrest rather than cell death. Thus, Ganetespib sensitizes ovarian carcinoma cells specifically towards ICL-inducing drugs such as Carboplatin, Cisplatin, or Mitomycin C, by inhibiting DNA repair and blocking the induction of a G2/M cell cycle arrest.

Our publication by Kramer et al. 2016 (5) showed that the combination of Carboplatin and Ganetespib (CG) strongly decreases viability of a large panel of human ovarian cancer (OC)-derived cell lines. Effects occur synergistically when compared to single-drug treatment. This was systematically quantified by the classic drug interaction algorithm of Chou and Talalay. By immunostaining and immunoblot analysis of phosphorylated histone H2AX and phospho-Kap1 (markers for DNA damage) it was shown that the combination of Carboplatin and Ganetespib increased detectable DNA damage to a greater extent than the single drugs. Consequently, the combination of Carboplatin and Ganetespib induces cell death in OC cells more strongly than Carboplatin or Ganetespib alone. In metaphase spreads massive chromosome fragmentation induced by combined Carboplatin and Ganetespib but not by the individual drugs was observed. In *in vivo* studies with OC xenografts, the combination of Carboplatin and Ganetespib strongly synergises in the inhibition of tumour growth and induction of tumour cell death. Importantly, the synergy of Carboplatin and Ganetespib is far superior when compared to the combination of Paclitaxel and Ganetespib (see Fig. 6e in Kramer et al.(5)), the drug combination that did not lead to favourable clinical results in a premature interim analysis of the randomised Phase II GANNET53 trial. This data justifies a new trial testing the combination of Carboplatin plus Ganetespib.

Another rationale for using Ganetespib as Fanconi Anemia (FA) repair inhibitor in the cohort of mutant p53 ovarian cancer patients studied in this clinical trial comes from recent studies by Jaber et al (6).This study shows in mouse and human tissues that wild type p53 downregulates the Fanconi Anemia DNA crosslink repair pathway by repressing 12 FA genes. The authors used the wtp53 activating drug Nutlin3a, as well as a knockin p53 delta 31 mouse expressing a truncated wt p53 which is missing the last 31 amino acids at the p53 C-terminus and generates a hyperactive (unregulated) “wt"p53. p53 delta 31 works by inducing repressive E2F4 binding at these 12 FA genes’ promoters.

This data implies that mutp53 cancer cells have *increased* FA repair activity. Indeed, Jabner et al. also showed that human mutp53 tumours correlate with increased expression of FA genes.Thus, in mutp53 tumours Ganetespib counteracts the aberrant upregulation of FA repair factors by inducing their degradation.

7.2.2 Rationale for Combination of Ganetespib with PARP-inhibitor Niraparib

The latest studies by Mirza et al. (4) suggest the use of PARP inhibitors (PARPis) to treat OC regardless of the BRCA status. Therefore, it will be more straight-forward to justify clinical studies using combinations of Ganetespib not only with Carboplatin but also with PARPis. We have addresses this in unpublished studies, as summarized in the attachment (APPENDIX H). PARPi and Ganetespib together induce more phosphorylated histone H2AX (indicative of DNA damage) than single drug treatment. This was observed by immunoblot analysis and by quantitative immunofluorescence. By Annexin V staining it was shown that PARPi and Ganetespib together induce apoptosis to a greater extent than each drug alone.

Mechanistically, we anticipate that Ganetespib and PARP inhibitors both inhibit multiple pathways required for repair of DNA damage caused by Carboplatin (e.g. Fanconi anemia, non-homologous end joining and homologous recombination). Of note, Ganetespib strongly reduces the amount of BRCA1 in the cell (2, 7). Thus, it creates a deficiency similar to BRCA1-mutant OC cells, which have long been known for their exquisite sensitivity towards PARP inhibitors. Thus, Ganetespib will broaden the synergy of BRCA loss and PARPi to include ovarian carcinomas regardless of their BRCA status (broadening of the sensitive ovarian cancer spectrum). Furthermore combination of Ganetespib and PARPi would prevent the evolvement of possible BRCA re-expression leading to acquired PARPi resistance (8).
All this argues for a combined treatment of HSP90 and PARP inhibitors.

Rationale to test our approach in a p53 mutant background

We will test our approach of broad DNA repair inhibition in ovarian carcinomas with a mutant p53 background (particular histological subtypes, ie. high-grade serous, high-grade endometrioid, undifferentiated, carcinosarcoma). This offers the highest potential for achieving the most profound survival benefit, as these tumours lack a functional G1 checkpoint. While in untransformed, wildtype p53 expressing cells GC treatment leads to the induction of an p53 mediated G1 arrest, mutant p53 expressing cells lacking the option of a G1 arrest. Consequently lack of wildtype p53 leads to high sensitivity towards GC induced loss of G2/M and accumulation of unrepaired DNA damage. Moreover, wildtype p53 is capable of repressing several components of the Fanconi anemia (FA) DNA repair pathway Jaber et al. 2016 (6) the primary mechanism to eliminate Carboplatin-induced DNA crosslinks. Conversely, ovarian cancer cells lacking wildtype p53 are expected to have increased levels of FA pathway activity. This further supports the model of enhanced dependence of p53 mutant ovarian cancer cells on the FA pathway, especially in the context of Carboplatin treatment. Tumour cell addiction would thus increase their vulnerability towards Ganetespib, which strongly suppresses FA components and thus confers Carboplatin sensitivity.

Data from clinico-pathological and molecular studies performed to date led to a model in which EOC can be divided into two broad categories, designated type I and type II tumours (9, 10). In this model, type I and type II refer to critical molecular tumourigenic pathways and not to specific histopathological patterns.
Type II tumours are highly aggressive. They evolve rapidly, have a high metastatic activity and therefore have almost always already spread beyond the ovaries at the time of diagnosis. Thus, this tumour type is the most problematic from a clinical point of view. Moreover, type II tumours account for the overwhelming majority (>70%) of epithelial ovarian cancer (EOC). Histologically, type II tumours are mainly high-grade serous (HGS) carcinomas, and the remainder are high-grade endometrioid, undifferentiated or a subset of clear cell carcinomas. HGS carcinomas account for ~ 85% of all ovarian cancer deaths.
Importantly, type II tumours are characterised by the near ubiquitous presence of *p53 missense* mutations (mut p53) - their preeminent molecular hallmark. Mut p53 proteins highly stabilize in tumour cells and many of them actively promote oncogenicity (called Gain-of-Function mutants). This strongly suggests that mut p53 is a central oncogenic driver in the pathogenesis of these tumours. Ahmed et al (11) sequenced exons 2-11 and intron-exon boundaries in 145 patients with HGS tumours and identified p53 mutations in 96.7% of cases. Also, the Cancer Genome Atlas Research Network (TCGA) completed whole-exome

sequencing on an unprecedented 316 cases of HGS tumours and established that *p53 mutations* are present in > 96 % (12).
In sharp contrast, type I tumours almost always lack *p53* mutations, but often harbour somatic mutations of protein kinase genes including *PIK3CA* and *ERRB2*, and other signalling molecules including *KRAS*, *BRAF, CTNNB1* and *PTEN* (13). Type I tumours are slow-growing, often confined to the ovary at diagnosis, and develop in a stepwise fashion from well-recognised precursors, in most cases borderline tumours. Type I tumours include low-grade serous carcinomas, low-grade endometrioid carcinomas, mucinous carcinoma and a subset of clear cell carcinomas.

8 INFORMATION ON THE INVESTIGATIONAL MEDICINAL PRODUCTS (IMPS) GANETESBIP

For detailed information about Ganetespib please refer to the Investigator's Brochure (IB).

8.1 Name and Chemical Information

Ganetespib exhibits its function by competitively inhibiting the ATPase activity of the Hsp90 core protein. The multicomponent HSP90 (which includes Hsp90 and Hsp70 ATPases, co-chaperones, CHIP) is a molecular chaperone machine from the heat shock family and includes many important signalling proteins that cancers depend on, such as chimeric Alk, Akt, bcr-abl, B-Raf, CDK4, KIT, c-MET, c-Src, EGFR, LCK, HER2 and VEGFR. Of central importance is the fact that mut p53 was recently found to be a Hsp90 client (14, 15).
In vitro, Ganetespib leads to degradation of oncogenic client proteins and is a potent inducer of cell death in many cancer cell lines that depend on high levels of the respective client.
In vivo, it inhibits the growth of human tumour cell lines in mouse xenograft models.

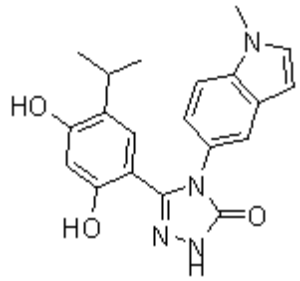

Figure 3: Chemical structure of Ganetespib

Chemical name: 5-[2,4-dihydroxy-5-(1-methylethyl)phenyl]-2,4 dihydro-4-(1-methyl-1H-indol-5-yl)-3H-1,2,4-triazole-3-one.
Ganetespib is a novel triazolone heterocyclic compound. Its molecular formula is C20H20N4O3. Ganetespib is a white-to-off-white solid with a molecular weight of 364.40 g/mol.

8.2 Preclinical experience

Absorption, Distribution, Metabolism and Elimination:
A series of nonclinical pharmacokinetic studies have been conducted in mice, rats, and monkeys. Ganetespib serum levels generally increased in a dose-proportional manner in all species after intravenous (iv) administration. No significant gender differences were observed. In mice, Ganetespib's terminal half-life was about 4 hours after intravenous administration. In rats, Ganetespib's terminal half-life ranged from 2.8 to 12.6 hours. In monkeys, its terminal half-life was 6.3 to 12.3 hours. Ganetespib did not appear to accumulate after repeat dosing. There was minimal cytochrome P450 (CYP) involvement in the metabolism of Ganetespib. The major metabolites were glucuronide conjugates.
Radioactively labelled Ganetespib in rats was widely distributed throughout the body except in the brain. Ganetespib-associated radioactivity was mainly excreted via faeces in rats, and via faeces and urine in monkeys. Ganetespib was extensively bound to plasma proteins in rats, monkeys and humans. Ganetespib appears to be an inhibitor of CYP2C19 and CYP3A4 (midazolam-specific), but does not appear to be an inducer of CYP or uridine diphosphate-glucuronosyltransferase (UGT) enzymes.

Toxicology:
Several studies have been conducted in animals to assess the safety of Ganetespib. Acute toxicity studies revealed that rats survived a single 30 mg/kg dose of Ganetespib. Ganetespib at doses of 85 or 250 mg/kg elicited more pronounced effects, including morbidity and mortality. Histopathological findings were present in the spleen, thymus, adrenal glands, gastrointestinal (GI) tract, and the epiphyseal regions of the bones. High-dosed rats were allowed to recover for 14 days generally returned to normal, although some effects persisted. In rats dosed with 30 mg/kg all findings reversed by 14 days. The maximum tolerated single-administration dose in cynomolgus monkeys was 11 mg/kg; clinical findings at that dose included emesis, watery faeces, and decreased activity. There was also a transient decrease in absolute lymphocyte counts. At 15 mg/kg, the clinical signs above were more pronounced and full recovery required 14 days.
Ganetespib administered once weekly at 4, 7 or 10 mg/kg for four weeks was generally well tolerated by cynomolgus monkeys. One female monkey given 10 mg/kg was euthanized after three doses due to Ganetespib-related toxicity. Monkeys that were analysed to scheduled necropsy had clinical signs that were mild and included soft or liquid faeces. Target organs identified in the treated groups were stomach, gallbladder, testes and the sternal bone marrow; histopathologic changes included degeneration, apoptosis/single cell necrosis and decreased spermatogenesis/spermiogenesis. After four weeks of dosing-free recovery, all changes in the stomach and sternal bone marrow had resolved completely, while in the gallbladder and testes the changes had resolved partially. The mean exposure (AUC 0-24 h) in monkeys after four weekly doses of Ganetespib at 7 mg/kg was 4729 ng/mL. The highest non-severely toxic dose administered once weekly was determined to be 7 mg/kg. In addition, a rising-dose cardiovascular assessment in cynomolgus monkeys showed acceptable cardiac effects, in particular no QT prolongation (Rising dose cardiovascular study, Study No: ECA00170, Charles River).

8.3 Clinical experience

8.3.1 General clinical experience with Ganetespib

Ganetespib has been studied in 11 completed Synta-sponsored clinical trials (Studies 9090-01,9090-02, 9090-03, 9090-04, 9090-05, 9090-06, 9090-07, 9090-08, 9090-09, 9090-11 and 9090-14), and 3 completed Synta-sponsored studies in normal healthy volunteers (9090-12, 9090-13, and 9090-15). Ganetespib has also been studied in 27 ISTs. The majority of ISTs are proof-of-concept studies across a variety of tumour types as well as haematologic malignancies. The ISTs with active patients are Phase I/II studies.

Since the submission of Development Safety Update Report (DSUR) Number 5, which was submitted by Aldeyra Therapeutics, Inc. on November 15, 2016, there have been two (2) additional patients exposed to Ganetespib (study 9090-IST-125) which brings the total estimated cumulative exposure to 1,611 individuals.

As of 21 September 2016, 1,609 individuals (patients and normal, healthy volunteers) have received at least 1 dose of Ganetespib in one of these 41 studies. A total of 402 patients have been treated with single-agent Ganetespib (Studies 9090-01 through Study 9090-06, Study 9090- 09, and Study 9090-11). A total of 412 patients have been enrolled in Studies 9090-07 and 9090-08, of which 222 have been treated with Ganetespib in combination with docetaxel. 696 patients were enrolled in Study 9090-14, of which 338 received Ganetespib. In Synta-

sponsored studies of normal healthy volunteers, 102 subjects have received Ganetespib: 8 in the Human Mass Balance study (9090-12), 46 in the Thorough QT study (9090-13), and 48 in the DDI study (9090-15). The remaining patients (545) have been treated in ISTs.

8.3.2 Phase I/II GANNET53 trial in platinum-resistant ovarian cancer patients (EUDRACT 2013-003868-31)

The clinical partners in this trial have gained extensive experience with the test drug Ganetespib in ovarian cancer in the Phase I and randomised Phase II GANNET53 trial.

Phase I dose escalation/de-escalation GANNET53 trial
Patients and Methods: Eligible patients had platinum resistant ovarian cancer (PROC). Patients with > 4 prior chemotherapy and low-grade carcinoma were not eligible. Weekly Paclitaxel (80 mg/m²) and increasing doses of Ganetespib (100, 150 mg/m²) were given i.v. on days 1, 8, 15 in a 28 days cycle until disease progression or unacceptable toxicity. A traditional 3+3 design was applied with no intra-patient dose escalation. End points were safety and determination of phase II dose. Dose limiting toxicity (DLT) was defined as grade 4 toxicity (with exceptions) occurring in cycles 1 & 2.
Results: In the Phase I dose escalation/de-escalation study a total of ten patients (median age 57 years; range 43-70) were enrolled. No DLT occurred in cohort 1 (4 patients treated with Paclitaxel + Ganetespib 100 mg/m²), nor in cohorts 2 and 3 (6 patients treated with Paclitaxel + Ganetespib 150 mg/m²). Ganetespib in combination with Paclitaxel has been generally well tolerated.

Randomised, open label, multicentre Phase II GANNET53 trial
Patients and Methods: Patients with high-grade serous, high-grade endometrioid or undifferentiated platinum resistant ovarian cancer were randomised in a 1:2 ratio and received either weekly Paclitaxel (80 mg/m²) or a combination of weekly Ganetespib (150 mg/m²) and Paclitaxel (80 mg/m²) i.v. on days 1, 8, 15 in a 28 days cycle. Patients received the respective therapy until disease progression or End of Treatment due to any other cause. After at least six cycles of Ganetespib combination therapy, the physician was allowed to discontinue Paclitaxel (e.g. in case of peripheral neuropathy) and to continue maintenance therapy with Ganetespib (i.e. Ganetespib once a week for 3 out of 4 weeks; at the dose level previously used in the combination or re-escalated to the Ganetespib dose level 0). The primary aim of the phase II study was to determine efficacy of Ganetespib in combination with weekly Paclitaxel compared to weekly Paclitaxel alone.

Preliminary results: The trial is still active but recruitment was terminated early due to the decision of the company to stop the production of Ganetespib. In total 133 of the originally planned 222 patients were included. 90 patients were enrolled in the experimental arm Ganetespib plus Paclitaxel and 43 patients in the active comparator arm receiving single agent Paclitaxel.

8.3.3 Phase I/II MESO-02 trial in patients with malignant pleural mesothelioma (EudraCT No.: 2012-001598-10)

The MESO-2 trial is a Phase I/II study of first line Ganetespib combined with Platinum in patients with malignant pleural mesothelioma. The Phase I dose-escalation trial was conducted at the University College London, UK (PI Prof. Dean Fennell).

Primary outcome measure of the Phase I trial was maximum tolerated dose (MTD) of Ganetespib. Primary endpoint of the Phase I trial was dose limiting toxicities (DLTs) for the Ganetespib, Cisplatin, Pemetrexed combination (during Cycles 1 and 2) and for Ganetespib, Carboplatin, Pemetrexed (during Cycle 1).

The Phase I trial consisted of three Ganetespib dose cohort:

- Cohort 1: 100 mg/m^2 iv on day 1 and day 15 of each cycle
- Cohort 2: 150 mg/m^2 iv on day 1 and day 15 of each cycle
- Cohort 3: 200 mg/m^2 iv on day 1 and day 15 of each cycle

Two experimental arms were investigated:

1) Combination of Ganetespib with **Cisplatin**/Pemetrexed
   Cisplatin 75 mg/m^2, day 1 every 21 days (q3w)
   Pemetrexed 500 mg/m^2, day 1 every 21 days (q3w)
2) Combination of Ganetespib with **Carboplatin**/Pemetrexed
   Carboplatin AUC5, day 1 every 21 days (q3w)
   Pemetrexed 500 mg/m^2, day 1 every 21 days (q3w)

Dose-escalation in the Ganetespib with Cisplatin/Pemetrexed followed a classical 3+3 design (with expansion so that 9 patients would be treated at the MTD). Dose-escalation in the Ganetespib with Carboplatin/Pemetrexed followed an accelerated titration run-in stage using single patients, which switched to a classical 3+3 upon observing first DLT (also with expansion so that 9 patients would be treated at the MTD).

Results of the Phase I trial:
A total of **16 patients** received Ganetespib/**Cisplatin**/Pemtrexed treatment (4 at 100 mg/m^2, 3 at 150 mg/m^2, 9 at 200 mg/m^2 Ganetespib respectively).
A total of **11 patients** received Ganetespib/**Carboplatin**/Pemtrexed treatment (1 at 100 mg/m^2, 1 at 150 mg/m^2, 9 at 200 mg/m^2).
For both experimental treatment arms (Cisplatin and Carboplatin combination) **MTD was established at 200 mg/m^2 Ganetespib dose level**, respectively. In the Cisplatin combination arm one DLT was observed in the 200 mg/m^2 Ganetespib cohort, i.e. nausea, grade 3 lasting longer than 48 hours, respectively. In the Carboplatin combination arm the same DLT, nausea, grade 3 lasting longer than 48 hours was observed in one patient in the 200 mg/m^2 Ganetespib cohort. Furthermore, a second DLT (infusion related reaction) was observed in the 200 mg/m^2 Ganetespib cohort in combination with Carboplatin/Pemetrexed. Two further patients experienced infusion related reactions in the 200 mg/m^2 Ganetespib cohort in combination with Carboplatin/Pemetrexed, but were not classified as formal DLTs as observed outside of the DLT observation time-frame of cycle 1.
In summary, the combination of Carboplatin and Ganetespib (and Pemtrexed as a third drug) was well tolerated in patients with malignant pleural mesothelioma. In the Carboplatin combination arm with Ganetespib two DLTs occurred at the identified MTD of Ganetespib (i.e. 200mg/m^2), which was nausea grade 3 lasting for more than 48 hours and one infusion related reaction, respectively.

8.3.4 Ganetespib Safety Profile

As of September 21, 2016 (data cut - off date for DSUR Number 5), 1,609 patients have been exposed to Ganetespib.

TREATMENT-RELATED SERIOUS ADVERSE EVENTS:

Single-agent Ganetespib (N=402):
Treatment-related **serious adverse events** (expected serious adverse reactions) occurring in ≥ 1% of patient are **diarrhoea (1.7%), asthenia (1.0%) and vomiting (1.0%).**

Ganetespib+Docetaxel combination (most commonly applied Ganetespib combination to date, N=560):
Treatment-related **serious adverse events** occurring in ≥1% of patients are **febrile neutropenia (7.9%), diarrhoea (5.2%), neutropenia (3.8%), asthenia (1.6%), vomiting (1.4%), sepsis (1.3%), anemia (1.2%), dehydration (1.1%), and pneumonia (1.1%).**

TREATMENT-EMERGENT / TREATMENT-RELATED NCI CTAE ≥ Grade 3 ADVERSE EVENTS

Single-agent Ganetespib (N=402):
Treatment-related AEs ≥ Grade 3 occurring in ≥ 1% of patients were **diarrhoea (9.7%), fatigue (6.0%), hyponatraemia (2.5%), lipase increased (2.5%), aspartate aminotransferase increased (2.0%), hypophosphataemia (2.0%), alanine aminotransferase increased (2.0%), nausea (2.0%), vomiting (1.7%), hypokalaemia (1.5%), lymphopenia (1.2%), asthenia (1.2%).**

Ganetespib+ Docetaxel combination (N=222) from Studies 9090-07 (phase I) and 9090-08 (phase II)
Treatment-emergent AEs Grade 4 occurring in ≥ 1% of patients were **neutropenia (26.1%;** in comparison to docetaxel alone in 18.8%**), febrile neutropenia (5.0%;** in comparison to docetaxel alone in 3.2%)**, and leukopenia (1.4%;** in comparison to docetaxel alone in 0%**).**

Ganetespib+ Docetaxel combination (N=338) from Studies 9090-14 (phase III)
Treatment-emergent AEs Grade 4 occurring in ≥ 1% of patients were **febrile neutropenia (3.0%;** in comparison to docetaxel alone in <1%**).**

TREATMENT-EMERGENT / TREATMENT-RELATED NCI CTCAE Grade 5 ADVERSE EVENTS

Single-agent Ganetespib (N=402):
Treatment emergent fatal AEs occurred in 10.9% of patients. The majority of which were due to disease progression (6.7%). Only the single events of cardia arrest (<1%) and acute renal failure (<1%) were considered to be related to Ganetespib treatment.

Ganetespib+ Docetaxel combination (N=222) from Studies 9090-07 (phase I) and 9090-08 (phase II)
17% of patients treated with Ganetespib in combination with docetaxel had experienced a Grade 5 event (death) during the treatment phase and within 30 days of last dose. This percentage is similar to that experienced in the docetaxel-alone arm (13%).
The most common Grade 5 event was neoplasm progression (5% G+D, 5% D). All other Grade 5 events in the combination arm occurred in less than 1% of patients with the exception of pulmonary embolism, pneumonia, and superior vena cava syndrome (1%). In the docetaxel-alone arm, 2% of patients experienced a Grade 5 event of pulmonary embolism, and 1% of patients experienced Grade 5 events of sudden cardiac death and sudden death.

Ganetespib+ Docetaxel combination (N=338) from Studies 9090-14 (phase III)
10% patients had a treatment-emergent AE that resulted in death: 12% in the combination treatment group and 9% in the docetaxel-alone group. Such events were assessed as treatment-related in 4 patients in each treatment group. The most frequent SAE resulting in death was neoplasm progression in both groups: 11 (3%) patients in the combination group and 10 (3%) patients in the docetaxel-alone group. All other Grade 5 events in the combination arm and the docetaxel-alone arm occurred in less than 1% of patients with the exception of "death" in the docetaxel-alone arm (1.2%).

DOSE-LIMITING TOXICITY OF GANETESPIB AND CLASS EFFECTS

Diarrhoea is the most frequent AE associated with the use of Ganetespib and also the well-known dose limiting toxicity of Ganetespib (please see topic 8.3.4.3. "events of special interest with respect to Ganetespib treatment", subtopic "diarrhoea" for detailed information on Ganetespib-induced diarrhoea).
Of importance for the current EUDARIO trial, the combination of Carboplatin and Ganetespib (and Pemtrexed as a third drug) was well tolerated in patients with malignant pleural mesothelioma in the MESO-2 trial. In the combination arm of Carboplatin with Ganetespib two DLTs occurred at the identified MTD of Ganetespib (i.e. 200mg/m^2), which was nausea grade 3 lasting for more than 48 hours and one infusion related reaction, respectively.

Events that may be class effect of HSP inhibitor (besides the already mentioned diarrhoea) include ocular toxicities and elevations in liver enzymes. Importantly, Ganetespib administered as a single agent was **devoid of liver toxicities and visual impairment** associated with other HSP90 inhibitors across all studies.
In patients treated with the HSP90 inhibitors 17-DMAG or AUY922 who experience visual disturbances, the mechanism of visual disturbances is linked to induction of apoptosis in cells in the outer nuclear layer of the retina (17, 18). In contrast, Ganetespib did not elicit induction of apoptosis in preclinical studies using rodent models, consistent with the very low number of reported visual disturbance cases in the clinic.
Liver toxicity in the 1st generation geldanamycin-derivative HSP90 inhibitors is an off-target effect. According to a study by Cysyk (19) the presence of benzoquinone moiety in the molecule is the suspected cause of liver toxicity. Ganetespib does not contain the benzoquinone moiety and, therefore, clinically significant liver toxicity is not expected. This is consistent with the safety information collected to date.

In addition, in single-agent Ganetespib studies there was **no evidence of myelosuppressive effect** (essentially no documented decrease in neutrophil count associated with Ganetespib administration).

8.3.4.1 Adverse Events with Ganetespib in combination with Paclitaxel in ovarian cancer patients (GANNET53 trial)

Phase I dose escalation/de-escalation GANNET53 trial

The most common adverse events (AEs) related to Ganetespib were transient grade 1/2 diarrhea (n=70). The most frequent grade 1/2 AEs were diarrhea (n=70), QT corrected interval prolonged (n=11), neutropenia (n=10), headache (n=7), nausea (n=6), abdominal pain (n=5), constipation (n=5), pain (n=4), fatigue (n=3), dyspnoea (n=3), anemia (n=3), and anorexia (n=3). AEs ≥ grade 3 were diarrhoea (n=5), ascites (n=4), anemia (n=3), neutropenia (n=2), subileus (n=2), acute cardiac failure (n=1), asthenia (n=1), pain (n=1), placement of Tenkhoff-catheter (n=1), polyneuropathy (n=1), syncope (n=1), and vomiting (n=1). There was 1 death on study (after DLT period) due to digestive tract hemorrhage from duodenal ulcer. Three patients discontinued due to SAEs (digestive hemorrhage n=1, cardiac failure n=1, anemia n=1), 5 due to progressive disease, one due to physicians decision. Two patients are still in follow-up. Detailed information on AEs which occurred in more than 1 patient (<10%) in the Phase I GANNET53 trial are summarised in Table 1.

Summary: The combination of Ganetespib 150 mg/m² with Paclitaxel 80 mg/m² once weekly for 3 out of 4 weeks was generally well tolerated with no DLTs, and therefore chosen for the ongoing randomised phase II trial. Comparison of all occurred AEs which were indicated as related (possibly, probably, definitely) to Ganetespib revealed a similar toxicity profile as it was described in the IB:

Table 1: Summary of Adverse events (AEs) (NCI CTCAE v4.03) which occurred in >1 patients in the **Phase I** dose escalation/de-escalation study (Total number of patients N=10)

Grade 1-2 AEs				**Grade 3-4 AEs**			
Reported Term	**number of patients (n=10)**	**number of events (n)**	**Relatedness* to G per patient (n)**	**Reported Term**	**number of patients (n=10)**	**number of events (n)**	**Relatedness* to G per patient (n)**
Diarrhoea	8	70	related (8/10)	**Anemia**	3	3	related (1/10) unrelated (2/10)
QT corrected interval prolonged	6	11	related (5) unrelated (1)	**Diarrhoea**	3	5	related (3/10)
Nausea	6	6	related (3/10) unrelated (3/10)	**Ascites**	2	4	unrelated (2/10)
Headache	5	7	related (3/10) unrelated (2/10)	**Neutropenia**	2	2	related (2/10)
Abdominal pain	5	5	related (1/10) unrelated (4/10)	**Acute cardiac insufficiency stage IV; loss of systolic LV-function**	1	1	related (1/10)
Neutropenia	3	10	related (3/10)	**Asthenia**	1	1	related (1/10)

Fatigue	3	3	related (3/10)	**Pain**	1	1	unrelated (1/10)
Dyspnoea	3	3	related (3/10)	**Placement of Tenckhoff catheter**	1	1	unrelated (1/10)
Pain	3	4	unrelated (3/10)	**Polyneuropathy**	1	1	unrelated (1/10)
Anemia	3	3	related (3/10)	**Subileus**	2	2	unrelated (2/10)
Anorexia	3	3	related (2/10) unrelated (1/10)	**Syncope**	1	1	related (1/10)
Asthenia	2	2	unrelated (2/10)	**Vomiting**	1	1	unrelated (1/10)
Constipation	2	5	unrelated (2/10)				
Alopecia	2	2	related (1/10) unrelated (1/10)				
Dysgeusia	2	2	related (1/10) unrelated (1/10)				
Oedema peripheral	2	2	related (2/10)				
Pruritus	2	2	unrelated (2/10)				
Peripheral neuropathy	2	2	related (2/10)				
Subileus	2	2	unrelated (2/10)				
Weight loss	2	2	related (2)				

* relatedness as evaluated by local PI; AEs categorised as related to study treatment included possibly, probably or definitely related
G…Ganetespib

Randomised, open label, multicentre Phase II GANNET53 trial

Final safety data are not available yet, as the trial is ongoing. A summary of AEs in the first 86 patients are given in Table 2 and Table 3. Two cases of gastrointestinal perforation (GIP) occurred in the randomised Phase II trial leading to a substantial protocol amendment excluding patients with pre-existing risk factors for GIP from study participation (see 8.3.4.3. for more information). This newly identified toxicity has been included into the IB. Besides GIP, comparison of occurred AEs which were indicated as related (possibly, probably, definitely) to Ganetespib revealed a similar toxicity profile as it was described in the IB. In general, good tolerability of Ganetespib in combination with Paclitaxel was seen in the randomised Phase II GANNET53 trial.

Table 2: Summary of preliminary results (as of 23.08.2017) of related Adverse events (AEs) Grade 1-2 (NCI CTCAE v4.03) which occurred in >10 % of patients in the **Phase II** study; included were all patients who received at least one dose of study medication in the experimental arm P+G. (Total number of patients N=86)

Event Grade 1-2 Arm P+G	**Number of patients n (%) (N=86)**	**Number of events**	**Relatedness to G per patient* n_1 (%) (N_1=n)**	**Relatedness to P per patient* n_2 (%) (N_2=n)**
Diarrhoea	75 (87,2)	376	75 (100,0)	37 (49,3)
Anemia	42 (48,8)	65	32 (76,2)	42 (100,0)
Nausea	37 (43,0)	90	36 (97,3)	34 (91,9)

Alopecia	36 (41,9)	37	11 (30,6)	34 (94,4)
Neuropathy peripheral	32 (37,2)	40	11 (34,4)	31 (96,9)
Vomiting	23 (26,7)	37	22 (95,7)	19 (82,6)
Fatigue	22 (25,6)	27	21 (95,5)	21 (95,5)
Abdominal pain	20 (23,3)	24	18 (90,0)	14 (70,0)
Neutrophil count decreased	18 (20,9)	26	12 (66,7)	18 (100,0)
White blood cell decreased	15 (17,4)	24	10 (66,7)	15 (100,0)
Asthenia	13 (15,1)	22	12 (92,3)	12 (92,3)
Insomnia	12 (14,0)	12	12 (100,0)	10 (83,3)
Constipation	11 (12,8)	19	9 (81,8)	9 (81,8)
Electrocardiogram QT corrected interval prolonged	11 (12,8)	26	11 (100,0)	4 (36,4)
Anorexia	10 (11,6)	17	9 (90,0)	9 (90,0)
Headache	9 (10,5)	10	9 (100,0)	7 (77,8)

* relatedness as evaluated by local PI; AEs categorised as related to study treatment included possibly, probably or definitely related
G…Ganetespib
P…Paclitaxel

Table 3: Summary of preliminary results (as of 23.08.2017) of realated Adverse events (AEs) Grade 3 – 5 (NCI CTCAE v4.03); included were all patients who received at least one dose of study medication in the experimental arm P+G (Total number of patients N=86).

Event Grade 3-5 Arm P+G	**Number of patients n (%) (N=86)**	**Number of events**	**Relatedness to G per patient* n_1 (%) (N_1=n)**	**Relatedness to P per patient* n_2 (%) (N_2=n)**
Neutrophil count decreased	11 (12,8)	16	7 (63,6)	11 (100,0)
Diarrhoea	10 (11,6)	14	10 (100,0)	0 (0,0)
Anemia	6 (7,0)	6	5 (83,3)	6 (100,0)
Asthenia	3 (3,5)	3	3 (100,0)	3 (100,0)
Fatigue	2 (2,3)	2	2 (100,0)	1 (50,0)
Febrile neutropenia	2 (2,3)	2	1 (50,0)	2 (100,0)
Lymphocyte count decreased	2 (2,3)	2	1 (50,0)	2 (100,0)
Nausea	2 (2,3)	2	2 (100,0)	1 (50,0)
Sepsis	2 (2,3)	2	2 (100,0)	1 (50,0)
Vomiting	2 (2,3)	2	2 (100,0)	2 (100,0)
White blood cell decreased	2 (2,3)	3	1 (50,0)	2 (100,0)
Alkaline phosphatase increased	1 (1,2)	1	1 (100,0)	1 (100,0)
Allergic reaction	1 (1,2)	1	1 (100,0)	1 (100,0)
Anal hemorrhage	1 (1,2)	1	1 (100,0)	1 (100,0)
Anorexia	1 (1,2)	1	1 (100,0)	1 (100,0)
Ascites	1 (1,2)	3	1 (100,0)	1 (100,0)
Dyspnoea	1 (1,2)	2	1 (100,0)	1 (100,0)
Esophagitis	1 (1,2)	1	1 (100,0)	0 (0,0)
Gastritis	1 (1,2)	1	1 (100,0)	0 (0,0)
General physical health deterioration	1 (1,2)	1	1 (100,0)	0 (0,0)
Hypertension	1 (1,2)	1	1 (100,0)	1 (100,0)
Hypertransaminasemia	1 (1,2)	1	1 (100,0)	1 (100,0)
Icterus	1 (1,2)	1	1 (100,0)	0 (0,0)

Insomnia	1 (1,2)	1	1 (100,0)	1 (100,0)
Intestinal perforation	1 (1,2)	1	1 (100,0)	0 (0,0)
Melaena	1 (1,2)	1	1 (100,0)	1 (100,0)
Rectal ulcer	1 (1,2)	1	1 (100,0)	1 (100,0)
Small intestinal obstruction	1 (1,2)	1	1 (100,0)	1 (100,0)
Small intestinal perforation	1 (1,2)	1	1 (100,0)	0 (0,0)
Transaminases increased	1 (1,2)	1	1 (100,0)	1 (100,0)
Visual acuity reduced	1 (1,2)	1	1 (100,0)	0 (0,0)

* relatedness as evaluated by local PI; AEs categorised as related to study treatment included possibly, probably or definitely related
G…Ganetespib
P…Paclitaxel

8.3.4.2 Adverse Events with Ganetespib in Pemetrexed/Carboplatin in malignant pleural mesothelioma (MESO-02 trial)

In general, the Ganetespib combination with Platin/Pemetrexed was well tolerated at a Ganetespib combination dose level of 150mg/m^2 (to be used in the present trial) in patients included into the MESO-2 trial. A summary of toxicities are given in the text and Table 4, Table 5, Table 6 and Table 7 below, which were kindly provided in personal communication with the studies PI, Sponsor and responsible trial statistician.

Adverse events in treatment cycles 1 and 2 only

Table 4 and Table 5 show the maximum grade (NCI CTCAE v4.0) per adverse event (AE) per patient observed in the MESO-02 trial (on treatment (Ganetespib, pemetrexed and cisplatin/Carboplatin), cycles 1 and 2 only). All patients (N=27) had at least one grade 1 or grade 2 AE [Table 4]. Common AEs include fatigue (n = 17), anemia (n=16), nausea (n=14), anorexia (n=10), constipation (n=10) and dyspnea (n=10). Eleven patients had at least one AE with maximum grade 3 (8 pts) or grade 4 (3 pts) [Table 5]. They included: one patient with hearing impairment (grade 4); two patients with neutrophil count decrease (grade 4); one patient with diarrhea, hyperkalemia, nausea, neutrophil count decrease and platelet count decrease (all grade 3); and one patient with ascites, pleural effusion and upper respiratory infection (all grade 3).

Table 4: Number of patients experiencing AEs of maximum grade 2 (NCI CTCAE v4.0) in treatment cycles 1 and 2

Results given by Organ Class (AE shown if 5 or more patients experience G1 or G2 AE)

Organ Class	**Adverse Event (if 5 or more patients affected)**	**Total**
Blood and lymphatic system		16
	Anemia	*16*
Cardiac		2
Ear and labyrinth		3
Eye		4
Gastrointestinal		19
	Abdominal pain	*6*
	Constipation	*10*
	Diarrhea	*8*

	Nausea	*14*
	Vomiting	*9*
	Weight loss	*5*
General disorders and administration site conditions		21
	Fatigue	*17*
Infections and infestations		9
Investigations		5
Metabolism and nutrition		10
	Anorexia	*10*
Musculoskeletal and connective tissues		8
	Back pain	*6*
Nervous system		2
Other (non CTCAE term)		2
Psychiatric		4
Renal and urinary		2
Respiratory, thoracic and mediastinal		14
	Cough	*7*
	Dyspnea	*10*
Skin and subcutaneous tissue		8
Vascular		3
Total patients experiencing at least one G1 or G2 AE		**27**

Table 5: Number of patients experiencing AEs of maximum grade 3 or 4 (NCI CTCAE v4.0) in treatment cycles 1 and 2

All Adverse Events shown

Organ Class	**Adverse Event**	**CTCAE Grade**	
		3	**4**
Ear and labyrinth	Hearing impaired	0	1
Gastrointestinal	Ascites	1	0
	Diarrhea	1	0
	Nausea	3	0
	Vomiting	1	0
Infections and infestations	Infections and infestations - Other	1	0
	Upper respiratory infection	1	0
Investigations	Neutrophil count decreased	1	2
	Platelet count decreased	2	0
Metabolism and nutrition	Hyperkalemia	1	0
Respiratory, thoracic and mediastinal	Dyspnea	1	0
	Pleural effusion	1	0
	Sleep apnea	1	0
Total patients with at least one Grade 3 or 4 AE	**(Total = 11)**	**8**	**3**

Adverse events at any time

Table 6 and Table 7 show the maximum grade (NCI CTCAE v4.0) per adverse event (AE) per patient observed in the MESO-02 trial (reported at any time on study). All patients (N=27) had at least one grade 1 or grade 2 AE [Table 6]. Common AEs include fatigue (n = 20), dyspnea (n=15), nausea (n=15), anemia (n=13), diarrhea (n=13), anorexia (n=12), constipation (n=12) and vomiting (n=12). Eighteen patients had at least one AE with maximum grade 3 (17 pts) or grade 4 (5 pts) [Table 7]. These included: one patient with hearing impairment (grade 4); one patient with neutrophil count decrease (grade 4) and anemia (grade 3); one patient with neutrophil count decrease (grade 4), syncope and upper respiratory infection (all grade 3); one patient with sepsis (all grade 4) and anxiety (grade 3); and one patient with platelet count decrease (grade 4), anemia, hypokalemia and hyponatremia (all grade 3).

Dose Limiting Toxicity (DLT) summary (copied from Scientific Milestone Report – 10/03/2016)

- "The 3 proposed dose cohorts of Ganetespib + Pemetrexed/Cisplatin have been completed with the top dose of Ganetespib (200 mg/m^2) confirmed as the MTD. One DLT was observed in the 200 mg/m^2 cisplatin cohort (nausea, grade 3 lasting longer than 48 hours)."
- "The 100 and 150 mg/m^2 cohorts for Carboplatin were completed without evidence of any DLTs. As per the dose escalation design, the next 3 patients were recruited to the 200 mg/m^2 cohort (1 DLT observed: infusion-related reaction), and expanded to recruit a further 3 patients. Two patients from the expansion group experienced infusion related reactions in cycle 2 (not classified as 'formal DLTs' as observed in cycle 2. DLT assessments in the Carboplatin cohort are assessed in cycle 1 only). The Trial Management Group (TMG) agreed the 3 occurrences of infusion-related reactions warranted further investigation, and it was agreed the 200 mg/m^2 cohort would be further expanded to include an additional 3 patients. Cohort 3 is now closed to recruitment (including the additional 3 patients as advised by the TMG). One patient from this final expansion group experienced a DLT during cycle 1 (nausea, grade 3 lasting longer than 48 hours). This completes phase I recruitment into the trial."
- "A DLT review meeting carried out for the last dose cohort of Ganetespib + pemetrexed/Carboplatin on 29th February 2016 confirmed that the MTD is 200mg/m^2."

Table 6: Number of patients experiencing AEs of maximum grade 2 (NCI CTCAE v4.0) at any time

Results given by Organ Class (AE specified if at least 5 patients experience G1 or G2 AE)

Organ Class	Adverse Event (if 5 or more patients affected)	Total
Blood and lymphatic system		13
	Anemia	*13*
Cardiac		2
Ear and labyrinth		4
Eye		4
Gastrointestinal		21
	Abdominal pain	*9*
	Constipation	*12*
	Diarrhea	*13*
	Dyspepsia	*5*

	Nausea	*15*
	Vomiting	*12*
	Weight loss	*8*
General disorders and administration site conditions		23
	Fatigue	*20*
	Non-cardiac chest pain	*9*
	Pain	*6*
Infections and infestations		9
	Infections and infestations - Other	*5*
	Upper respiratory infection	*7*
Investigations		7
Metabolism and nutrition		13
	Anorexia	*12*
Musculoskeletal and connective tissue		10
	Back pain	*8*
Nervous system		11
	Peripheral sensory neuropathy	*5*
Other (non CTCAE term)		5
	Other (non CTCAE term)	*5*
Psychiatric		6
	Insomnia	*6*
Renal and urinary		2
Respiratory, thoracic and mediastinal		18
	Cough	*8*
	Dyspnea	*15*
Skin and subcutaneous tissue		11
Vascular		4
Total patients experiencing at least one G1 or G2 AE		**27**

Table 7: Number of patients experiencing AEs of maximum grade 3 or 4 (NCI CTCAE v4.0) at any time

All Adverse Events shown

Organ Class	**Adverse Event**	**CTCAE Grade**	
		3	**4**
Blood and lymphatic system	Anemia	6	0
Ear and labyrinth	Hearing impaired	0	1
Eye	Glaucoma	1	0
Gastrointestinal	Ascites	1	0
	Diarrhea	2	0
	Nausea	4	0
	Vomiting	2	0
Infections and infestations	Infections and infestations - Other	1	0
	Lung infection	1	0
	Sepsis	0	1
	Upper respiratory infection	2	0

	Wound infection	2	0
Investigations	Neutrophil count decreased	3	2
	Platelet count decreased	2	1
Metabolism and nutrition	Hyperglycemia	1	0
	Hyperkalemia	1	0
	Hypokalemia	1	0
	Hyponatremia	1	0
Nervous system	Syncope	1	0
Psychiatric	Anxiety	1	0
Respiratory, thoracic and mediastinal	Apnea	1	0
	Dyspnea	1	0
	Pleural effusion	1	0
	Sleep apnea	1	0
Vascular	Vasculitis	1	0
Total patients with at least one AE of Grade 3 or 4	**(Total = 18)**	**17**	**5**

8.3.4.3 Events of special interest with respect to Ganetespib treatment

Diarrhoea

Diarrhoea is the most frequent adverse event associated with the use of Ganetespib and the well-known dose limiting toxicity of Ganetespib.

The postulated mechanism of action for Ganetespib - induced diarrhoea is inhibition of EGFR in cells that line the gastrointestinal tract, leading to a transient secretory diarrhoea, typically limited to 24 to 48 hours following Ganetespib infusion. This AE is manageable with Loperamide. Prophylactic use of loperamide can reduce the occurrence of diarrhoea from >80% to approximately 40%.

As expected, diarrhoea seen in the Phase I GANNET53 dose escalation/de - escalation study patients was always transient and always, but once, mild or moderate in grade. Only one grade 3 diarrhoea was seen in a patient who was not compliant with respect to Loperamide intake. This led to an aggravation of the grade 2 diarrhoea to a grade 3 diarrhoea.

Also, in the Phase II GANNET53 trial (first 100 patients evaluated) diarrhoea was typically transient and self-limited and mild or moderate in grade.

ECG QT prolonged

The results from a thorough QT study conducted in healthy volunteers (Study 9090-13) reported a modest increase in QT interval 24 hours post Ganetespib dose. The mean ΔΔQTcF reached 21.5 msec. ΔΔQTcF was back to baseline 7 days after Ganetespib dose. One (2 %) subject exhibited QTcF > 450 msec and none greater than 480 msec after Ganetespib administration. Two (4 %) subjects exhibited ΔQTcF > 30 msec and none greater than 60 msec after Ganetespib administration. To date, clinical experience with Ganetespib does not support an evidence of a clinical safety risk for QTc interval prolongation and Torsade de Pointes or other uncontrolled arrhythmias.

Also, in the Phase I GANNET53 dose escalation/de-escalation study a thorough evaluation and review of QT times in all patients was performed. QT prolongations were seen in 6/10

patients. Importantly, all QT prolongations were grade 1. Of note, 5/6 patients already showed a grade 1 QT prolongation prior to the first dosing of ganetetspib. In 1/6 patients a new grade 1 QT prolongation occurred in an ECG 24-hours after Ganetespib dosing. In this patient with a new 24-hours post dose QT prolongation, QT time normalized after switch of Paclitaxel premedication from Odansetron to Granisetron during repeated treatment. Odansetron (in contrast to Granisetron) is known to cause QT prolongation and should not be combined with Ganetespib. In 3/10 patients QT prolongation were evaluated as related (possibly or probably) to Ganetespib by the sponsor. Among these 3 patients, only one patient showed a grade 1 QT prolongation solely in the 24h post Ganetespib dose ECG, probably relating this QT prolongation to the Ganetespib.

Gastrointestinal perforation (GIP)
Gastrointestinal perforation (GIP) has been added as new important identified risk to the IB Edition 11 of 13-November-2015 since two SUSARs of GIP occurred in the randomised Phase II GANNET53 trial. Within the safety database of Synta Pharmaceuticals a total of 6 perforation cases were identified in 1,524 patients (as of 21-September-2015) resulting in a reporting rate of 0.39%. However, within the GANNET53 trial a total of 133 ovarian cancer patients have been included into the randomised Phase II GANNET53 trial, of which 86 were treated with Ganetespib by 26-July-2017 (90 patients were randomised into the Ganetespib combination arm, but 4 never received a single dose of Ganetespib). Two patients with GIP were identified resulting in a reporting rate of 2.33%. Of note, both of these two patients had pre-existing risk factors for GIP (prior to inclusion into the GANNET53 trial).

As a response to the two GIP cases occuring in the GANNET53 phase II trial (first GIP case on 19-July-2015, second GIP case on 26-August-2015), a substantial amendment has been implemented with new in- and exclusion criteria excluding pre-existing risk factors for GIP. With this measure, patient safety with respect to GIP was significantly increased. No case of GIP occurred since the implementation of the adjusted in- and exclusion criteria.
Importantly, these adjusted in- and exclusion criteria are implemented in the current protocol in platinum-sensitive ovarian cancer patients in order to exclude patients with a risk profile for GIP from study participation.

8.3.4.4 Potential overlapping toxicities of the combination of Ganetespib and Niraparib

Potential overlapping toxicities of the Ganetespib/Niraparib combination were estimated based on the available safety data 1) of single-agent Ganetespib in the Investigator`s Brochure (IB edition 13, release date: 07 November 2018), 2) on the combination of Ganetespib with Paclitaxel in platinum-resistant ovarian cancer (randomised Phase II GANNET53 trial, NCT02012192, preliminary safety data in 86 patients have been included into the protocol under the topic 8.3.4.1, for the estimate of overlapping toxicities the final unpublished data in 133 patients have been used herein) and 3) on Niraparib as single-agent maintenance therapy in platinum-sensitive, recurrent ovarian cancer (randomised, placebo controlled Phase III ENGOT-OV16/NOVA trial, NCT01847274; the safety profile has been included into the protocol under topic 9.3.2 and is also published in Mirza et al, NEJM 2016; a total of 553 patients were enrolled).

The most frequent and well-known AE associated with the use of Ganetespib is diarrhoea which is typically low grade and transient, lasting 24-48 hours after Ganetespib administration (postulated mechanism of action is inhibition of EGFR in enterocyte cells that line the GI tract, leading to a transient secretory diarrhoea). Single-agent Ganetespib studies showed no evidence of a myelosuppressive effect. Treatment-related SAEs (Expected Serious Adverse Reactions) occurring in ≥ 1% of patients treated with single-agent Ganetespib (n=402) are diarrhoea (1,7%), vomiting (1%), and asthenia (1%) according to the IB.

In platinum-resistant ovarian cancer patients treated with a Ganetespib/Paclitaxel combination (Phase II GANNET53 trial) transient grade 1/2 diarrhoea occurred in 78.9% of patients and 11.1% of patients experienced ≥ grade 3 diarrhoea (as compared to 25.6% and 4.7% in the Paclitaxel only arm, respectively). In patients treated with the Ganetespib/Paclitaxel combination, nausea ≥ grade 3 was present in 2.2% of and also vomiting ≥ grade 3 occurred in 2.2% of patients (while both were not reported in the Paclitaxel only arm).

Neutrophil count decrease ≥ grade 3 was seen in 12.0% of ovarian cancer patients treated with the Ganetespib/Paclitaxel combination (as compared to 9.3% in the control arm with Paclitaxel alone). Febrile neutropenia occurred in 2.2% of patients treated with the Ganetespib/Paclitaxel combination while no febrile neutropenia was seen in the single agent Paclitaxel arm. Anemia ≥ grade 3 was seen in 7.8% of patients treated with the Ganetespib/Paclitaxel combination (as compared to 9.3% in the Paclitaxel only arm). Of note, no ≥ grade 3 thrombocytopenia occurred, neither in the Ganetespib/Paclitaxel arm nor in the Paclitaxel only arm. Grade 1/2 thrombocytopenia occurred in 6% of patients treated with the Ganetespib/Paclitaxel combination and was not present in the Paclitaxel only arm.
Fatigue grade 1/2 occurred in 23.3% of patients treated with the Ganetespib/Paclitaxel combination and grade ≥ 3 fatigue was seen in 2.2% (as compared to 16.3% and 0% in the Paclitaxel only arm, respectively).

The most relevant AE of Niraparib single agent maintenance treatment in platinum-sensitive ovarian cancer patients (ENGOT-OV16/NOVA trial, (4) is thrombocytopenia, occurring at any grade in 61.3% of patients with 33.8% of patients experiencing grade 3/4 thrombocytopenia (in comparison to 5.6% and 0.6% on the placebo group, respectively). Neutropenia of any grade occurred in 30.2% of patients and 19.6% of patients experienced grade 3/4 neutropenia (in comparison to 6.1% and 1.7% in the placebo group, respectively; no grade 5 events were observed in this ENGOT-OV16 study). The rate of febrile neutropenia was not reported in a table listing all AEs of any grade in at least 10% of patients. Anemia of any grade occurred in 50.1% of patients and at grade 3/4 in 25.3% (in comparison to 6.7% and 0% the placebo group).
Fatigue of any grade occurred in 59 and 0.6% in the placebo arm, respectively).
Diarrhoea of any grade occurred in 19.1% of patients and was grade 3/4 in 0.3% of patients (as compared to 20.7% and 1.1% in the placebo group, respectively). Nausea of any grade occurred in 73.6% of patients with 3% experiencing grade 3/4 nausea (compared to 35.2% and 1.1% in the placebo group, respectively). 34% of patient experienced any grade vomiting and 1.9% of patients had grade 3/4 vomiting (as compared to 16.2% and 0.6% in the placebo group, respectively).
Of note, after dose adjustment on the basis of an individual adverse event profile, the incidence of grade 3/4 neutropenia, thrombocytopenia, or fatigue was infrequent beyond cycle 3 of treatment. Thrombocytopenia was transient and platelet levels stabilised beyond cycle 3.

In summary, while single agent Ganetespib has not shown evidence for a myelosuppressive effect, potential overlapping toxicities of Ganetespib and Niraparib are of hematologic nature. Particularly febrile neutropenia is a potential important risk for combination treatment in ovarian cancer patients. Thrombocytopenia and anemia are important risks in the maintenance treatment of platinum-sensitive ovarian cancer patients with single agent Niraparib. However, the addition of Ganetespib to Paclitaxel has to date not shown to aggravate thrombocytopenia or anemia in platinum-resistant ovarian cancer patients. However, we cannot exclude Ganetespib to aggravate these AEs in combination with Niraparib in platinum-sensitive ovarian cancer patients.
Overlapping toxicities of Ganetespib and Niraparib might also include fatigue and gastro-intestinal adverse events such as diarrhoea, vomiting and nausea.

8.3.4.5 Potential overlapping toxicities of the combination of Ganetespib and Carboplatin

By now, first safety data on the combination of Ganetespib 150mg/m^2 with Carboplatin AUC5 are available in platinum-sensitive ovarian cancer patients treated in the EUDARIO trial. A first IDMC evaluation took place on 2 July 2019 after the first 6 patients were treated with this combination (pre-planned according to protocol) and IDMC concluded that there are no objections to continuation of the study.

The safety data of the first 6 patients is available (Safety data on Carboplatin/Ganetespib combination in the first 6 patients treated within the EUDARIO trial for IDMC evaluation). Meanwhile 11 patients (status 24 July 2019) have been treated with the Ganetespib/Carboplatin combination in the EUDARIO trial without any unexpected safety signal or safety concern.

Further evaluation of potential overlapping toxicities of Ganetespib in combination with Carboplatin by the Sponsor and the Coordinating Investigator are provided herein based on

1) The well-known safety profile of Carboplatin, demonstrating a cornerstone of ovarian cancer treatment (condensed in the Summary of Product Characteristics of Carboplatin (ANNEX III).
2) Ganetespib safety data provided in the Investigator`s Brochure (IB edition 13, release date: 07 November 2018),

The most frequent and relevant AEs and SAEs associated with the use of Ganetespib have already been pointed out above (under the topic of potential overlapping toxicities with Niraparib).
Thus, we focus in the following on Carboplatin and potential overlapping toxicities of both drugs.

Myelosupression is the well-known dose limiting toxicity of Carboplatin and belongs to the very common (>=1/10) carboplatin side-effects. While single agent Ganetespib has not shown evidence for a myelosuppressive effect, potential overlapping toxicities of Ganetespib and Carboplatin are of hematologic nature. Particular febrile neutropenia is a potential important

risk for carboplatin-based combination treatment in ovarian cancer patients. Neutropenia with granulocyte counts below 1000/mm^3 is seen in 18% of patients treated with Carboplatin. Febrile neutropenia is a rare (>=1/10000, <1/1000) adverse event reported with the use of Carboplatin. In patients with normal baseline values, thrombocytopenia with platelet counts below 50.000/m^3 occurs in 25% of patients. Anemia with hemoglobin values of less than 9,5 mg/100ml occurs in about 48% of patients treated with Carboplatin. We cannot exclude Ganetespib to aggravate these AEs in combination with Carboplatin in the ovarian cancer patient population treated in the EUDARIO trial.

Overlapping toxicities of Ganetespib and Carboplatin might also occur with respect to gastro-intestinal adverse events such as diarrhoea, vomiting and nausea. In patients treated with Carboplatin vomiting occurs in 65% of patients (very common), in one-third of whom it is severe. Nausea occurred in an additional 15% (very common), diarrhoea in about 6% (common) and constipation in about 5% (common). Treatment-related SAEs (Expected Serious Adverse Reactions) in patients treated with single-agent Ganetespib include diarrhoea (1,7%), vomiting (1%), and nausea (0.7%) according to the IB edition 13. Of note, nausea grade 3 lasting for more than 48 hours demonstrated a DLT event in the MESO-2 trial when combining Carboplatin with a Ganetespib at the MTD dose of 200mg/m^2 (in a triple combination also involving Pemtrexed). Thus, there is a risk for overlapping toxicity with respect to gastrointestinal adverse events when combining Carboplatin and Ganetespib.

Hepatotoxicity is common in patients treated with Carboplatin. About one third of patients with normal liver function tests show elevated values after treatment with Carboplatin (including elevation of total bilirubin in 5%, SGOT in 15%, and alkaline phosphatase in 24% of patients). However, these modifications are generally mild and reversible in about one half of the patients. Clinically significant liver toxicity in not expected in patients treated with single-agent Ganetespib. Importantly, liver toxicity seen in the 1st generation geldanamycin-derivative HSP90 inhibitor is an off-target effect. The presence of a benzoquinone moiety in the molecule is suspected to have caused liver toxicity. Ganetespib does not contain such a benzoquinone moiety. This is consistent with the safety information collected to date that hepatotoxicity reported as a related serious adverse events in patients treated with single agent Ganetespib occurred in only 0.2% of patients.

Other typical and common (>=1/100, <1/10) adverse events associated with the use of Carboplatin include peripheral neuropathy (in about 6% of patients after treatment with Carboplatin), clinical ototoxicity (about 1% of patients, usually manifestation as tinnitus), lowering of renal function (common AE, defined as decrease in creatinine clearance below 60ml/min) and alopecia. None of these are expected to worsen in a combination treatment with Ganetespib considering the single agent safety profile of Ganetespib.

8.4 Clinical Pharmacokinetics

The PK of Ganetespib, administered at various doses on a weekly or twice weekly schedule, is under investigation in three Phase I trials. Preliminary data and calculated parameters are available from these trials in patients with solid and haematologic tumours and normal healthy male subjects, and are summarised below.

Ganetespib PK shows distribution and elimination phases with concentrations declining by approximately 10-fold within the first hour and nearly 100 fold within 10 hours following infusion termination. Mean terminal half-lives have ranged from approximately 5 to 15 hours in most studies. In the human mass balance study, where PK sampling was most complete and longest (through 96 hours), the mean plasma terminal half-life was 17.9 h (n=8). Ganetespib plasma concentrations following the first and subsequent doses are comparable following either once or twice weekly dosing, indicating the lack of drug accumulation. Ganetespib plasma concentrations are also comparable in the solid and haematologic tumour patients. Cmax and AUC increase in approximate proportion to dose irrespective of dosing day with virtually identical dose exposure ratios for doses given on different days, indicating linear PK (r2 = 0.6680 and 0. 7234 for C_{max} and AUC versus dose, respectively). At doses of 150 mg/m² and 200 mg/m², AUC values of approximately 5600 ng•h/mL and 7600 ng•h/mL are generally expected, respectively. At these same doses, C_{max} values of approximately 3800 ng/mL and 5000 ng/mL, respectively, are generally expected. Ganetespib C_{max} correlates well with AUC (r2 = 0.9309). CL and Vd are approximately constant across therapeutic doses. Ganetespib median CL is approximately 27 L/h/m2.

Two Ganetespib glucuronide metabolites (STA-12-0671 and STA-12-0672) were quantified in three studies; studies 9090-07 (Ganetespib in combination with docetaxel), 9090-12 (human mass balance), and 9090-13 (thorough QT). Metabolite STA-12-0671 mean half-life values ranged from 11.9 to 27 hours. Metabolite STA-12-0672 mean half-life values ranged from 9.4 to 17.9 hours. For both metabolites, T_{max} was typically at the end of the Ganetespib infusion and PK parameters were consistent across sampling days (days 1, 8, and 15).

In study 9090-12 following a single 1-hour IV infusion of 86 mg/m^2 [14C] Ganetespib, median T_{max} total radioactivity in plasma and whole blood occurred at the end of the IV infusion. Total plasma radioactivity half-life was 26.4 hours and 19.6 hours in whole blood.

Ganetespib was extensively metabolised to STA-12-0671, and moderately metabolised to STA-12-0672. Based on the comparison of AUC0-∞, exposure to Ganetespib accounted for approximately 14 % of the total radioactivity in plasma, with exposure to metabolites STA-12-0671 and STA-12-0672 accounting for approximately 50 % and 6 % of the total radioactivity, respectively, resulting in the classification of STA-12-0671 as a “major” metabolite according to the Metabolites in Safety Testing (MIST) guidance.

9 INFORMATION ON THE INVESTIGATIONAL MEDICINAL PRODUCTS (IMPS) NIRAPARIB

9.1 Name and Chemical Information

Niraparib (formerly MK-4827), or 2-{4-[(3*S*)-piperidin-3-yl]phenyl}-*2H*-indazole-7-carboxamide 4-methylbenzenesulfonate hydrate (1:1:1), is an orally available, potent, highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) -1 and -2 inhibitor. The crystalline tosylate monohydrate salt of Niraparib is being developed as a monotherapy agent for tumours with defects in the homologous recombination deoxyribonucleic acid (DNA) repair pathway, as a sensitizing agent in combination with cytotoxic agents and radiotherapy, and in combination with immune-oncology biologics. The Niraparib drug product is formulated as a dry-filled capsule (100 mg) for oral administration.

9.2 Preclinical experience

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

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

9.3 Clinical experience

9.3.1 Phase III NOVA trial in relapsed platinum-sensitive ovarian cancer patients (EudraCT No.: 2013-000685-11)

The primary efficacy and safety data of Niraparib as maintenance treatment in patients with platinum-sensitive recurrent ovarian cancer are derived from a Phase III study (NOVA), which included a total of 367 Niraparib-treated patients at the time of data cut. Niraparib, as a daily oral treatment, prolonged the effect of platinum-based chemotherapy, improved progression-free survival (PFS), and reduced the risk of recurrence or death in a broad population of patients.

Within the germline BRCA mutation (gBRCAmut) cohort, the median PFS was 21.0 months in patients on Niraparib versus 5.5 months on placebo (hazard ratio [HR], 0.27; $p < 0.0001$). PFS was also significantly longer with Niraparib in the homologous recombination deficient-positive (HRDpos) group of the non-gBRCAmut (without germline BRCA mutation) cohort (median, 12.9 months versus 3.8 months; HR, 0.38; $p < 0.0001$) and in the overall non-gBRCAmut cohort (median, 9.3 months versus 3.9 months; HR, 0.45; $p < 0.0001$).

Secondary endpoints, including chemotherapy-free interval (CFI), time to first subsequent treatment (TFST), and progression-free survival 2 (PFS2), confirmed the PFS benefit of Niraparib treatment in both cohorts, provided evidence that niraparib does not diminish responsiveness to subsequent therapy, and demonstrates a persistent treatment effect of Niraparib. There was no evidence of a detrimental impact of Niraparib treatment on overall survival (OS). Dose reductions had no impact on PFS.

Patient-reported outcomes data were similar for patients in the Niraparib and placebo treatment arms. Data from the Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI) and European Quality of Life Scale, 5-Dimensions (EQ-5D-5L) questionnaires showed equivalent outcomes for Niraparib versus placebo for both generic and disease-specific outcomes in the gBRCAmut and the overall non-gBRCAmut cohorts.

The non-gBRCAmut cohort represents patients with diverse tumour biology. Exploratory analyses were conducted to identify any potential drivers of Niraparib treatment effect in these biomarker subgroups (HRDpos/somatic BRCA mutation [sBRCAmut], HRDpos/BRCA wild type [BRCAwt], and HRD negative [HRDneg]). The benefit of Niraparib treatment within the HRDpos group as a whole was not due to patients with somatic BRCA mutations. In the HRDpos primary efficacy population, the median PFS for Niraparib was similar to that seen in HRDpos/BRCAwt patients. The treatment effect observed in the gBRCAmut cohort was comparable to the results observed in HRDpos/sBRCAmut subgroup. Review of data for patients with BRCA mutations (germline or somatic) combined across both the gBRCAmut and non-gBRCAmut cohorts also showed a significant treatment effect.

The overall population of the non-gBRCAmut cohort included patients with tumours that were HRDneg, and exploratory analyses demonstrated that this population experienced a benefit from Niraparib treatment. At 18 months, more than twice as many Niraparib-treated patients than placebo-treated patients were considered progression-free.

9.3.2 Niraparib Safety Profile

Niraparib was evaluated in a series of Phase I clinical trials in patients with solid tumours. 144 patients have been treated with Niraparib at doses up to 400 mg once daily (QD) in Phase I studies. The dose-limiting toxicity (DLT) at this dose was thrombocytopenia; the recommended Phase II dose (RP2D) was determined to be 300 mg QD.

Overall, Niraparib appears to have a predictable adverse event (AE) profile that is readily managed through routine laboratory testing (ie, complete blood count [CBC]) and clinical surveillance (ie, blood pressure monitoring) and adherence to the recommended dose modifications. The most commonly observed non-haematologic treatment-emergent adverse events (TEAEs) (any grades) were nausea, fatigue, constipation, and vomiting; the majority of the non-haematological TEAEs were mild to moderate in severity. The most commonly observed haematologic TEAEs (any grades) were anemia, thrombocytopenia, and neutropenia. The incidence of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) in patients who received Niraparib was similar to that in patients who received placebo. Although Grade 3/4 haematologic laboratory events were common at the initiation of treatment, no severe clinical sequelae were observed and relatively few patients

discontinued due to these AEs. Dose adjustment based on individual tolerability during the first 3 cycles substantially reduced the incidence of these events beyond Cycle 3.

Baseline Platelet Count and Weight as Predictors of Thrombocytopenia.

An analysis was conducted using the data collected in ENGOT-OV16/NOVA and the initial phase I study, PN001. This analysis determined that only baseline platelets had an impact on platelet nadir; lower baseline platelets (<180 109/L) were associated with an increased frequency of thrombocytopenia Grade ≥1 (76 %) or Grade ≥ 3 (45 %) compared to patients with higher baseline platelet counts. Further, an exploratory analysis of clinical data versus baseline body weight from ENGOT-OV16/NOVA was conducted. For this analysis, the weight categories were based on quartiles with the lowest quartile (patients with a body weight less than 58 kg at baseline) compared to the highest quartile (patients with a body weight greater than or equal to 77 kg at baseline). While TEAEs occurred in most patients regardless of body weight, Grade ≥3 TEAEs, SAEs, and TEAEs leading to dose modification or treatment discontinuation occurred more commonly in the weight <58 kg cohort than in the ≥77 kg cohort. In the cohort of patients with a body weight <58 kg, approximately 80 % of patients had a dose reduction compared to 59 % of patients with a weight greater than or equal to 77 kg. Treatment discontinuations were increased in the subjects with lower body weight (24 %) compared to patients in the highest quartile (10 %).

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

Finally, a classification tree approach was used to refine the best cut-off points for predicting the likelihood of a patient developing ≥Grade 3 thrombocytopenia within 30 days after the first dose of Niraparib. The results of the model show that the subgroup of patients with a baseline body weight <77 kg or baseline platelet count <150,000 µL had a grade 3/4 thrombocytopenia rate in the first 30 days of 35.4 % compared to 11.5 % in the group of patients with a body weight >77 kg and a platelet count >150,000 µL. Further, the average daily dose was 258 mg through the first two cycles for patients with a body weight >77 kg and platelet count >150,000 µL, and was only 206 mg for patients with body weight < 77 kg or platelet count <150,000 µL. Thus, the actual delivered dose approximated a starting dose of 200 mg despite the intended delivery of a starting dose of 300 mg. These observations are to be confirmed in the present study with the inclusion of study treatment dosed at 200 mg (2 capsules of Niraparib or placebo) in patients whose baseline weight is <77 kg or baseline platelet count is <150,000 µL.

Influence of Moderate Hepatic Impairment at Baseline

Niraparib dose adjustment is recommended for patients with moderate hepatic impairment. For patients with moderate hepatic impairment, reduce the starting dose of niraparib to 200 mg once daily. The pharmacokinetics of niraparib have been assessed in patients with

moderate hepatic impairment (see Section 9.4.1 Absorption), but have not been assessed in patients with severe hepatic impairment.

9.4 Clinical Pharmacokinetics

9.4.1 Absorption

Following a single-dose administration of 300 mg Niraparib under fasting conditions, Niraparib was measurable in plasma within 30 minutes and the mean peak plasma concentration (C_{max}) for Niraparib was reached in about 3 hours [804 ng/mL (%CV:50.2 %)]. Following multiple oral doses of Niraparib from 30 mg to 400 mg once daily, accumulation of Niraparib was approximately 2 fold.

The systemic exposures (C_{max} and AUC) to Niraparib increased in a dose proportional manner when the dose of Niraparib increased from 30 mg to 400 mg. The absolute bioavailability of Niraparib is approximately 73 %, indicating minimal first-pass effect.

Concomitant administration of a high fat meal did not significantly affect the PK of Niraparib after administration of 300 mg of Niraparib.

In a recently completed clinical study of cancer patients using NCI-ODWG criteria to classify the degree of hepatic impairment, niraparib AUC_{inf} in patients with moderate hepatic impairment was 1.56 (90% CI: 1.06 to 1.30) times the niraparib AUC_{inf} in patients with normal hepatic function following administration of a single 300 mg dose.

9.4.2 Distribution

Niraparib was moderately protein bound to human plasma (83.0 %). The apparent Vd/F was 1220 L, indicating extensive tissue distribution of Niraparib. In a population PK analysis, the Vd/F of Niraparib was 1074 L in cancer patients.

9.4.3 Metabolism

Niraparib is metabolized primarily by CEs to form a major inactive metabolite, M1. In a mass balance study, M1 and M10 (the subsequently formed M1 glucuronides) were the major circulating metabolites. The mean half-life of M1 was 88 hours. The exposure ratio of M1 to Niraparib was approximately 1.3-2.2 fold in plasma.

9.4.4 Elimination

Following a single oral 300-mg dose of Niraparib, the mean terminal half-life of Niraparib ranged from 48 to 51 hours (approximately 2 days). In a population PK analysis, the apparent total clearance of Niraparib was 16.2 L/h in cancer patients.

Niraparib is eliminated primarily through the hepatobiliary and renal routes. Following administration of a single oral 300 mg dose of [14C]-Niraparib, on average 86.2 % (range 71 % to 91 %) of the dose was recovered in urine and feces over 21 days. Radioactive recovery in the urine accounted for 47.5 % (range 33.4 % to 60.2 %) and the feces for 38.8 % (range 28.3 % to 47.0 %) of the dose. In pooled samples collected over 6 days, 36.7 % of the dose

was recovered in the urine primarily as metabolites and 21.1 % of the dose was recovered in the feces primarily as unchanged Niraparib.

9.4.5 Specific Populations

Geriatric Patients: Population PK analyses indicated that age had no significant impact on the PK of Niraparib.

Pediatric Patients: No studies have been conducted to investigate the PK of Niraparib in pediatric patients.

Racial or Ethnic Groups: Population PK analyses indicated that race had no significant impact on the PK of Niraparib.

10 INFORMATION ON THE COMPARATOR PRODUCTS (NON-IMP)

Study treatment with Ganetespib will be compared to two different options of standard treatment which are combined with Carboplatin in arm A. Therefore these products are investigational products, however treatment with these will be performed according to the local standard of care of the hospital.

10.1 Gemcitabine

Commercially available Gemcitabine will be utilized in this study, all available products are allowed. See the Gemcitabine SmPC, for more details.

10.2 Paclitaxel

Commercially available Paclitaxel will be utilized in this study, all available products are allowed. See the Paclitaxel SmPC, for more details.

11 INFORMATION ON THE NON-INVESTIGATIONAL PRODUCT (NON-IMP)

11.1 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 to obtain an AUC5 or AUC4 regarding on the combination drug. For more details see the Carboplatin SmPC.

12 STUDY DESIGN

12.1 Description of study

This is a multicentre, international, open-label, three-arm, randomised (1:1:1) Phase II study. The study design is depicted in Figure 4: Study design.

TREATMENT ARMS:

ARM A (standard arm):
Choice of two regimens, based on investigator decision: Carboplatin (AUC4; d1, q3w) + Gemcitabine (1000 mg/m²; d1 + d8, q3w) or Carboplatin (AUC5; d1, q3w) + Paclitaxel (175 mg/m²; d1, q3w); followed by maintenance treatment with Niraparib (200 mg/ 300 mg oral daily, q4w)

ARM B (first experimental arm):
Carboplatin (AUC5, d1, q3w) + Ganetespib (150 mg/m²; d1, q3w);
followed by maintenance treatment with Niraparib (200 mg/ 300 mg oral daily, q4w)

ARM C (second experimental arm):
Carboplatin (AUC5, d1, q3w) + Ganetespib (150 mg/m², d1, q3w);
followed by maintenance treatment with Niraparib (200 mg oral daily, q4w) + Ganetespib (100 mg/m²; d1, d8, d15, d22, iv q4w)

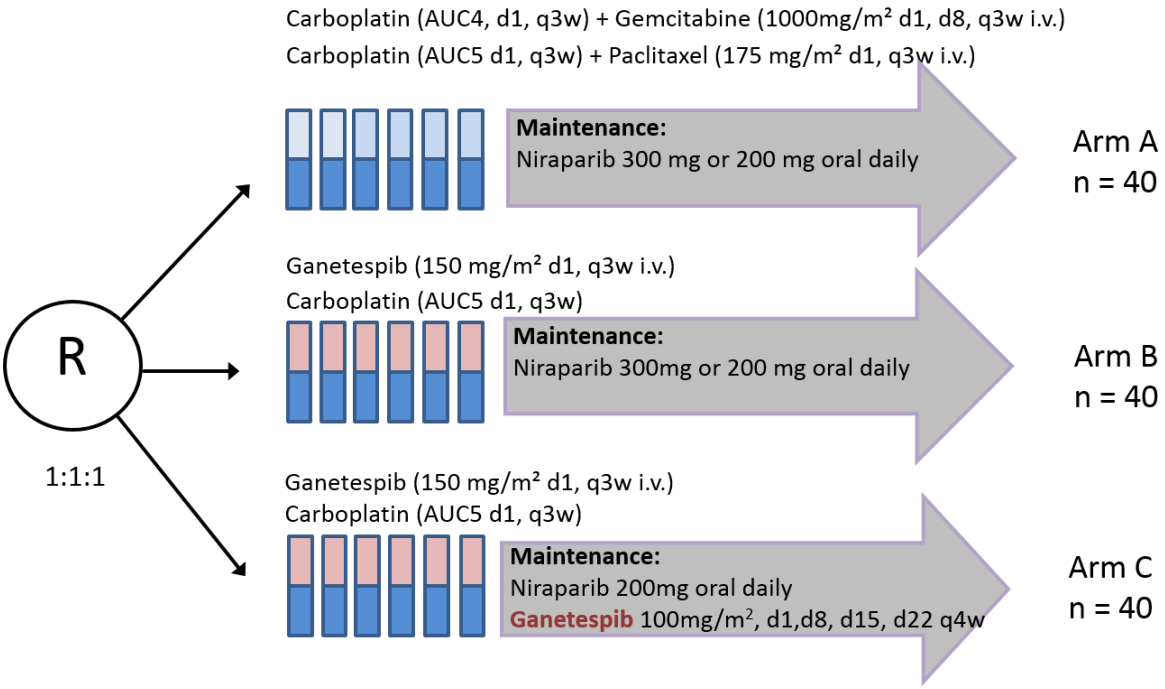

Figure 4: Study design

12.2 Subject population

The study target population consists of female patients with high-grade serous, high–grade endometrioid, undifferentiated epithelial ovarian cancer, carcinosarcoma, fallopian tube or primary peritoneal cancer. By definition, patients will have experienced progressive disease > 6 months after previous platinum based treatment. There are no limits in number of prior treatment lines.

12.3 Subject eligibility

Before any study-specific procedure, the appropriate written informed consent must be obtained.

1. Inclusion criteria

Patients must meet the following criteria to be eligible for study entry:

- Signed and dated written informed consent prior to admission to the study in accordance with ICH-GCP guidelines and with the local legislation.
- Female patients ≥ 18 year of age
- High-grade serous, high grade endometrioid, undifferentiated epithelial ovarian, or carcinosarcoma, fallopian tube or primary peritoneal cancer
- Platinum-sensitive relapse > 6 months after previous platinum-based treatment (calculated from the first day of the last cycle of the last platinum based chemotherapy until the date of progression confirmed according to RECIST 1.1 on imaging)
- No limits in number of prior treatment lines
- Measurable or evaluable disease according to RECIST 1.1
- ECOG performance status 0-1
- Adequate functions of the bone marrow:
    - Platelets ≥ 100 x 10^9/L
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    - Hemoglobin ≥8.5 g/dl (patients may not receive a transfusion within 4 weeks prior to initiating study treatment)
- Adequate function of the organs:
    - Creatinine ≥ 30ml/min, as calculated using the Cockroft-Gault equation
    - Total bilirubin ≤ 1.5 x upper limit of normal (≤ 2.0 in patients with known Gilberts syndrome) OR direct bilirubin ≤ 1 x ULN
    - SGOT/SGPT (AST/ALT) ≤ 2.5 x upper limit of normal unless liver metastases are present, in which case they must be ≤ 5 x ULN
    - Urinanalysis or urine dipstick for proteinuria less than 2+. Patients with ≥ 2+ on dipstick should undergo 24-hour urine collection and must demonstrate < 1 g of protein/24 hours; except the proteinuria is clearly related to a catheter in the urinary system.
- Adequate coagulation parameter: aPTT ≤ 1.5 x ULN (patients on heparin treatment must have an aPTT between 1.5-2.5 x ULN), or INR ≤ 1.5. (In patients receiving anticoagulants (such as warfarin) INR must be between 2.0 and 3.0 in two consecutive measurements 1-4 days apart).

- Participant receiving corticosteroids (dose < 10 mg/day methylprednisolone equivalent), including inhaled steroids, may continue as long as their dose is stable for at least 4 weeks prior to initiating protocol therapy.
- Participant must agree to not donate blood during the study or for 90 days after the last dose of study treatment.
- Female participant has a negative serum pregnancy test within 7 days prior to taking study treatment if of childbearing potential and agrees to abstain from activities that could result in pregnancy from screening through 180 days after the last dose of study treatment, or is of nonchildbearing potential. Nonchildbearing potential is defined as follows (by other than medical reasons):
    - ≥ 45 years of age and has not had menses for >1 year
    - Patients who have been amenorrhoeic for < 2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range upon screening evaluation
    - Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by imaging. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must be willing to use 2 adequate barrier methods throughout the study, starting with the screening visit through 180 days after the last dose of study treatment. See below for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.
    - Birth Control: Participants of childbearing potential who are sexually active and their partners must agree to the use of a highly effective form of contraception throughout their participation beginning with time of consent, during the study treatment and for 180 days after last dose of study treatment(s):
        - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
            - Oral route
            - Intravaginal route
            - Transdermal route
        - Progestogen-only hormonal contraception associated with inhibition of ovulation
            - Oral
            - Injectable
            - Implantable
        - Intrauterine device
        - Intrauterine hormone-releasing system
        - Bilateral tubal occlusion
        - Vasectomized partner
        - Sexual abstinence, if the preferred and usual lifestyle of the subject
- Participant must agree to not breastfeed (or store breast milk for use) during the study or for 180 days after the last dose of study treatment.
- Able to take oral medications

- Availability of archival ovarian cancer tissue from primary diagnosis (delivery of FFPE block or slides is prerequisite for randomisation)

2. Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Ovarian tumours with low malignant potential (i.e. borderline tumours)
- Any prior radiotherapy to the pelvis or abdomen, or any radiotherapy encompassing > 20 % of the bone marrow within 2 weeks, or any radiotherapy within 1 week prior to Day 1 of protocol therapy.
- Surgery (including open biopsy and traumatic injury) within 4 weeks prior to first dose of Ganetespib, or anticipation of the need for major surgery during study treatment
- Minor surgical procedures, within 24 hours prior to the first study treatment
- Known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).
- Any serious, uncontrolled medical disorder, non-malignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, chronic obstructive pulmonary disease, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
- Current or recent (within 10 days prior to the first study drug dose) chronic daily treatment with aspirin (> 325 mg/day).
- Patients with a history of diagnosis, detection or treatment of any prior malignancies ≤ 2 years prior to initiating protocol therapy, except: basal or squamous cell carcinoma of the skin and cervical cancer that has been definitively treated.
- Clinically significant gastro-intestinal (GI) tract abnormalities that may increase the risk for GI bleeding and / or perforation including but not limited to: active peptic ulcer disease, known intraluminal metastatic lesion/s with risk of bleeding; inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease), history of bowel obstruction within 1 year prior to first study treatment (excluding postoperative, i.e. within 4 weeks post surgery), other GI condition with increased risk of perforation such as recurrence deeply infiltrating into the muscularis or mucosa of the rectosigmoid or the mucosa of the bladder, or history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess
- Non-healing wound or non-healing bone fracture
- Patients with symptomatic brain or leptomeningeal metastases (patients who are asyptomatic since treatment of brain or leptomeningeal metastases, eg after irradiation, are eligible)
- Left ventricular ejection fraction (LVEF) defined by ECHO below the institutional lower limit of normal
- Cerebrovascular accident (CVA)/ stroke or transient ischemic attack (TIA) or sub-arachnoid haemorrhage within ≤ 6 months prior to first study treatment.
- Significant cardiac disease: New Yourk Heart Assiciation (NYHA) Class 3 or 4; myocardial infarction within the past 6 months; unstable angina; coronary angioplasty or coronary atrial or ventricular cardiac arrhythmias
- History of prolonged QT syndrome, or family member with prolonged QT syndrome
- QTc interval > 470 msec when 3 consecutive ECG values are averaged

- Ventricular tachycardia or a supraventricular tachycardia that requires treatment with a Class Ia antiarrhythmic drug (e.g. sotalol, amiodarone, dofetilide). Use of other antiarrhythmic drugs is permitted
- Second- or third-degree atrioventricular (AV) block, except: treated with a permanent pacemaker
- Complete left bundle branch block (LBBB)
- Concomitant use of drugs which prolong QTc interval and have a known risk to cause Torsade de Pointes (see appendix F for a non-exhaustive list)
- History of evidence of haemorrhagic disorders, patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorders, coagulopathy or tumour involving major vessels.
- Participation in another clinical study with experimental therapy within 28 days or five half-lives (whichever is shorter) of experimental therapy before start of treatment.
- Participant must not be simultaneously enrolled in any interventional clinical trial.
- Women who are pregnant or are lactating
- Patients unable to be regularly followed for any reason (geographic, familiar, social, psychologic, housed in an institution eg. prison because of a court agreement or administrative order)
- Subjects that are dependent on the sponsor/CRO or investigational site as well as on the investigator.
- History of known hypersensibility against any medication used in the study
- Intolerance / Hypersensitivity reactions to components and exipients of study drugs
- Peripheral neuropathy of grade >2 per NCI CTCAE, version 5, within 4 weeks prior to randomization
- Administration of a live, attenuated vaccine within 30 days prior to Cycle1 Day 1 or anticipation that such a live attenuated vaccine will be required during the study. Examples of live vaccines incluse but are not limited to: measles, mumps, rubella, varicella zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), typhoid and intranasal influenza vaccines (eg. Flumist®). Inactivated influenza vaccinations can be administered during the flu season.
- Any other condition that, in the opinion of the investigator, may compromise the safety, compliance of the patient, or would preclude the patient from successful completion of the study

3. Conditions for the start of maintenance therapy with Niraparib and/or Ganetespib

Before start of the maintenance therapy patients must have following lab values:

- Absolute neutrophil count ≥ 1,500/µL
- Platelets ≥ 100,000/µL
- Hemoglobin ≥ 9 g/dL
- Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault equation
- Total bilirubin ≤ 1.5 x ULN (≤2.0 in patients with known Gilberts syndrome) OR direct bilirubin ≤ 1 x ULN
- Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x ULN unless liver metastases are present, in which case they must be ≤ 5 x ULN

12.4 Study duration

First patient in (FPI): Nov 2018

Last patient in (LPI): Feb 2020

Last patient last treatment (LPLT) with Ganetespib: May 2021

Estimated End of study (EOS) (evaluation of the secondary endpoint overall survival): Aug 2022

12.5 End of study

The Eudario clinical trial is suggested to end in January 2022 (evaluation of secondary endpoint overall survival).

12.5.1 Premature termination of the study

The trial must be terminated prematurely by the sponsor or the IDMC in the following cases:

- If adverse events occur which are so serious that the risk-benefit ratio is not acceptable
- If the number of dropouts is so high that a proper completion of the trial cannot realistically be expected
- For other medical, scientific, operational or administrative reasons.

In that case the Independent Ethics Committee (IEC) and the competent regulatory authority must be informed within 15 days of early termination.

In the event of a premature termination of the trial the TESARO and Aldeyra Therapeutics will continue to provide study treatment(s), in accordance with the procedures in the protocol, for patients until it is no longer a viable clinical option, in the event the Investigator believes, after discussion with the Sponsor, that some patients are continuing to receive clinical benefit that would otherwise be out of reach.

12.5.2 Study site discontinuation

The Sponsor must terminate this study or discontinue a site participating in this trial at any time for reasons including, but not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients (recommendation of the IDMC)
- Patient enrolment is unsatisfactory
- Administrative reasons

The Sponsor will notify the investigator if the study is placed on hold, or if the sponsor decides to discontinue the study or the participation of a study site.

12.5.3 Withdrawal and replacement of subjects

Criteria for withdrawal

Subjects have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.
Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the subject's study data, but no further information will be collected unless a separate consent has been given. Any subject may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the subject appropriate procedures for withdrawal from the study.

Withdrawal of partial consent means that the subject does not wish to take protocol-specified product(s) any longer but is still willing to collaborate in providing further data by continuing on study (e.g., participate in the EOT or safety follow-up visit, provided samples can be evaluated and do not need to be destroyed and/or provide overall survival information).

Should a subject request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information and the primary reason for withdrawal should be reported on the applicable eCRFs.

Reasons for removal from investigational treatment or observation might include:

- progression of disease
- withdrawal of consent
- administrative decision by the investigator
- pregnancy
- significant protocol deviation
- subject noncompliance
- adverse event
- other safety concern of the investigator or sponsor
- death
- lost to follow-up.

For any patient who has received IMP and withdrew prematurely from the study every effort should be made for attendance of the safety follow-up visit 28 days after the last dose of IMP. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn, unless a separate consent has been given for further survival data collection.

12.5.4 Discontinuation from IMP or non-IMP

The investigator should permanently discontinue a subjects' treatment with the study drugs in the event of:

- Unequivocal disease progression
- Intolerable Adverse Events (CTCAE 5) that cannot be managed by dose reduction
- Withdrawal of informed consent
- Change in the patient's status creating an unfavourable risk/benefit in favour to stop study treatment
- Eligibility criteria are violated and represent a safety issue for patient

Further dose reductions considered necessary but not allowed according to the protocol. More detailed information on IMP and non-IMP modifications and discontinuation is found in section 18.

Patients who discontinue IMP and non-IMP prematurely (i.e., before disease progression) will receive local standard of care according to physician's choice, should undergo the safety follow-up visit 28 days after the last dose of IMP and may undergo follow-up assessments.

The primary reason for premature IMP or non-IMP discontinuation should be documented on the appropriate eCRF.

12.6 Study objectives

The primary aim of this study is to determine the efficacy of ganetespib in combination with 3 weekly carboplatin followed by maintenance therapy with Niraparib (+/-Ganetespib) compared to platinum-based combination therapy (according to physicans choice) followed by Niraparib.

Seconary aims of this study are determination of tollerabilty and evaluation of quality of life of patients treated with ganetespib in combination with 3 weekly carboplatin followed by maintenance therapy with Niraparib (+/-Ganetespib) compared to platinum-based combination therapy (according to physicans choice) followed by Niraparib.

Primary endpoint:
Progression-free survival (PFS) by RECIST 1.1
PFS is defined as the days between randomisation and the date of documented progression or death of any cause whatever comes first.

Secondary endpoints:

- Post-progression PFS (PFS2) by RECIST 1.1
  PFS2 is defined as time from randomisation in this trial to objective tumour progression by RECIST 1.1 on next-line treatment or death from any cause.
- Time to First Subsequent Therapy (TFST)
  TFST is defined as the days between randomisation and start date of the first subsequent (post-progression) anticancer therapy or death.
- Time to Second Subsequent Therapy (TSST)
  TSST is defined as the days between randomisation and start date of the second subsequent (post-progression) anticancer therapy or death.
- Overall survival (OS):
  OS is defined as the days between randomisation and the date of documented death from any cause.
- Safety: Adverse events (AEs), measure according to NCI CTCAE, version 5, laboratory parameters, ECOG PS, vital signs
- Objective response rate (ORR): best ORR; confirmed ORR
  ORR is defined as proportion of responders, defined as a patient whose best overall response is partial response (PR) or complete response (CR) during the treatment period (best ORR). ORR is considered confirmed when the result is repeated in the

following efficacy assessment, no less than four weeks later. Response is measured by RECIST 1.1.
- Patient-reported outcome (PRO):
  measured by EORTC QLQ-C30, EORTC QLQ-OV28; responders are defined as improvement of >10 points on the PRO scales

Predefined Subgroup analyses:
PFS will be analysed according to the following pre-defined subgroups:
- BRCA mutation status: yes *versus* no or unknown
- 1 prior line of chemotherapy *versus* >1 prior chemotherapy line
- prior PARPi treatment: yes *versus* no

Experimental endpoints:
Biomarker analysis on DNA, RNA and protein level (e.g. free circulating tumour DNA, circulating tumour cells etc.)

12.7 Randomisation and stratification
Randomisation will be performed in a 1:1:1 ratio to the treatment arms.

Stratification factors:
- BRCA mutation (germline or somatic): yes *versus* no or unknown
- 1 prior line of chemotherapy *versus* >1 prior chemotherapy line
- prior PARPi treatment: yes *versus* no

The randomisation code will be generated by the study statistician using permutated blocks and implemented into the electronic CRF system. Patients will be randomised automatically via the electronic CRF system after verification of inclusion and exclusion criteria as well as stratification status and after all screening assessments have been performed.

13 STATISTICAL ANALYSIS

13.1 Analysis populations

The following populations will be used for statistical analysis

Safety population
The safety population will include all patients who received at least one dose of study drug. In the safety analyses, patients will be included in the treatment arm into which they have actually been randomised.

Intention-to-treat population
The intention-to-treat (ITT) population will consist of all randomised patients. Analyses of this population will assign patients the treatment they were scheduled to receive, regardless of any errors of dosing or dose modifications.

Per-protocol population
The per-protocol (PP) population will include all patients who received at least one cycle of study treatment without major protocol deviations. Major protocol deviations will be determined and documented prior to database lock.

13.2 Sample size calculation

A randomised, open-label, three-arm study will be performed. Group allocation ratio will be 1:1:1. Twice as many patients will be on the Carboplatin-combination therapy with Ganetespib (arms B and C) as are in the standard chemotherapy treatment group (arm A).
The primary aim of this study is to determine the efficacy of the new agent regarding progression-free survival (PFS). The main analysis will combine the two study arms with Ganetespib (arms B and C) and compare it against the standard arm (arm A).

With a minimum of 78 PFS events, the study provides 80 % power to detect a PFS hazard ratio (HR) of 0.60 with 2-sided α=0.2, assuming a median PFS of 10 months with standard chemotherapy (arm A) and 16.7 months with Ganetespib combination arms (arms B+C), and a randomisation ratio of 2:1 between arms B+C vs arm A. With a total sample size of 120 (arm B+C=80; arm A=40), this study has 15 months accural, and 15 months additional follow up.

13.3 Efficacy analysis

Efficacy analyses will be performed on the ITT and PP populations. The analysis of the ITT population will be considered as the primary analysis. All statistical tests are two-sided with a significance level of 0.2.

Progression-free survival (PFS) serves as the primary endpoint of the study. PFS is defined as the days between randomisation and the date of documented progression or death of any cause whatever comes first. For patients whose progression status cannot be determined, their PFS data will be censored at the last assessment date that the patient is confirmed to have no progression.

Regarding PFS Hypothesis testing between the two treatment arms (A vs. B+C) will be performed using a log-rank test. For each treatment arm the median time to progression will

be estimated using the Kaplan-Meier method and the 95% confidence interval of the median will be reported. The restricted mean as a measure for PFS will be calculated using the area under the survival curve (AUC) at the end of the study (approximately 15 months after the last patient was randomised). In addition, Cox proportional hazards regression analysis adjusting for the stratification factors will be applied. The same procedure will be applied to exploratively compare the different treatment arm (A vs. B, A vs. C, B vs. C)

Secondary endpoints with respect to efficacy are post progression PFS (PFS2), time to first subsequent therapy (TFST), time to second subsequent therapy (TSST), overall survival (OS), and objective response rate (ORR: best and confirmed ORR).

Post progression PFS (PFS2) is defined as time from randomisation in this trial to objective tumour progression on next-line treatment or death from any cause. Patients will be followed-up for secondary progression status regularly following the progression event used for the primary variable PFS (PFS). Patients alive and for whom a second disease progression has not been observed should be censored at the date of the last known tumour assessment. Regarding PFS2, comparisons will be performed pooling arms B and C and comparing them jointly against arm A (A vs. B+C) and also separately between study arms (A vs. B, A vs. C, B vs. C).

Time to First Subsequent Therapy (TFST) is defined as the days between randomisation and start date of the first subsequent (post-progression) anticancer therapy or death. Any patient with unknown subsequent therapy or death status will be censored at the last documented time-point to have not received subsequent anticancer therapy. Regarding TFST, comparisons will be performed pooling arms B and C and comparing them jointly against arm A (A vs. B+C) and also separately between study arms (A vs. B, A vs. C, B vs. C).

Time to Second Subsequent Therapy (TSST) is defined as the days between randomisation and start date of the second subsequent (post-progression) anticancer therapy or death. Any patient with unknown second subsequent therapy or death status will be censored at the last documented time-point to have not received second subsequent anticancer therapy. Regarding TSST, comparisons will be performed pooling arms B and C and comparing them jointly against arm A (A vs. B+C) and also separately between study arms (A vs. B, A vs. C, B vs. C).

OS is defined as the days between randomisation and the date of documented death from any cause. For patients whose survival status cannot be determined, their OS data will be censored at the last documented date that the patient is confirmed to be alive. Statistical analysis of OS will be carried out in the same way as described for PFS. Regarding OS, comparisons will be performed pooling arms B and C and comparing them jointly against arm A (A vs. B+C) and also separately between study arms (A vs. B, A vs. C, B vs. C).

Statistical analyses for all time-to-event variables (PFS2, TFST, TSST, OS) will be carried out in the same way as described for PFS with the Kaplan-Meier method and Cox proportional hazards regression.

ORR will be estimated as the proportion of responders, defined as a patient whose best overall response is partial response (PR) or complete response (CR) during the treatment period (best

ORR). ORR is considered confirmed when the result is repeated in the following efficacy assessment, no less than four weeks later. Hypothesis testing regarding ORR testing between the two treatment arms will be performed using a Mantel-Haenszel test and a logistic regression analysis adjusting for the stratification factors. The odds ratio and 95% confidence interval of the odds ratio will be presented. Regarding ORR, comparisons will be performed pooling arms B and C and comparing them jointly against arm A (A vs. B+C) and also separately between study arms (A vs. B, A vs. C, B vs. C).

Patient-reported outcome (PRO) is also a secondary study endpoint.

PRO will be assessed using validated questionnaires (the EORTC QLQ-C30 and the EORTC QLQ-OV28) (see section 16.2.1 and appendix B). Statistical analysis of PROs will be based on linear mixed models. These models will include the PRO scales as dependent variables, study group and time point as fixed effects, the group-by-time interaction effect, a random intercept on patient level and a first-order autoregressive covariance matrix. Main PRO endpoints will be gastrointestinal symptoms measured by the EORTC QLQ-OV28 Gastrointestinal Scale and overall quality of life as measured by the EORTC QLQ-C30 Summary Score (19). These scales will be tested for non-inferiority of the two treatment arms (group B and C) compared to the control arm (group A). Based on descriptive statistics for the QLQ-C30 Summary Score in the literature we estimated the standard deviation (SD) of the score to be 20 points in the EUDARIO trial (taking into account that patients in the EUDARIO trial are on treatment and in an advanced disease stage). Based on this estimate we defined the minimal important difference (MID) to be 10 points (i.e. 0.5 SD). The MID will be used as non-inferiority margin (δ) in our analysis. For the individual domains of the EORTC QLQ-C30 and QLQ-OV28 (in particular the Gastrointestinal scale) the MID is considered to be 10 points as well. Additional analyses will be done for frequencies of responders (improvement of >10 points on the PRO scales) and for time until definitive deterioration (20). Sensitivity analyses will be done using different methods for data imputation, to investigate robustness of results. Regarding PRO analysis, comparisons will be performed pooling arms B and C and comparing them jointly against arm A (A vs. B+C) and also separately between study arms (A vs. B, A vs. C, B vs. C).

Predifined subgroup analyses:
PFS in the following predefined subgroups of patients will be analysed:

- BRCA mutation status: yes *versus* no or unknown
- 1 prior line of chemotherapy *versus* >1 prior chemotherapy line
- prior PARPi treatment: yes *versus* no

The same statistical methods as outlined for the overall study population will be applied regarding these subgroup analyses with the exception of adjusted analyses in respect to the concerned subgroup.

13.4 Safety analysis

Safety evaluations will be based on the incidence, type, severity and consequences (e.g. study discontinuation) of an adverse event (AE) as well as on clinically significant changes in the patient's physical examination, vital signs, and clinical laboratory results. Statistical analysis includes tabulation per treatment group using descriptive measures which are absolute and relative frequencies for categorical data and means, standard deviations, medians and interquartile ranges for continuous data.

All safety analyses will be performed on the safety population.

13.5 Subgroup analysis

Efficacy analyses will be done for the following predefined subgroups of patients:

- BRCA mutation status: yes *versus* no or unknown
- 1 prior line of chemotherapy *versus* >1 prior chemotherapy line
- prior PARPi treatment: yes *versus* no

13.6 Comparability of treatment arms

The three treatment arms will be assessed descriptively for comparability of demographic and baseline characteristics. Administered study treatment, medical history, disease duration, use of prior treatments and concomitant medications will be summarised by treatment arm using descriptive statistics.

13.7 Interim analysis

No interim analysis will be performed.

14 RISK-BENEFIT CONSIDERATIONS

The aim of EUDARIO is to improve survival and wellbeing of platinum-sensitive ovarian cancer patients by combining standard platinum-based chemotherapy and PARPi-maintenance therapy with the HSP90 inhibitor Ganetespib.
Our EU-project consortium has produced solid basic research findings strongly supporting synergy of these drug combinations. The suggested mechanism of action is broad DNA repair inhibition after induction of DNA damage by Carboplatin to achieve maximum cancer cell death. With this clinical trial we aim to translate robust research findings into patient benefit therewith prolonging survival and wellbeing of ovarian cancer patients. This aim links the awareness of human dignity, quality of patient's life and the patient's best interest, as pronounced in the Declaration of Helsinki (§3 - §5) and the Charter of Fundamental Rights of the European Union (2000/C 364/01; Article 1-3).

Epithelial Ovarian Cancer is the most lethal among gynaecological malignancies. Despite high initial response rates to primary therapy, the vast majority of patients will inevitably relapse within a short period of time and ultimately die of the disease. There is a pressing need for innovative new treatment strategies to prolong progression-free survival and overall survival in EOC patient. This risk for disease relapse and death is opposed by the risk to harm patients with the experimental treatment applied in the current clinical trial.

All patients in this trial receive platinum-based chemotherapy, which is the standard treatment in relapsed, platinum-sensitive EOC patients. Maintenance treatment with PARPi is approved for BRAC1/2 mutated, relapsed platinum-sensitive OC in Europe. The recent NOVA trial has shown clear benefit also for relapsed, platinum-sensitive OC patients without BRCA1/2 mutations. In March 2017 Niraparib was approved by the FDA for maintenance treatment of relapsed platinum-sensitive ovarian cancer independent of BRCA status. EMA approval process is ongoing. Within this clinical trial all platinum-sensitive patients have access to proven efficaceous PARPi treatment.

The clinical partners participating in this trial have gained extensive experience with the IMP Ganetespib in the ongoing GANNET53 trial in platinum-*resistant* ovarian cancer. In general, the applied Ganetespib Paclitaxel combination was well tolerated in these heavily pre-treated ovarian cancer patients. One new toxicity signal was identified during the randomised Phase II GANNET53 trial which was considered possibly related to Ganetespib, i.e. gastrointestinal perforation. As a consequence, in-/exclusion criteria have been adapted in a substantial amendment to exclude ovarian cancer patients with a pre-existing risk profile for GIP from participation in the GANNET53 trial. Since adaptation of in-/exclusion criteria no further GIP cases occurred. In general, Ganetespib has been applied in 1,611 patients of various different malignant diseases without major safety concerns.
In the present trial we implemented these strict in-/exclusion criteria excluding patients at risk of GIP right from the start in order to minimise patients risk.
In the present trial Ganetespib is applied in two different combinations, together with Carboplatin on one hand and together with Niraparib on the other hand.
The risk to harm patients with the experimental treatment of both Ganetespib combinations is minimised via 1) safety run-ins for both applied Ganetespib combinations with repeated IDMC evaluations, 2) thorough choice of dose levels of combination treatment, 3) careful determination of dose-reduction steps in the trial protocol in response to potential side-effects

and 4) re-assuring safety data on the Carboplatin/Ganetespib combination from a previous trial (MESO-02) in mesothelioma.

Carboplatin/Ganetespib combination (arms B and C): Safety will be evaluated by IDMC 4 weeks after first 6 and 12 patients have been included.
Prior to this current trial, the combination of Ganetespib with Carboplatin AUC5, q3w (corresponds to the Carboplatin schedule in the present study) has been tested and was established as being well tolerated. A dose- escalation trial aiming to determine MTD has been performed at the University College London, UK, (PI Prof. Dean A Fennell) in 27 patients with malignant pleural mesothelioma (MESO-02 trial). The PI confidentially reported good tolerability and has confidentially shared with us re-assuring safety data (which are included in this protocol). In the MESO-02 trial Ganetespib was escalated up to > 200 mg/m^2. No safety concerns arose even in a triplicate combination including Carboplatin AUC5, 3qw. In the present trial we will apply Ganetespib at a dose level of 150 mg/m^2 in combination with Carboplatin (AUC5, 3qw). This is a lower Ganetspib dose to be used in a dual combination than found to be well tolerated in a triple combination in the MESO-02 trial. Furthermore, Ganetespib 150 mg/m^2 is the recommended general combination dose of Ganetespib based on previous trials. We expect a favourable safety profile of this combination.

Niraparib/Ganetespib combination (maintenance treatment in arm C): Two safety evaluations by IDMC are planned 4 weeks after the start of maintenance therapy of 6 and 12 patients, respectively. Thus a total of 12 patients will be evaluated by the IDMC. To minimise risk to patients receiving this new combination, a stop of entering maintenance treatment will be performed until recommendations of the IDMC are available. Only in case of positive evaluation of the safety profile of the Niraparib/Ganetespib combination by the IDMC after 6 and 12 patients, respectively, subsequent patients in arm C will start maintenance treatment with this drug combination. In case of negative evaluation of safety by the IDMC, patients in arm C will proceed with Niraparib single agent maintenance treatment. In addition, we have thoroughly chosen the dose levels of both drugs. The standard single agent Niraparib dose in maintenance treatment is 200-300 mg orally per day. In the present trial we apply a starting dose of 200 mg Niraparib in combination with Ganetespib. From the NOVA trial data we expect no negative impact on efficacy but less toxicity using this lower Niraparib combination dose level. Furthermore, we will use a lower Ganetespib dose in the combination with Niraparib, namely 100 mg/m^2, than the established Ganetespib combination dose of 150 mg/m^2. Close monitoring of patients on this new drug combination have been implemented in this trial protocol with weekly laboratory evaluation. This is of particular importance, as the main side-effects expected are of haematologic nature. Close monitoring will allow us to guide potentially necessary dose-reduction steps and to individualise dosing levels of both Ganetespib and Niraparib in this combination treatment. With these safety measures we will minimise patients risk receiving this treatment combination.

There is a risk in the EUDARIO trial by treating patients with Ganetespib who may not benefit from this treatment but may experience adverse effects due to the experimental therapy. This risk is opposed by a potential benefit for these patients in terms of a possible survival advantage and a possibly higher life quality through better disease control derived from this new innovative therapeutic approach. An IDMC consistent of 4 independent experts in the field of gynaecologic oncology and statistics will closely and continuously monitor patient safety and

trial development. The IDMC can, if required, propose a protocol amendment and in case the risk to the patients outweighs the potential benefit, propose termination of the study.

15 STUDY PROCEDURES

15.1 Before treatment start/screening (days -28 to -1)

All subjects must provide written informed consent before any study-specific assessments or procedures are performed.
The screening examinations must be performed between 1 and 28 days before being assigned to one of the three treatment arms. Only subjects who meet all the inclusion and none of the exclusion criteria will be accepted into the study.
An Eligibility Screening Form (ESF) documenting the investigator's assessment of each screened subject with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator. Furthermore, a screen failure log must be maintained by the investigator.

Within 4 weeks (28 days) prior to randomisation:

- Obtain signed and dated informed consent
- Register the patient in the eCRF
- Record current and past medical history, significant diseases and medical procedures (at Investigator's discretion) and concurrent illnesses
- Record ovarian cancer history and all previous anticancer treatments
- Platinum-free interval (PFI) for the most recent platinum-based therapy must be calculated
- Record all surgical interventions performed for ovarian cancer
- Demographic data (date of birth, ethnicity, marital status, highest level of education, current employment status)
- Tumour assessment which is not older than 28 days at the time of randomisation: chest, abdomen and pelvis CT scan or MRI abdomen/pelvis and chest CT/MRI or X-ray. Pre-operative chest X-ray is allowed. PET scans are allowed; the same technique is to be used for all assessments (see section 16.1).
- Archival tissue samples from primary diagnosis sent to central histopathological review (for confirmation of high-grade serous, high-grade endometrioid, or undifferentiated epithelial ovarian cancer, carcinosarcoma of the ovary, fallopian tube or primary peritoneal carcinoma (see section 16.7).
- Whenever technically feasible CT- or sonographically-guided biopsy samples of the actual relapse should be performed after informed consent has been obtained but prior to the first study drug administration. Alternatively tissue of the actual relapse which was sampled during debulking surgery in the relapsed situation can be provided (see section 16.7).

- Concomitant medications: Document all medications (other than previous anticancer treatment) and significant non-drug therapies (see section 16.3).
- Adverse Events (AEs): report any serious adverse events (SAEs) considered to be related to a protocol-mandated intervention (see section 19.1).

Within 2 weeks (14 days) prior to randomisation:

- Urine/serum pregnancy test in WOCBP (for definition see section 6)
- Electrocardiogram (ECG; average of triplicate ECG recording) (see section 16.5)
- Assess left ventricular ejection fraction (LVEF) by ECHO (see section 16.5)
- Physical examination including vital signs and measured body height and weight (see section 16.4)
- Determine ECOG PS (see Appendix A)
- Laboratory assessments: Haematology, Biochemistry panel, Coagulation and urinanalysis (see section 16.6
- Perform measurement of CA-125 at least once during the screening period. (see section 16.1).
- Completion of PRO questionnaires [EORTC QLQ-C30, EORTC QLQ-OV28 (Appendix C)] (see section 16.2)

Randomisation:

- Verification of inclusion and exclusion criteria
- All eCRF Screening pages need to completed
- Patient must receive the first dose of study treatment within 7 days of randomisation

Table 8: Screening Schedule of Events

Procedures / Assessments	**Screening**		**Randomisation**
Week number prior to randomisation	**- 4**	**- 2**	
Days prior to randomisation	***- 28 to -1***	***-14 to -1***	
Informed consent	X		
Registration in the eCRF	X		
Medical history[a]	X		
Ovarian Cancer History and Previous anticancer treatments	X		
Confirmation of PFI	X		
Past Surgical Interventions for Ovarian Cancer	X		
Demographic data	X		
CT/MRI[b]	X		
Archival tissue sample from primary diagnosis[c]	X		
Biopsy of the actual relapse[d]	X		
Pregnancy test[e]		X	

ECG[f]		X	
LVEF[g]		X	
Height		X	
Physical examination incl. vital signs[h] (BP, HR, T)		X	
Body weight		X	
ECOG Performance status		X	
Haematology[i]		X	
Biochemistry Panel[j]		X	
Coagulation[k]		X	
Urinanalysis[l]		X	
CA-125[m]		X	
PRO questionnaire[n]		X	
Adverse events[o]	X (if applicable)		
Concomitant medication	X (if applicable)		
Verify all Inclusion / Exclusion criteria			X
Randomise Patient via eCRF[p]			X

[a] Record current and past medical history, significant diseases and medical procedures (at Investigator's discretion) and concurrent illnesses

[b] Tumour assessments for response and progression require CT scans of the pelvis and abdomen and (by X-ray or preferably by CT-scan) of the chest. MRI scans can be used for patients who are allergic to radiographic contrast agents. Throughout the study, the same assessment technique must be used. Ultrasound scanning is not an acceptable substitute for CT scanning.

[c] Archival tissue samples from primary diagnosis are mandatory for central histopathological review (for confirmation of high-grade serous, high-grade endometrioid, or undifferentiated epithelial ovarian, fallopian tube or primary peritoneal carcinoma) at screening and for the determination of p53 mutational status.

[d] CT- or sonographically-guided biopsy samples of the actual relapse (after informed consent has been obtained, but prior to the first study drug administration) should be performed whenever technically feasible after informed consent has been obtained but prior to the first study drug administration. Alternatively tissue of the actual relapse which was sampled during debulking surgery in the relapsed situation can be provided.

[e] Urine/serum pregnancy testing is not required in patients after surgical sterilisation or bilateral ovarectomy or hysterectomy; > 12 months amenorrhea, age > 60 years.

[f] ECGs for each patient should be obtained from the same machine whenever possible. A consistent method of QTc calculation must be used for each patient's QTc measurements. QTcF (Fridericia's formula) is preferred. For the screening ECG averaged values of triplicate recordings are necessary.

[g] Assess left ventricular ejection fraction (LVEF) by ECHO

[h] Blood pressure and heart rate will be measured after patient was in a sitting position for at least 10 minutes.

[i] Haematology laboratory tests include assessment of:

§ Hemoglobin, haematocrit, RBC, WBC, absolute neutrophil count, differential (%)[†],platelets

[†] Neutrophils, eosinophils, basophils, lymphocytes, monocytes

[j] Biochemistry panel laboratory tests include assessment of:

§ Sodium, potassium, calcium
§ Serum albumin, serum urea
§ ALT, AST, LDH, AP, total bilirubin
§ Creatinine

[k] Coagulation parameter tests include assessment of aPTT or INR

[l] Urinanalysis or urine dipstick for proteinuria

[m] Measured at least once during the screening period. Measurement needs to be within 2 weeks of treatment start.

[n] Questionnaires EORTC QLQ-C30, EORTC QLQ-OV28.

[o] Between consent and first study drug dose only SAEs that are protocol-related will be recorded. Thereafter all AEs until Safety FU and all SAEs through Safety FU until resolved

[p] Patients must receive their first dose of study treatment within 7 days of randomisation.

15.2 Treatment period

The trial treatment will start after archival tissue from primary diagnosis has been sent (for later histopathological review and companion diagnostics) and the patient has been randomised into one of the three treatment arms.
Treatment should begin within 7 days of randomisation.
A total of six cycles of platinum-based combination therapy (Gemcitabine or Paclitaxel or Ganetespib) are planned to be administered to all patients (arms A, B and C). Platinum-based combination therapy is followed by maintenance treatment if the patient has experienced a stable disease (SD), partial response (PR), or complete response (CR) after completion of platinum-based therapy.

Platinum-based chemotherapy: One treatment cycle lasts 3 weeks, q3w. Each patient will receive 6 cycles of platinum-based chemotherapy. Patients in the standard chemotherapy arm A will receive Carboplatin plus Gemcitabine or Carboplatin plus Paclitaxel (investigators choice). In the two experimental treatment arms B and C Carboplatin will be combined with Ganetespib.

Maintenance treatment: Platinum-based chemotherapy is followed by maintenance treatment if the patient has experienced stable disease (SD), partial response (PR), or complete response (CR), by CT measurement, after completion of 6 cycles of a platinum-based therapy. Furthermore, specific laboratory findings have to be fulfilled to enter maintenance treatment (please see respective sections 15.2.4 and 15.2.5). Patients must not have received transfusions and colony stimulating factors ≤ 4 weeks before Niraparib maintenance therapy, and must have a negative pregnancy test 7 days before start of the therapy. Any known grade 3 or 4 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted > 4 weeks would also be detriminal for maintenance therapy. Niraparib will either be given alone (arms A and B) or in combination with Ganetespib (arm C). In arm C the combination of Niraparib and Ganetespib will be given for 9 months, thereafter Ganetespib treatment will be stopped and Niraparib maintenance therapy will be continued as single agent.
Maintenance treatment is not allowed to start prior to 6 weeks after last platinum-based treatment. Maintenance treatment *should preferentially start between 6 and 9 weeks*, but will be allowed until up to 12 weeks after last platinum-based treatment. *Exception:* Patients in Arm C whos maintenance treatment start is delayed due to necessary IDMC evaluation after 6 and 12 patients are allowed to start maintenance treatment beyond the 12 weeks.

15.2.1 Chemotherapy Arm A: Carboplatin and Gemcitabine (Standard platinum-based chemotherapy, investigators choice)

Day 1 of treatment cycles, Carboplatin and Gemcitabine

Only applicable for day 1 **cycle 1** (which is the first day of dosing): If performed at Screening within 3 days prior to start of dosing, physical examination including vital signs, measurement of body weight and height, determination of ECOG PS, pregnancy test, blood collection for haematology, biochemistry panel and urinanalysis as well as CA-125 evaluation, do not have to be repeated.

The following tests and procedures should be performed on day 1 of treatment cycles.

- Day 1 of cycles 1, 3 and 5: Completion of PRO questionnaires (see section 15.2)
- Physical examination including vital signs and measurement of body weight (see section 16.4
- Determine ECOG PS (see Appendix A)
- Laboratory assessments; Haematology and Biochemistry panel (see section 16.6)
- Evaluation of tumour marker CA-125
- Urine/serum pregnancy test in WOCBP (for definition see section 6).
- Day 1 of cycles 1 and 4: Blood sampling for biomarker analysis prior to administration of study drug (please see section 16.7)
- Administration of premedication for Carboplatin Gemcitabine treatment according to institutional standards (please see section 17.1)
- Administration of Gemcitabine as an i.v. infusion, provided that there are no significant findings at the Day 1 visit (e.g. physical examination, ECOG PS, laboratory assessments or pregnancy test) prior to administration (see section 17.1).
- Administration of Carboplatin as an i.v. infusion, provided that there are no significant findings at the Day 1 visit (e.g. physical examination, ECOG PS, laboratory assessments or pregnancy test) prior to administration (see section 17.1).
- Record concomitant medications (see section 16.3)
- Evaluate and document adverse events (AEs) (see section 19.1 and Appendix B)

Day 8 Carboplatin and Gemcitabine

- Physical examination including vital signs and measurement of body weight (see section 16.4
- Determine ECOG PS (see Appendix A)
- Laboratory assessments; Haematology (see section16.6)
- Administration of premedication according to institutional standards (please see section 17.1)
- Administration of Gemcitabine as an i.v. infusion, provided that there are no significant findings at the Day 8 visit (e.g. physical examination, ECOG PS, laboratory assessments or pregnancy test) prior to administration (see section 17.1).
- Record concomitant medications (see section 16.3)
- Evaluate and document adverse events (AEs) (see section 19.1 and Appendix B)

After completion of chemotherapy treatment, Carboplatin and Gemcitabine

- Tumour assessment has to be done after completion of last cycle of chemotherapy treatment to confirm SD, PR or CR in order to evaluate if patient is eligible to continue with maintenance therapy.

Table 9: Carboplatin Gemcitabine Schedule of Events (arm A, Investigator`s choice)

Procedures / Assessments	**TREATMENT (-1/+2 days)**					
	Cycle 1			**Cycle 2-6**		
Week number	**1**	**2**	**3**	**4**	**5**	**6**
Cycle day	**1**	**8**	**15**	**1**	**8**	**15**
Physical examination incl. vital signs[a] (BP, HR, T)	X	X	No treatment	X	X	No treatment
Body height and weight[b]	X	X		X	X	
ECOG Performance status	X	X		X	X	
Haematology[c]	X	X		X	X	
Biochemistry Panel[d]	X			X		
Pregnancy test[e]	X			X		
PRO questionnaire[f]	X			(X)		
Administration of Carboplatin	X			X		
Administration of Gemcitabine	X	X		X	X	
CA-125	X			X		
CT/MRI[g]				(X)		
Blood sample collection for biomarker analysis[h]	X			(X)		
Biopsy of the actual relapse[i]		X				
Adverse events[j]	Continuously					
Concomitant medication	Continuously					

[a] Blood pressure and heart rate will be measured after patient was in a sitting position for at least 10 minutes

[b] Body height is only to be measured at C1D1

[c] Haematology laboratory tests include assessment of:

§ Hemoglobin, haematocrit, RBC, WBC, absolute neutrophil count, differential (%)†,platelets

† Neutrophils, eosinophils, basophils, lymphocytes, monocytes

[d] Biochemistry panel laboratory tests include assessment of:

§ Sodium, potassium, calcium

§ Serum albumin, serum urea

§ ALT, AST, LDH, AP, total bilirubin

§ Creatinine

[e] Urine/serum pregnancy testing is not required in patients after surgical sterilisation or bilateral ovarectomy or hysterectomy; > 12 months amenorrhea, age > 60 years.

[f] Questionnaires EORTC QLQ-C30, EORTC QLQ-OV28 on day 1 of cycles 1, 3 and 5.

[g] Tumour assessments will be made every 12 weeks and after completion of chemotherapy and require CT scans of the pelvis and abdomen and (by X-ray or preferably by CT-scan) of the chest. MRI scans can be used for patients who are allergic to radiographic contrast agents. Throughout the study, the same assessment technique must be used. Ultrasound scanning is not an acceptable substitute for CT scanning. After completion of 6 chemotherapy cycles, tumour assessment has to be done to confirm SD, PR or CR in order to evaluate if patient is eligible to continue with maintenance therapy.

[h] Blood collection for biomarker analysis will be performed before the administration of study drug on day 1 of cycle 1 and thereafter on day 1 of **cycle 1 and cycle 4**, *prior* to administration of study drug. An additional blood sample for biomarker analysis will be taken at disease progression (first visit after diagnosis of progression).

[i]. An additional biopsy 24h (+/-2h) after the first study treatment will be taken in a subset of ~10 patients enrolled at participating sites. This biopsy will only be done if technically feasible and for subjects that had an uncomplicated fresh biopsy procedure for this trial during the screening period.

[j] After initiation of study drug, all AEs and SAEs regardless of relationship to the study drug, will be reported until safety follow-up at 28 days after the last dose of IMP or EOT or until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent

15.2.2 Chemotherapy Arm A: Carboplatin and Paclitaxel (standard platinum-chemotherapy, investigators choice)

Day 1 of treatment cycle: Carboplatin and Paclitaxel

Only applicable for day 1 cycle 1: The following tests and procedures should be performed on Cycle 1 Day 1 (which is the first day of dosing). The physical examination including vital signs, measurement of body weight and height, determination of ECOG PS, pregnancy test, blood collection for haematology, biochemistry panel and urinanalysis as well as CA-125 evaluation do not have to be repeated if performed at Screening within 3 days prior to start of dosing.

- Day 1 of cycles 1, 3 and 5: Completion of PRO questionnaires (see section 15.2)
- Physical examination including vital signs and measurement of body weight (see section 16.4
- Determine ECOG PS (see Appendix A)
- Laboratory assessments; Haematology and Biochemistry panel (see section 16.6)
- Evaluation of Tumour marker CA-125
- Urine/serum pregnancy test in WOCBP (for definition see section 6).
- Day 1 of cycles 1 and 4: Blood sampling for biomarker analysis prior to administration of study drug (please see section 16.7)
- Administration of premedication for Carboplatin and Paclitaxel treatment according to institutional standards. (please see section 17.1)
- Administration of Paclitaxel as an i.v. infusion, provided that there are no significant findings at the Day 1 visit (e.g. physical examination, ECOG PS, laboratory assessments or pregnancy test) prior to administration (see section 17.1).
- Administration of Carboplatin as an i.v. infusion, provided that there are no significant findings at the Day 1 visit (e.g. physical examination, ECOG PS, laboratory assessments or pregnancy test) prior to administration (see section 17.1).
- Record concomitant medications (see section 16.3)
- Evaluate and document adverse events (AEs) (see section 19.1 and Appendix B)

After completion of chemotherapy treatment, Carboplatin and Paclitaxel

- Tumour assessment has to be done after completion of 6 cycles of platinum-based chemotherapy treatment to confirm SD, PR or CR in order to evaluate if patient is eligible to continue with maintenance therapy.

Table 10: Carboplatin Paclitaxel Schedule of Events (arm A, investigators choice)

Procedures / Assessments	**TREATMENT (-1/+2 days)**					
	Cycle 1			***Cycle 2-6***		
Week number	**1**	**2**	**3**	**4**	**5**	**6**
Cycle day	**1**	**8**	**15**	**1**	**8**	**15**
Physical examination incl. vital signs[a] (BP, HR, T)	X	Nio treatment	No treatment	X	No treatment	No treatment
Body height and weight[b]	X			X		
ECOG Performance status	X			X		
Haematology[c]	X			X		
Biochemistry Panel[d]	X			X		
Pregnancy test[e]	X			X		
PRO questionnaire[f]	X			(X)		
Administration of Carboplatin	X			X		
Administration of Paclitaxel	X			X		
CA-125	X			X		
CT/MRI[g]				(X)		
Blood sample collection for biomarker analysis[h]	X			(X)		
Biopsy of the actual relapse[i]		X				
Adverse events[j]	Continuously					
Concomitant medication	Continuously					

[a] Blood pressure and heart rate will be measured after patient was in a sitting position for at least 10 minutes

[b] Body height is only to be measured at C1D1

[c] Haematology laboratory tests include assessment of:

§ Hemoglobin, haematocrit, RBC, WBC, absolute neutrophil count, differential (%)[†],platelets

[†] Neutrophils, eosinophils, basophils, lymphocytes, monocytes

[d] Biochemistry panel laboratory tests include assessment of:

§ Sodium, potassium, calcium

§ Serum albumin, serum urea

§ ALT, AST, LDH, AP, total bilirubin

§ Creatinine

[e] Urine/serum pregnancy testing is not required in patients after surgical sterilisation or bilateral ovarectomy or hysterectomy; > 12 months amenorrhea, age > 60 years.

[f] Questionnaires EORTC QLQ-C30, EORTC QLQ-OV28.on day 1 of cycles 1, 3 and 5.

[g] Tumour assessments will be made every 12 weeks and after completion of chemotherapy and require CT scans of the pelvis and abdomen and (by X-ray or preferably by CT-scan) of the chest. MRI scans can be used for patients who are allergic to radiographic contrast agents. Throughout the study, the same assessment technique must be used. Ultrasound scanning is not an acceptable substitute for CT scanning. After completion of 6 platinum-based

chemotherapy cycles, tumour assessment has to be done to confirm SD, PR or CR in order to evaluate if patient is eligible to continue with maintenance therapy.

[h] Blood collection for biomarker analysis will be performed before the administration of study drug on day 1 of cycle 1 and cycle 4, *prior* to administration of study drug. An additional blood sample for biomarker analysis will be taken at disease progression (first visit after diagnosis of progression).

[i]. An additional biopsy 24h (+/-2h) after the first study treatment will be taken in a subset of ~10 patients enrolledat participating sites. This biopsy will only be done if technically feasible and for subjects that had an uncomplicated fresh biopsy procedure for this trial during the screening period.

[j] After initiation of study drug, all AEs and SAEs regardless of relationship to the study drug, will be reported until safety follow-up at 28 days after the last dose of IMP or EOT or until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent

15.2.3 Chemotherapy based treatment Arms B and C: Carboplatin and Ganetespib (experimental platinum-combination)

Day 1 of treatment cycle: Carboplatin and Ganetespib

Only applicable for day 1 cycle 1: The following tests and procedures should be performed on Cycle 1 Day 1 (which is the first day of dosing). The physical examination including vital signs, measurement of body weight and height, determination of ECOG PS, pregnancy test, blood collection for haematology, biochemistry panel and urinanalysis as well as for CA-125 evaluation, do not have to be repeated if performed at Screening within 3 days prior to start of dosing.

- Day 1 of cycles 1, 3 and 5: Completion of PRO questionnaires (see section 15.2)
- Physical examination including vital signs and measurement of body weight (see section 16.4
- Determine ECOG PS (see Appendix A)
- Day 1 of each cycle: Electrocardiogram (ECG) (see section 16.5)
- Laboratory assessments; Haematology and Biochemistry panel (see section 16.6)
- Evaluation of Tumour marker CA-125
- Urine/serum pregnancy test in WOCBP (for definition see section 6).
- Day 1 of cycles 1 and 4: Blood sampling for biomarker analysis prior to administration of study drug (please see section 16.7)
- Administration of premedication as described unter 17.1
- Administration of Carboplatin as an i.v. infusion, provided that there are no significant findings at the Day 1 visit (e.g. physical examination, ECOG PS, laboratory assessments or pregnancy test) prior to administration (see section 17.1).
- Administration of Ganetespib (150 mg/m^2) as an i.v. infusion, provided that there are no significant findings at the Day 1 visit (e.g. physical examination, ECOG PS, laboratory assessments or pregnancy test) prior to administration (see section 17.1).
- Record concomitant medications (see section 16.3)
- Evaluate and document adverse events (AEs) (see section 19.1 and Appendix B)

After completion of chemotherapy based treatment, Carboplatin and Ganetespib

- Tumour assessment has to be done after completion of 6 cycles of platinum-based chemotherapy treatment to confirm SD, PR or CR in order to evaluate if patient is eligible to continue with maintenance therapy.

Table 11: Carboplatin Ganetespib Schedule of Events (Arm B and C)

Procedures / Assessments	**TREATMENT (-1/+2 days)**						
	Cycle 1				**Cycle 2-6**		
Week number	**1**		**2**	**3**	**4**	**5**	**6**
Cycle day	**1**	**2**	**8**	**15**	**1**	**8**	**15**
Physical examination incl. vital signs[a] (BP, HR, T)	X		No treatment	No treatment	X	No treatment	No treatment
Body height and weight[b]	X				X		
ECOG Performance status	X				X		
ECG[c]	X	X			X		
Haematology[d]	X				X		
Biochemistry Panel[e]	X				X		
Pregnancy test[f]	X				X		
PRO questionnaire[g]	X				(X)		
Administration of Carboplatin	X				X		
Administration of Ganetespib	X				X		
CA-125	X				X		
CT/MRI[h]					(X)		
Blood sample collection for biomarker analysis[i]	X				(X)		
Biopsy of the actual relapse[j]		X					
Adverse events[k]	Continuously						
Concomitant medication	Continuously						

[a] Blood pressure and heart rate will be measured after patient was in a sitting position for at least 10 minutes

[b] Body height is only to be measured at C1D1

[c] ECGs for each patient should be obtained from the same machine whenever possible. A consistent method of QTc calculation must be used for each patient's QTc measurements. QTcF (Fridericia's formula) is preferred. For the screening ECG averaged values of triplicate recordings are necessary. ECGs during treatment period needs to be done only in patients who receive Ganetespib. A pre-Ganetespib dose ECG will be performed on day 1 of each cycle (on the day of medication dosing, or one day prior). In addition, a 24-hours post-Ganetespib-dose ECG (+/- 4 hours) will be performed on day 2 of cycle 1. In case of QTc prolongation (pre- or post-dose), further intensified ECG monitoring will be performed at the next dosing of Ganetespib. At a minimum pre-dose ECGs will be performed on days 1 of each cycle of Ganetepib treatment.

[d] Haematology laboratory tests include assessment of:

§ Hemoglobin, haematocrit, RBC, WBC, absolute neutrophil count, differential (%)[†],platelets

[†] Neutrophils, eosinophils, basophils, lymphocytes, monocytes

[e] Biochemistry panel laboratory tests include assessment of:

§ Sodium, potassium, calcium

§ Serum albumin, serum urea

§ ALT, AST, LDH, AP, total bilirubin

§ Creatinine

[f] Urine/serum pregnancy testing is not required in patients after surgical sterilisation or bilateral ovarectomy or hysterectomy; > 12 months amenorrhea, age > 60 years.

[g] Questionnaires EORTC QLQ-C30, EORTC QLQ-OV28 on day 1 of cycles 1, 3 and 5.

[h]. Tumour assessments will be made every 12 weeks and after completion of chemotherapy and require CT scans of the pelvis and abdomen and (by X-ray or preferably by CT-scan) of the chest. MRI scans can be used for patients who are allergic to radiographic contrast agents. Throughout the study, the same assessment technique must be used. Ultrasound scanning is not an acceptable substitute for CT scanning. After completion of platinum-based chemotherapy cycles, tumour assessment has to be done to confirm SD, PR and CR in order to evaluate if patient is eligible to continue with maintenance therapy.

[i] Blood collection for biomarker analysis will be performed before the administration of study drug on day 1 of cycle 1 and 4, *prior* to administration of study drug. An additional blood sample for biomarker analysis will be taken at disease progression (first visit after diagnosis of progression).

[j]. An additional biopsy 24h (+/-2h) after the first study treatment will be taken in a subset of 10 patients ~enrolled at participating sites. This biopsy will only be done if technically feasible and for subjects that had an uncomplicated fresh biopsy procedure for this trial during the screening period.

[k] After initiation of study drug, all AEs and SAEs regardless of relationship to the study drug, will be reported until safety follow-up at 28 days after the last dose of IMP or EOT or until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent

15.2.4 Maintenance treatment in arms A and B: Niraparib single agent

Criteria to assess eligibility to start with Niraparib maintenance therapy (Arm A and B)

- CT scan after completion of 6 cycles of platinum-based treatment showing SD, PR or CR (confirmed by tumour assessment according to RECIST 1.1)
- Patients must have received 6 cycles of platinum-based treatment to start maintenance treatment
- With respect to laboratory findings:
    - Absolute neutrophil count ≥ 1,500/µL
    - Platelets ≥ 100,000/µL
    - Hemoglobin ≥ 9 g/dL
    - Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault equation
    - Total bilirubin ≤ 1.5 x ULN (≤2.0 in patients with known Gilberts syndrome) OR direct bilirubin ≤ 1 x ULN
    - Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x ULN unless liver metastases are present, in which case they must be ≤ 5 x ULN
- Participant must not have received a transfusion (platelets or red blood cells) ≤ 4 weeks prior to start of Niraparib.
- Participant must not have received colony-stimulating factors (eg. granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, or recombinant erythropoietin) ≤ 4 weeks prior to start of Niraparib.
- Participant must have a negative pregnancy test within 7 days prior to start of Niraparib.
- Any known grade 3 or 4 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted > 4 weeks and was related to the induction chemotherapy part of this study.

Maintenance treatment is not allowed to start prior to 6 weeks after last platinum-based treatment. Maintenance treatment *should preferentially start between 6 and 9 weeks*, but will be allowed until up to 12 weeks after last platinum-based treatment. *Exception:* Patients in Arm C who's maintenance treatment start is delayed due to necessary IDMC evaluation after 6 and 12 patients are allowed to start maintenance treatment beyond the 12 weeks.

Please refer to section 16.1 to determine the starting dose of Niraparib for maintenance treatment..

Maintenance visits will be performed in a 4-weeks cycle, q4w.

Day 1 of all treatment cycles Niraparib single agent

- Day 1 of cycle 1 and than on day 1 of **every other** cycle, i.e. cycles **3**, **5**, **7** etc : Completion of PRO questionnaires (see section 16.2)
- Physical examination including vital signs and measurement of body weight and height (height only at Day 1 of cycle 1) (see section 16.4)
- Determine ECOG PS (see Appendix A)
- Laboratory assessments; Haematology and Biochemistry panel (see section 16.6)
- Evaluation of tumour marker CA-125
- Urine/serum pregnancy test in WOCBP (for definition see section 6).
- Day 1 of cycle 1 and than on day 1 of **every third** cylcle, i.e. cycles **4**, **7**, **10** etc.: Blood sampling for biomarker analysis prior administration of study drug (please see section 16.7)
- Day 1 of cycle 1: Niraparib capsules dispensed; first dose administered at site
- Day 1 of all other cycles: Niraparib capsules dispensed / collected*
- Record concomitant medications (see section 16.3)
- Evaluate and document adverse events (AEs) (see Appendix B)

* Please note: In case not all capsules were used, please count the remaining capsules first and instruct the patient afterwards to use up the remaining capsules before starting the new bottle.

Weekly in the first 2 cycles of maintenance treatment

- Laboratory assessments: Haematology (see section 16.6)

Every 12 Weeks starting from day 1 cycle 1 of maintenance treatment

- Tumour assessments through CT/MRI (see section 16.1)

Table 12: Niraparib single agent Maintenance Schedule of Events (Arm A and B)

Procedures / Assessments	***Cycle 1+2***				***Cycle 3***				
Cycle day	**1**	**8**	**15**	**22**	**1**	***8***	***15***	***22***	
Physical examination incl. vital signs[a] (BP, HR, T)	X				X	No tstudy center visit	No tstudy center visit	No tstudy center visit	***Follow schedule cycle 3 for all subsequent cycles until progression***
Body height and weight[b]	X				X				
ECOG Performance status	X				X				
Haematology[c]	X	X	X	X	X				
Biochemistry Panel[d]	X				X				
Pregnancy test[e]	X				X				
PRO questionnaire[f]	X				(X)				
Niraparib dispensed / collected	X				X[j]				
CA-125	X				X				
CT/MRI[g]	X				(X)				
Blood sample collection for biomarker analysis[h]	X				(X)				
Urinalysis	x				x				
Adverse events[i]	Continuously								
Concomitant medication	Continuously								
Bone Marrow Aspirate and Biopsy	At any time of MDS or AML diagnosis								

[a] Vital signs include weight, temperature, systolic and diastolic blood pressure (BP) and heart rate (HR); BP and HR will be measured after patient was in a sitting position for at least 10 minutes

[b] Body height is only to be measured at C1D1[c] Haematology laboratory tests include assessment of :

§ Hemoglobin, haematocrit, RBC, WBC, absolute neutrophil count, differential (%)[†],platelets

[†] Neutrophils, eosinophils, basophils, lymphocytes, monocytes

and needs to be done weekly in the first two cycles.

[d] Biochemistry panel laboratory tests include assessment of:

§ Sodium, potassium, calcium
§ Serum albumin, serum urea
§ ALT, AST, LDH, AP, total bilirubin
§ Creatinine

[e] Urine/serum pregnancy testing is not required in patients after surgical sterilisation or bilateral ovarectomy or hysterectomy; > 12 months amenorrhea, age > 60 years.

[f] Questionnaires EORTC QLQ-C30, EORTC QLQ-OV28, on day 1 of cycle 1 and than on day 1 of **every other** cycle , i.e. cycles 3, 5, 7 etc.

[g] Tumour assessments every 12 weeks for response and progression require CT scans of the pelvis and abdomen and (by X-ray or preferably by CT-scan) of the chest. MRI scans can be used for patients who are allergic to radiographic contrast agents. Throughout the study, the same assessment technique must be used. Ultrasound scanning is not an acceptable substitute for CT scanning. Tumour assessment has to be done before start of maintenance therapy to confirm SD, PR or CR.

[h] Blood collection for biomarker analysis will be performed before the administration of study drug on day 1 of cycle 1 and thereafter on day 1 of **every third cycle**, cycles 4, 7, 10 etc *prior* to administration of study drug. An additional blood sample for biomarker analysis will be taken at disease progression (first visit after diagnosis of progression).

[i] After initiation of study drug, all AEs and SAEs regardless of relationship to the study drug, will be reported until safety follow-up at 28 days after the last dose of IMP or EOT or until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent

[j] In case not all capsules were used, please count the remaining capsules first and instruct the patient afterwards to use up the remaining capsules before starting the new bottle

15.2.5 Maintenance Treatment Arm C: combination maintenance treatment Niraparib and Ganetespib

Criteria to assess eligibility to start with Niraparib + Ganetespib combination maintenance therapy (arm C)

- CT scan after completion of 6 cycles of platinum-based treatment showing SD, PR or CR.
- Patients must have received 6 cycles of platinum-based treatment to start maintenance treamtment
- With respect to laboratory findings:

    - Absolute neutrophil count ≥ 1,500/µL
    - Platelets ≥ 100,000/µL
    - Hemoglobin ≥ 9 g/dL
    - Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault equation
    - Total bilirubin ≤ 1.5 x ULN (≤2.0 in patients with known Gilberts syndrome) OR direct bilirubin ≤ 1 x ULN
    - Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x ULN unless liver metastases are present, in which case they must be ≤ 5 x ULN

- Participant must not have received a transfusion (platelets or red blood cells) ≤ 4 weeks prior to start of Niraparib.
- Participant must not have received colony-stimulating factors (eg. granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, or recombinant erythropoietin) ≤ 4 weeks prior to start of Niraparib.
- Participant must have a negative pregnancy test within 7 days prior to start of Niraparib.
- Any known grade 3 or 4 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted > 4 weeks and was related to induction chemotherapy part in this study.

Maintenance treatment is not allowed to start prior to 6 weeks after last platinum-based treatment. Maintenance treatment *should preferentially start between 6 and 9 weeks*, but will be allowed until up to 12 weeks after last platinum-based treatment. *Exception:* Patients in Arm C whos maintenance treatment start is delayed due to necessary IDMC evaluation after 6 and 12 patients are allowed to start maintenance treatment beyond the 12 weeks.

Please refer to section 16.1 to determine the starting dose of Niraparib for maintenance treatment.

Of note, in case of negative safety evaluation of the Niraparib and Ganetespib combination by the IDMC, patients in arm C will proceed with Niraparib single agent maintenance treatment. Maintenance visits will be performed in a 4-weeks cycle, q4w.

Day 1 all treatment cycles Niraparib and Ganetespib

- Day 1 cycle 1 and than on day 1 of **every other** cycle, i.e. cylces **3, 5, 7** etc: Completion of PRO questionnaires (see section 15.2)
- Physical examination including vital signs and measurement of body weight and height (height only at Day 1 of cycle 1) (see section 16.4)
- Determine ECOG PS (see Appendix A)
- Laboratory assessments; Haematology and Biochemistry panel (see section 16.6)
- Evaluation of tumour marker CA-125
- Urine/serum pregnancy test in WOCBP (for definition see section 6).
- Day 1 of cycle 1 and than on day 1 of **every third** cylcle, i.e. cycles **4**, **7**, **10** etc.: Blood sampling for biomarker analysis prior to administration of study drug (please see section 16.7)
- Day 1 of each cycle: Electrocardiogram (ECG) (see section 16.5)
- Day 1 of cycle 1: Niraparib capsules dispensed; first dose administered at site
- Day 1 of all other cycles: Niraparib capsules dispensed / collected*
- Administration of Ganetespib (100 mg/m^2) as an i.v. infusion
- Record concomitant medications (see section 16.3)
- Evaluate and document adverse events (AEs) (see Appendix B)

* Please note: In case not all capsules were used, please count the remaining capsules first and instruct the patient afterwards to use up the remaining capsules before starting the new bottle

Day 8, 15, 22 all cycles Niraparib + Ganetespib

- Physical examination including vital signs and measurement of body weight (see section 16.4)
- Determine ECOG PS (see Appendix A)
- Laboratory assessments; Haematology panel (see section 16.6)
- Administration of Ganetespib as an i.v. infusion, provided that there are no significant findings at the Day of administration (e.g. physical examination, ECOG PS, laboratory assessments or pregnancy test, see section 16)

Every 12 Weeks starting from day 1 cycle 1 of maintenance treatment

- Tumour assessments through CT/MRI (see section 16.1)

Table 13: Niraparib + Ganetespib Maintenance Schedule of Events (Arm C)

Procedures / Assessments	***Cycle 1 and 2***					***Cycle 3 and beyond***				***Follow schedule of cycle 2 for all subsequent cycles until progression. The combination of Niraparib and Ganetespib will be given for 9 months. Thereafter Ganetespib treatment will be stopped and Niraparib maintenance therapy will be continued as single agent until disease progression.***
Cycle day	**1**	**2**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	
Physical examination incl. vital signs[a] (BP, HR, T)	X		X	X	X	X	X	X	X	
Body height and weight[b]	X		X	X	X	X	X	X	X	
ECOG Performance status	X		X	X	X	X	X	X	X	
ECG[c]	X	X	(X)	(X)	(X)	X	(X)	(X)	(X)	
Haematology[d]	X		X	X	X	X	X	X	X	
Biochemistry panel[e]	X					X				
Pregnancy test[f]	X					X				
PRO questionnaire[g]	X					(X)				
Administration of Ganetespib	X		X	X	X	X	X	X	X	
Niraparib dispensed / collected[k]	X					X				
CA-125	X					X				
CT/MRI[h]	X					(X)				
Blood sample collection for biomarker analysis[i]	X					(X)				
Urinalysis	X					X				
Adverse events[j]	Continuously									
Concomitant medication	Continuously									
Bone Marrow Aspirate and Biopsy	At any time of MDS or AML diagnosis									

[a] Vital signs include weight, temperature, systolic and diastolic blood pressure (BP) and heart rate (HR); BP and HR will be measured after patient was in a sitting position for at least 10 minutes

[b] Body height is only to be measured at C1D1

[c] ECGs for each patient should be obtained from the same machine whenever possible. A consistent method of QTc calculation must be used for each patient's QTc measurements. QTcF (Fridericia's formula) is preferred. For the screening ECG averaged values of triplicate recordings are necessary. ECGs during treatment period needs to be done only in patients who receive Ganetespib. A pre-Ganetespib dose ECG will be performed on day 1 of each cycle (on the day of medication dosing, or one day prior). In addition, a 24-hours post-Ganetespib-dose ECG (+/- 4 hours) will be performed on day 2 of cycle 1. In case of QTc prolongation (pre- or post-dose), further intensified ECG monitoring will be performed at the next dosing of Ganetespib. At a minimum pre-dose ECGs will be performed on days 1 of each cycle of Ganetepib treatment.

[d] Haematology laboratory tests include assessment of:

§ Hemoglobin, haematocrit, RBC, WBC, absolute neutrophil count, differential (%)†,platelets

† Neutrophils, eosinophils, basophils, lymphocytes, monocytes

[e] Biochemistry panel laboratory tests include assessment of:

§ Sodium, potassium, calcium
§ Serum albumin, serum urea
§ ALT, AST, LDH, AP, total bilirubin
§ Creatinine

[f] Urine/serum pregnancy testing is not required in patients after surgical sterilisation or bilateral ovarectomy or hysterectomy; > 12 months amenorrhea, age > 60 years.

[g] Questionnaires EORTC QLQ-C30, EORTC QLQ-OV28, on day 1 of cycle 1 and than on day 1 of **every other** cycle, i.e. cycles **3, 5, 7** etc.

[h] Tumour assessments every 12 weeks for response and progression require CT scans of the pelvis and abdomen and (by X-ray or preferably by CT-scan) of the chest. MRI scans can be used for patients who are allergic to radiographic contrast agents. Throughout the study, the same assessment technique must be used. Ultrasound scanning is not an acceptable substitute for CT scanning. Tumour assessment has to be done before start of maintenance therapy to confirm SD, PR or CR.

[i] Blood collection for biomarker analysis will be performed before the administration of study drug on day 1 of cycle 1 and thereafter on day 1 of **every third** cycle, i.e. **4**, **7**, **10** *prior* to administration of study drug. An additional blood sample for biomarker analysis will be taken at disease progression (first visit after diagnosis of progression).

[j] After initiation of study drug, all AEs and SAEs regardless of relationship to the study drug, will be reported until safety follow-up at 28 days after the last dose of IMP or EOT or until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent

[k] In case not all capsules were used, please count the remaining capsules first and instruct the patient afterwards to use up the remaining capsules before starting the new bottle

15.3 End of treatment / Safety Follow-up

All patients will receive a safety follow-up 28 days (+/- 7 days) after the last dose of Ganetespib (maximum of 9 months maintenance treatment) as well as after the last dose of Niraparib (treatment until progression) or prior to initiation of a new anti-cancer treatment, whichever occurs earlier.

Safety follow-up includes the following (see Table 14):

- Completion of PRO questionnaires (see section 15.2)
- Physical examination including vital signs and measurement of body weight (see section 16.4)
- Determine ECOG PS (see Appendix A)
- Laboratory assessments; Haematology and Biochemistry panel (see section 16.6)
- Blood sampling for biomarker analysis (this blood sample at progression can be taken at the visit following diagnosis of progressive disease or the latest at safety follow-up)
- Evaluation of Tumour marker CA-125
- Electrocardiogram (ECG) (see section 16.5)
- Assess left ventricular ejection fraction (LVEF) by ECHO (see section 16.5)
- Urine/serum pregnancy test in WOCBP (for definition see section 6).
- Record concomitant medications (see section 16.3)
- Evaluate and document adverse events (AEs) (see section 19.1 and Appendix B)

15.4 Longterm FU prior to progression

Patients who discontinue study treatment without having developed progressive disease will first continue to be followed **monthly** (+/- 7 days) as listed below until progression and will then continue with long-term follow-up after progression as described below under 15.5.

- Completion of PRO questionnaires every 8 weeks (see section 16.2)
- Tumour assessments through CT/MRI every 12 weeks (see section 16.1)

- Evaluation of Tumour marker CA-125 every 4 weeks
- Additional cancer therapy
- Date of progression
- Evaluate any deaths, serious adverse events (SAEs), or other adverse events (AEs) of concern that are believed to be related to prior treatment with the study drug (see section 19.1 and Appendix C)

15.5 Longterm FU after progression

In all patients a long-term follow-up period will be performed after the safety follow-up visits (arm A, B and C, see Table 14).
In patients who had end of treatment due to progression of disease, the following assessments should be recorded in **three-monthly** intervals (+/- 14 days) until death of the patient or the end of study, whichever occurs first.

- Additional cancer therapy
- Date of next progression, following the subsequent cancer therapy
- Evaluate any deaths, serious adverse events (SAEs), or other adverse events (AEs) of concern that are believed to be related to prior treatment with the study drug (see section 19.1 and Appendix B)

Table 14: Longterm follow-up Schedule of Events

Procedures / Assessments	**Safety FU**	**Follow-up PRIOR** to progression: **every month**	**Follow-up AFTER** progression: **every 3 months**
Physical examination incl. vital signs[a] (BP, HR, T)	X		
Body weight	X		
ECOG Performance status	X		
ECG[b]	X		
LVEF	X		
Haematology[c]	X		
Biochemistry Panel[d]	X		
Pregnancy test[e]	X		
PRO questionnaire[f]	X	(X)	
CA-125	X	X	
CT/MRI[g]		(X)	
Survival status, MDS/AML monitoring (for 5 years), additional cancer therapy, date of subsequent progression		X	X
Adverse events[h]	Continuously		

[a] Blood pressure and heart rate will be measured after patient was in a sitting position for at least 10 minutes

[b] ECGs for each patient should be obtained from the same machine whenever possible. A consistent method of QTc calculation must be used for each patient's QTc measurements. QTcF (Fridericia's formula) is preferred.

[c] Haematology laboratory tests include assessment of:

§ Hemoglobin, haematocrit, RBC, WBC, absolute neutrophil count, differential (%)†,platelets
† Neutrophils, eosinophils, basophils, lymphocytes, monocytes

[d] Biochemistry panel laboratory tests include assessment of:

§ Sodium, potassium, calcium
§ Serum albumin, serum urea
§ ALT, AST, LDH, AP, total bilirubin
§ Creatinine

[e] Urine/serum pregnancy testing is not required in patients after surgical sterilisation or bilateral ovarectomy or hysterectomy; > 12 months amenorrhea, age > 60 years.

[f] Questionnaires EORTC QLQ-C30, EORTC QLQ-OV28 every 8 weeks prior to progression. .

[g] Tumour assessments every 12 weeks for response and progression require CT scans of the pelvis and abdomen and (by X-ray or preferably by CT-scan) of the chest. MRI scans can be used for patients who are allergic to radiographic contrast agents. Throughout the study, the same assessment technique must be used. Ultrasound scanning is not an acceptable substitute for CT scanning.

[h] After initiation of study drug, all AEs and SAEs regardless of relationship to the study drug, will be reported until safety follow-up at 28 days after the last dose of IMP or EOT or until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. After the safety follow-up, investigators should report any deaths, SAEs, or other AEs of concern that are believed to be related to prior treatment with the study drug.

16 STUDY ASSESSMENTS

Details of the timing of assessments are presented in the Schedule of Assessments (see details in section 15).

16.1 Tumour response assessment

Patients will be assessed for disease response or progressive disease throughout the clinical trial.

Response or progression will be evaluated in this study according to RECIST 1.1 (see Appendix D). Evidence of progressive disease is considered clear radiological evidence. CA-125 elevation alone is not defined as disease progression. An objective response should be confirmed by repeated assessment not earlier than 4 weeks after initial documentation or at the next scheduled tumour assessment if it is to occur more than 4 weeks after the initial response.

Radiologic tumour assessments

Tumour assessments require CT scans of the pelvis and abdomen and (by X-ray or preferably by CT scan) of the chest. MRI scans can be used for patients who are allergic to radiographic contrast agents. The same method of tumour assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Positron emission technology scans are not acceptable for monitoring target lesions. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

Baseline tumour assessment of the chest (by X-ray of preferably by CT scan), abdomen and pelvis by CT scan (or MRI scan in case of allergic reactions to radiographic contrast agents) must be performed within a maximum of 28 days before first dose of study drug treatment.

Already existing CT scan can be used as screening CTs, if not older than 28 days at the time of randomisation.

Post-baseline tumour assessments are to be performed every 12 weeks during platinum-based therapy and after completion of platinum-based therapy (independent of any treatment interruptions using the same imaging technique as used during screening). Patients evaluated with SD, PR, or CR after completion of platinum-based therapy will start with maintenance treatment. During maintenance treatment tumour assessment will be performed every 12 weeks (+/- 1 week) starting from day 1 cycle 1 of maintenance treatment until disease progression (independent of any treatment interruptions using the same imaging technique as used during screening)
If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed.

16.2 Patient-reported outcome (PRO)

16.2.1 PRO instruments

The following PRO questionnaires will be used in all study arms of this study: EORTC QLQ-C30, EORTC QLQ-OV28 (Appendix C).

The EORTC QLQ-C30, an internationally validated and widely used cancer-specific QOL-instrument, assesses various facets of functioning and symptoms common in cancer patients. It comprises five functioning scales (physical, social, role, emotional, cognitive), a scale for global QOL, and nine symptom scales (fatigue, nausea/vomiting, pain, dyspnoea, sleeping disturbances, appetite-loss, constipation, diarrhoea, and financial impact).

The QLQ-OV28 module is a supplement of the QLQ-C30 for assessing issues relevant to ovarian cancer patients. The module covers abdominal/gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side-effects, hormonal/menopausal symptoms, body image, attitude to disease/treatment and sexual functioning.

All scales are scored according to EORTC guidelines resulting in a score range from 0 to 100 points.

16.2.2 PRO assessment schedule

The PRO questionnaires should be given to the patient to complete during their visit (i.e. patients should not be sent home with the questionnaires to complete and return at their next visit), but prior to administration of investigational product. These will be assessed during screening, event-driven on **day 1 of every second cycle** (d1c1, d1c3, d1c5) during platinum-based therapy. During maintenance treatment PRO questionnaires will be filled in event-driven on **day 1 of every second cycle** (d1c1, d1c3, d1c5, d1c7…). Patients who discontinue study treatment without having developed progressive disease will complete PRO questionnaires every 8 weeks until progression. In the long-term follow-up after progression no further PRO evaluations will take place.

15.2.3 PRO assessment procedure

The patient will be approached by a study nurse or an investigator and will be asked to complete the PRO questionnaires on her own. The PRO assessments will take place prior to patient-clinician consultation to avoid the immediate impact of issues discussed in the clinical encounter. A quiet place providing sufficient privacy will be provided to the patient for questionnaire completion. The study nurse or investigator will be available for any questions arising during questionnaire completion. In case of problems with reading (e.g. due to limited literacy or impaired eyesight) the questionnaire will be conducted as a structured interview.

16.3 Concomitant medications/therapies

All medication (other than study drug) and significant non-drug therapies (including, but not limited to, herbal/natural medications and blood transfusions) will be recorded at screening and on an ongoing basis thereafter. Any surgical and medical procedures (i.e. paracentesis) will also be recorded.

16.4 Physical examination

Physical examinations will be performed by trained medical personnel.
Vital signs (blood pressure, heart rate and temperature, as appropriate) and body weight will be measured per institutional standards as part of the physical examination. Height will be measured only at Screening. All physical examinations occurring on dosing days must be performed prior to study drug administration. Any treatment-emergent abnormal findings will be recorded as AEs.
Heart rate and blood pressure will be measured after patient has been in a sitting position for 10 minutes.

16.5 Electrocardiography (ECG) and Left ventricular ejection fraction (LVEF)

ECG:
A standard 12-lead ECG assessment will be performed at screening and at EOT/safety follow-up.

Each patient receiving Ganetespib: A pre-Ganetespib dose ECG will be performed on **day 1 of each cycle** (on the day of medication dosing, or one day prior). This applies to both, all treatment cycles during platinum-based combination (arms B and C) and all treatment cycles of Niraparib combination (arm C). In addition, a **24-hours post-Ganetespib-dose ECG** (+/- 4 hours) will be performed on **day 2 of cycle 1**. This also applies to both, the first cycle of platinum-based combination therapy and the first cycle of Niraparib combination treatment.

The **investigator will evaluate ECG findings in the first cycle of Ganetespib combination treatments** (this applies again to both the Carboplatin Ganetespib combination as well as to the Niraparib Ganetespib combination) and will decide on an **individualized risk-adjusted continued ECG monitoring schedule.** At a minimum pre-dose ECGs will be performed on days 1 of each cycle of Ganetepib treatment.

ECGs for each patient should be obtained from the same machine whenever possible. A consistent method of QTc calculation must be used for each patient's QTc measurements.

QTcF (Fridericia's formula) is preferred. For the screening ECG averaged values of triplicate recordings are necessary.
To minimise variability, it is important that patients be in a resting position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws. For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at site as part of the patient's file.

LVEF:
Cardiac ejection fraction will be assessed by transthoracic echocardiography (ECHO) at Screening and at EOT/Safety Follow up (time points specified in section 15, schedule of assessments).

16.6 Laboratory assessments

Samples for laboratory tests will be analysed at the local laboratory of each participating site.

Blood analysis will be done as part of regular safety assessments at screening/baseline, every treatment cycle (prior to study drug administration), and at the post-treatment safety follow-up. Assessments must be performed at each cycle within 3 days (with results available) prior to the administration of study medication.

16.7 Biomarker analysis

Blood samples for analysis of biomarkers (including cell free tumour DNA and CTCs analyses) will be taken before and during study treatment in all patients (arm A, B and C) on days 1 of **every third treatment cycle** during platinum-based therapy (d1c1, d1c4) as well as on days 1 of **every third treatment cycle during** maintenance treatment (d1c1, d1c4, d1c7, d1c10 etc.) as outlined in section 15.

The following biosamples will be collected to determine potential prognostic or predictive biomarkers (such as but not exclusively p53 status and other HSP90 clients) and to confirm high-grade serous, high-grade endometrioid, undifferentiated ovarian cancer, carcinosarcoma, fallopian tube or primary peritoneal cancer in all patients treated in this trial:

- Mandatory archival tumour tissue from **primary** diagnosis (formalin-fixed paraffin-embedded tissue, FFPE). **Chemo-naive** tumour tissues (instead of tissue after neo-adjuvant chemotherapy) will preferentially be collected.
- Mandatory blood collection before and during experimental therapy on days 1 of **every third treatment cycle** (during both platinum-based therapy and maintenance treatment)
- Whenever technically feasible, it is recommended to collect tissue of the actual platinum-sensitive relapse. This can be obtained by CT- or sonography guided biopsy of the actual relapse after informed consent has been obtained but prior to the first

study drug application or during routine debulking surgery in the actual relapsed situation. Both, FFPE and/or fresh frozen tissue samples (preferred) can be collected and provided to the consortium for biomarker analysis.
In a subset of ~10 patients who are treated at participating sites, a second biopsy will be collected 24 hours (+/- 2 hours) after the first application of study treatment (Cycle 1 Day 2) if technically feasible. These paired biopsies will be used to analyse the underlying "mechanism of action" of the study treatment (i.e. DNA damage response). It is aimed that this subset of 10 patients consists of 3 patients in the control arm A and 7 patients in the experimental arms B + C (in line with the ratio 2:1 of randomisation).

Prospectively collected biomaterials for biomarker analysis will be stored in a biobank. Tumour samples from screen-failed patients will also be included in a biobank.
Details of tissue requirements, processing, and handling instructions of collected biomaterials are given separately in the Sample Handling Manual and Logistics Manual.

Determination of p53 status and other biomarkers in collected biomaterials
Archival tissues (FFPE) and tissues of of the actual relapse (FFPE and/or fresh-frozen tissues) will be collected in this trial. DNA, RNA and/or protein will be extracted from collected tissues. The p53 status and other biomarkers (including e.g. analysis of the p53-homologues p73 and p63, or other HSP90 clients) will be analysed. No germline BRCA testing will be performed, only retrospective somatic testing in the tumour tissues together with other relevant biomarkers e.g. involved in DNA repair.
Blood samples for biomarker analysis (including e.g. circulating tumour cells and cell free tumour DNA) will be taken before and during study treatment in all patients.

17 STUDY MEDICATION

17.1 Dosage and Administration

An expected number of 120 patients will be treated with:

Treatment arms:

Standard arm A:
6 cycles of standard platinum-based chemotherapy, q3w
<u>One of the two listed regimens, according to investigator decision:</u>
- Carboplatin (AUC4, d1, iv) and Gemcitabine (1000 mg/m²; d1+d8, iv) or
- Carboplatin (AUC5, d1,iv) and Paclitaxel (175 mg/m²; d1, iv) and
  followed by maintenance treatment with Niraparib continuous oral daily (q4w) until progression, as below:

Niraparib dosing according to body weight and thrombocyte values:

Baseline Criteria	**Starting Dose**
≥77 kg **and** ≥150,000 µL	300 mg (3 X 100 mg capsules) daily
<77 kg **or** <150,000 µL	200 mg (2 X 100 mg capsules) daily

Table 15 Niraparib dosing for arm A and arm B

First experimental arm B:
6 cycles of Carboplatin (AUC5; d1,iv) + Ganetespib (150 mg/m²; d1, iv), q3w
Carboplatin infusion needs to be given first, followed by Ganetespib infusion.
6 cycles of Carboplatin Ganetespib treatment are followed by maintenance treatment with Niraparib continuous oral daily (q4w) until progression, according to the Niraparib dosing table above.

Second experimental arm C:
6 cycles of Carboplatin (AUC5; d1, iv) + Ganetespib (150 mg/m², d1,iv), q3w
Carboplatin infusion needs to be given first, followed by Ganetespib infusion.
6 cycles of Carboplatin Ganetespib treatment are followed by maintenance treatment with Niraparib 200 mg oral daily (q4w) until progression + Ganetespib 100 mg/m² weekly (d1, d8, d15, d22, q4w) for 9 months. After 9 months Ganetespib treatment will be stopped and Niraparib maintenance therapy will be continued as single agent treatment.

Ganetespib administration in general:
Ganetespib is given as infusion intravenously over 1 hour. The IMP Ganetespib must be diluted prior to administration. The drug product is a clear, colourless-to-pale-yellow solution. The appropriate drug administration instructions per the preparation guidelines must be carefully followed prior to use.
The use of vascular access devices (VADs) such as ports and peripherally-inserted central catheters (PICCS) containing silicone for Ganetespib administration is permitted. Use of VADs made of any other material is not permitted. Following Ganetespib administration through a VAD, care should be taken to flush the line after each dose of study drug.
Ganetespib dose is calculated based on the patient's body surface area (BSA). No dose capping will be performed in case of greater BSA.
Please refer to the Pharmacy Manual for detailed Ganetespib preparation guidelines.

Premedications:
Ganetespib*:* Prophylactic medication with Loperamide 2 mg is strongly recommended in all patients who receive Ganetespib (this applies for both combinations, ie. Ganetespib in combination with Carboplatin and Ganetespib in combination with Niraparib) and should be given 1-2 hours before Ganetespib administration, to be repeated every 4 hours for the first 12 hours. Sufficient hydration should be provided in all patients. This applies for both Ganetespib combination in this trial, i.e. the Ganetespib Carboplatin and the Ganetspib Niraparib combination.

Carboplatin Paclitaxel and Carboplatin Gemcitabine (standard platinum-based chemotherapy): **Local pre-medication standard at clinical site can be used**.

Carboplatin Ganetespib: **Local pre-medication standard at clinical site can be used for Carboplatin.** With respect to Ganetespib, prophylactic medication with Loperamide 2 mg is strongly recommended and should be given 1-2 hours before Ganetespib administration, to be repeated every 4 hours for the first 12 hours. Sufficient hydration should be provided in all patients**.** Of note, Carboplatin infusion needs to be given first, followed by Ganetespib infusion.

Ganetespib Niraparib: With respect to Ganetespib, prophylactic medication with Loperamide 2 mg is strongly recommended and should be given 1-2 hours before Ganetespib administration, to be repeated every 4 hours for the first 12 hours. Sufficient hydration should be provided in all patients.

18 DOSING SELECTION/ DOSE MODIFICATION/ DELAYS

18.1 Dose modifications for Carboplatin and Gemcitabine (Arm A)

The following dose modifications for standard chemotherapy Carboplatin/Gemcitabine are recommended:

Dose reduction levels for Gemcitabine and Carboplatin are given in Table 16: Dose levels for Gemcitabine and Carboplatin.

Table 16: Dose levels for Gemcitabine and Carboplatin

Drug	**Protocol Starting Dose**	**Protocol Dose Level -1**	**Protocol Dose Level -2**	**Indication for further dose reductions**
Gemcitabine	1000 mg/m^2	800 mg/m2	-	Discontinue study medication
Carboplatin	AUC4	AUC3	-	Discontinue study medication

18.1.1 Haematologic toxicity

Treatment should be delayed if either of the following occurs within 24 hours prior to the administration of therapy:

- Absolute neutrophile count (ANC) < 1.5 x 10^9/L (or < 1.0 x 10^9/L if the patient is planned to receive G-CSF)
- Platelet (PLT) count < 100 x 10^9/L

Complete blood cell count (CBC) should be repeated, at least weekly, until haematologic recovery has occurred (ANC ≥ 1.5 x 10^9/L or > 1.0 x 10^9/L if the patient is planned to receive G-CSF and PLT ≥ 100 x 10^9/L). If haematologic recovery occurs within 7 days, no dose modification is mandated and any dose modification is left to the discretion of the individual investigator. If haematologic recovery occurs beyond 7 days doses of Carboplatin/ Gemcitabine should be modified according to the blood count. G-CSF should be used as stipulated by the ASCO guidelines or according to local practice guidelines.

Patients who fail to recover adequate counts after a delay of 2 weeks or more, or who have consecutive dose-limiting toxicities, are not likely to be able to tolerate standard chemotherapy treatment. Significant modifications to the chemotherapy dose may be required. Such extreme

modifications are likely to be rare and should therefore be discussed on a case by case basis with the Sponsor.
Table 17 gives recommendations for dose modifications for Gemcitabine on day 8.

Table 17: Recommendations for Gemcitabine dose adjustments on day 8 for haematologic toxicities

Finding			**Modification**
ANC (x 10^9/L)		Platelets (x 10^9/L)	
≥ 1.5	and	≥ 100	100 %
≥1.0 to 1.4	and/or	75 – 99	50 %
< 1.0	and/or	< 75	Omit dose

Patients may receive erythropoietin (EPO), iron supplements and/or blood transfusions as clinically indicated for the management of their anemia.
Dose adjustment for Gemcitabine in combination with Carboplatin for subsequent cycles is based on toxicity observed during the preceding cycle. The dose of Gemcitabine should be permanently reduced on day 1 and day 8 in case of any of the following haematological toxicities:

- Absolute Neutrophil Count < 500 x 10^6/L for more than 5 days
- Absolute Neutrophile Count < 300 x 10^6/L for more than 3 days
- Febrile Neutropenia
- Platelets < 25 x 10^9/L
- cycle delay of more than one week due to toxicity

If any of the above toxicities recur after the initial dose reduction for the subsequent cycles, Gemcitabine and Carboplatin should be reduced according to Table 16. Gemcitabine should be given only on day 1 (omit Gemcitabine on day 8).

18.1.2 Non-haematologic toxicity

Renal toxicity
The combination of Gemcitabine and Carboplatin is not directly expected to cause renal toxicity. Therefore, no specific dose modifications are recommended for renal toxicity. Any concerns should be discussed with the Sponsor.
However, the administered dose of Carboplatin must be recalculated, based on a recalculated or remeasured GFR, for

- renal toxicity (CTC Grade 2, serum creatinine > 1.5 x ULN)
- changes in serum creatinine of ≥ 10%
- each dose modification of Carboplatin
- cycle 2 if there has been significant doubt about the true GFR at cycle 1 (e.g. due to significant ascites).

Hepatic toxicity
If Gemcitabine will be administered to patients with liver metastases or hepatitis in their history a deterioration of the existing liver insuffiency is possible. Transaminases should be checked on a regular basis.

Other
There are no dose modifications planned for alopecia, nausea, diarrhea or constipation. These side effects should be treated with supportive medical measures. Non-steroidal anti-inflammatory agents can be used prophylactically or symptomatically, as per local practice.
Any CTC grade 4 non-haematologic AE (except nausea or vomiting) will require the patient to be taken off treatment. For any grade 3 non-haematologic toxicity (except nausea or vomiting) the drugs should be withheld until symptoms resolve to ≤ grade 1. If the grade 3 event persists for ≥ 3 weeks, or recurs, then discussion with the Sponsor is recommended.

18.1.3 Hypersensitivity to Carboplatin (regardless of combination)

If there is a hypersensitivity reaction to Carboplatin this should be managed as per local institutional protocols. Cisplatin can be substituted for Carboplatin at the discretion of the treating physician. Cisplatin (75 mg/m^2) would be administered i.v. over 30 minutes every 3 weeks. For patients who experience dose-limiting toxicity with Cisplatin, the dose can be reduced to 60 mg/m^2 and subsequently to 50 mg/m^2 if further dose-limiting toxicity occurs.

18.2 Dose modifications for Carboplatin/Paclitaxel (Arm A)

The following dose modifications for standard chemotherapy Carboplatin/Paclitaxel are recommended:
Dose reduction levels for Carboplatin and Paclitaxel are given in Table 18.

Table 18: Dose reduction levels for Paclitaxel and Carboplatin

Drug	**Protocol Starting Dose**	**Protocol Dose Level -1**	**Protocol Dose Level -2**	**Indication for further dose reductions**
Paclitaxel	175 mg/m^2	135 mg/m2	110 mg/m2	Discontinue study medication
Carboplatin	AUC5	AUC4	AUC3	Discontinue study medication

- Dose levels are adjusted individually for each drug.
- Up to 2 dose-reductions are acceptable for Paclitaxel and Carboplatin in cases of severe haematologic toxicity.
- No dose re-escalations are permitted following dose-reduction for toxicity.

18.2.1 Haematologic toxicity

Treatment should be delayed if either of the following occurs within 24 hours prior to the administration of therapy:

- Absolute neutrophil count (ANC) < 1.5 x 10^9/L (or < 1.0 x 10^9/L if the patient is planned to receive G-CSF)
- Platelet (PLT) count < 100 x 10^9/L.

CBC should be repeated, at least weekly, until haematologic recovery has occurred (ANC ≥ 1.5 x 10^9/L or > 1.0 x 10^9/L if the patient is planned to receive G-CSF and PLT ≥100 x 10^9/L). If haematologic recovery occurs within 7 days, no dose modification is mandated and any dose modification is left to the discretion of the individual investigator. If haematologic recovery occurs beyond 7 days, doses of Carboplatin and Paclitaxel should be modified according to the day 22 blood count (or subsequent CBC if lower).
G-CSF should be used as stipulated by the ASCO guidelines, or according to local practice guidelines. In particular, to prevent severe infections linked to febrile neutropenia prophylactic G-CSF should be initiated according to the ASCO guidelines, or according to local practice guidelines such as the INCa recommendations in France.

Patients who fail to recover adequate counts after a delay of 2 weeks or more, or who have consecutive dose-limiting toxicities, are not likely to be able to tolerate standard chemotherapy treatment. Significant modifications to the chemotherapy dose may be required. Such extreme modifications are likely to be rare and should therefore be discussed on a case by case basis with the Sponsor.
Haematologic dose-limiting toxicities and permitted dose modifications are described in Table 19. Patients developing any other dose-limiting toxicity require dose modification independently of the ANC and platelets on day 22.
Patients may receive erythropoietin (EPO), iron supplements and/or blood transfusions as clinically indicated for the management of their anemia.

Table 19: Guidelines for Paclitaxel and Carboplatin dose modification for delayed haematologic recovery according to the blood test on day 22

		Delayed ANC recovery (> 7 days)	
	Results on day 22	**ANC ≥ 1.5 x 10^9/L (≥ 1.0x10^9/L if G-CSF is planned to be given)**	**ANC < 1.5 x 10^9/L (< 1.0x10^9/L if G-CSF is planned to be given)**
Delayed PLT Recovery (>7 days)	**PLT ≥ 100 x 10^9/L**	Paclitaxel: No modification Carboplatin: No modification	Paclitaxel: Either: Use G-CSF and continue current dose Or Reduce by 1 dose level Carboplatin: No modification

	PLT < 100 x 10^9/L	Paclitaxel: No modification Carboplatin: Reduce by 1 AUC unit	Paclitaxel: Either: Use G-CSF and continue current dose Or Reduce by 1 dose level Carboplatin: Reduce by 1 AUC unit

Table 20: Guidelines for Paclitaxel and Carboplatin dose modification due to dose-limiting toxicity

	Dose-Limiting Toxicity: ANC[1]	
Dose-Limiting Toxicity: PLT[2]	No	Yes
No	Paclitaxel: No modification	Paclitaxel: Either: Use G-CSF and continue current dose or Reduce by 1 dose level
	Carboplatin: No modification	Carboplatin: No modification
Yes	Paclitaxel: No modification	Paclitaxel: Either: Use G-CSF and continue current dose or Reduce by 1 dose level
	Carboplatin: Reduce by 1 AUC unit	Carboplatin: Reduce by 1 AUC unit

[1] This is defined by the occurrence of either, or both, of

- febrile neutropenia (defined as fever with or without clinically or microbiologically documented infection with an ANC less than 1 x 10^9/L and fever ≥ 38.5 °C [CTCAEv5]) or
- prolonged grade 4 neutropenia (defined as ANC < 0.5 x 10^9/L) persisting ≥ 7 days

There are no planned dose modifications for uncomplicated grade 4 neutropenia lasting less than 7 days.

[2] This is defined by the occurrence of either, or both, of

- grade 4 thrombocytopenia (defined as PLT < 25 x 10^9/L) or
- bleeding associated with grade 3 thrombocytopenia (PLT 25 – 50 x 10^9/L) There are no modifications planned for uncomplicated grade 3 thrombocytopenia.

18.2.2 Non-haematologic Toxicity

Renal toxicity

The combination of Carboplatin and Paclitaxel is not directly expected to cause renal toxicity. Therefore, no specific dose modifications are recommended for renal toxicity. Any concerns should be discussed with the Sponsor.

However, the administered dose of Carboplatin must be recalculated, based on a recalculated or remeasured GFR, for

- renal toxicity (CTC Grade 2, serum creatinine >1.5 x ULN)
- changes in serum creatinine of ≥10%
- each dose modification of Carboplatin
- Cycle 2, if there has been significant doubt about the true GFR at Cycle 1 (e.g. due to significant ascites).

Hepatic toxicity (elevated transaminases)

If hepatic toxicity occurs and the transaminases are < 2.5 x ULN then treatment can be continued as per the protocol without any dose modifications or delays. If the transaminases become elevated to 2.5 – 5 x ULN, then treatment can still be continued at the discretion of the treating investigator. Dose reductions of Paclitaxel can be performed according to local practice. If the transaminases are elevated to > 5 x ULN (grade 3 CTCAE v5.0) then treatment with all drugs should be withheld until resolution≤ to grade 1.

Neuropathy

Grade ≥ 2 sensory or motor neuropathy requires Paclitaxel treatment to be interrupted until neuropathy has resolved to grade 1. On recovery, Paclitaxel should be reduced by 1 dose level. If this requires a delay of more than three weeks then the Paclitaxel should be omitted from subsequent cycles and treatment continued with single-agent Carboplatin at the same AUC used in combination with Paclitaxel. Alternatively to stop of Paclitaxel, a switch to Docetaxel combination is allowed.

Grade ≥ 3 sensory or motor neuropathy requires Paclitaxel to be omitted from subsequent cycles, and treatment continued either with single-agent Carboplatin at the same dose as previously used.

Mucositis

For mucositis grade ≥ 3, chemotherapy should be delayed until the mucositis has resolved to grade ≤ 1. Paclitaxel can be reduced by one dose level in subsequent cycles at the discretion of the treating physician. If the mucositis persists at grade ≥ 3 for more than three weeks, or recurs, then chemotherapy dose modifications should be discussed with the Sponsor.

Hypersensitivity to Paclitaxel

Prior to Paclitaxel administration, hypersensitivity prophylaxis should be implemented according to local institutional guidelines.

A hypersensitivity reaction to Paclitaxel is not a dose-limiting toxicity. The acute management should occur as per local practice.

If a hypersensitivity reaction occurs then patients may be retreated with Paclitaxel at full dose, according to local protocols. This is likely to require increased prophylactic medications and/or a slowing of the initial infusion rate. The infusion rate can be gradually increased in the absence of further hypersensitivity reactions.

Emergency resuscitation equipment and personnel should be available during the period of re-challenge. If the re-challenge occurs within 72 hours of the original intended dose and a negligible quantity, i.e. 50 ml or less, of the original dose was administered, re- administer the full dose. If a substantial proportion has been given then the balance of the full original dose should be administered.

If the re-challenge is being considered more than 72 hours after the original intended dose then a full blood count should be taken to check suitability.

The Paclitaxel can be deceased at the discretion of the treating physician, i.e. the patient can continue on treatment with single agent Carboplatin and remain on study. Alternatively to stop of Paclitaxel, a switch to Docetaxel combination is allowed.

Hypersensitivity to Carboplatin

See section 18.1.3 (Hypersensitivity to Carboplatin (regardless of combination))

Other

A patient in whom enterocolitis is suspected should be urgently addressed for specialized advice in connection with the oncology team who should inform about the enterocolitis risk due to taxanes and specify the details of treatment and administered dose schedule as well as the date of last treatment. A permanent discontinuation of treatment by Paclitaxel is recommended in case of any suspected enterocolitis. The patient should be re-disussed during Multidisciplinary Team meeting and the Sponor needs to be informed.

There are no dose modifications planned for alopecia, nausea, diarrhoea or constipation. These side effects should be treated with supportive medical measures. Non-steroidal anti-inflammatory agents can be used prophylactically or symptomatically, as per local practice.

Any CTC grade 4 non-haematologic AE (except nausea or vomiting) will require the patient to be taken off study. For any grade 3 non-haematologic toxicity (except nausea or vomiting) the drugs should be withheld until symptoms resolve to ≤ grade 1. If the grade 3 event persists for ≥ 3 weeks, or reoccurs, then discussion with the Sponsor.

Expected toxicities of Paclitaxel and Carboplatin

A list of expected AEs (based on the current SPCs) associated with Paclitaxel and Carboplatin is given in the Investigator File. This list should be used to assist the treating physician in the classification of SAEs. The SPC should be referred to for specific guidance.

18.3 Dose modification for Carboplatin/Ganetespib combination

Dose reduction levels for Ganetespib and Carboplatin are given in Table 21.

Table 21: Dose reduction levels for Ganetespib and Carboplatin given in combination

* if Ganetespib dose needs to be reduced below 75 mg/m², then discontinue Ganetespib.

Drug	Protocol Starting Dose	Protocol Dose Level -1	Protocol Dose Level -2	Protocol Dose Level -3	Indication for further dose reductions
Ganetespib	150 mg/m^2	125 mg/m2	100 mg/m2	75 mg/m2	Discontinue study medication
Carboplatin	AUC5	AUC4	AUC3	-	Discontinue study medication

In addition to the specific toxicities presented in the tables in section 18.3.1 if a patient develops any other significant and clinically relevant grade 3 or 4 toxicity thought **to be related specifically** to Ganetespib, Ganetespib will be held until the symptoms resolve to grade ≤ 1 or to the baseline grade. When treatment is resumed, Ganetespib dose is reduced by 1 dose level or discontinued if the patient is already receiving 75 mg/m^2.

If grade ≥ 3 toxicity persists for more than 2 weeks from the last planned study drug administration or recurs after the maximum dose reduction, the patient will discontinue Ganetespib treatment and receive a safety follow-up and will continue to be followed for unresolved adverse events and SAEs. The patient will receive long-term follow-up according to 15.3.

For Ganetespib no dose reduction is necessary due to a body surface area (BSA) above 2.0.

18.3.1 Haematologic Toxicity

Table 22: Dose modifications for the combination therapy of Carboplatin and Ganetespib on day 21 (q3w)

Finding	Modification
Platelet count <100 x 10^9 /L	Carboplatin and Ganetespib must be interrupted until platelet counts are ≥ 100 x 10^9 /L with weekly blood counts for CBC monitored until recovery. **Carboplatin and Ganetespib** shall than be resumed **at the same dose level**, i.e. Carboplatin AUC5 and Ganetespib 150mg/m^2.
2nd (or more) occurrence of platelet count <100 x 10^9 /L *or*	Carboplatin and Ganetespib must be interrupted until platelet counts are ≥ 100 x 10^9 /L with weekly blood counts

prolonged platelet count <100.000/µl until day 35 (2 weeks from the last planned Ganetespib administration)	for CBC monitored until recovery. **Carboplatin** shall than be resumed at a **reduced dose level**, while remaining the Ganetespib dose level. If Carboplatin is already reduced to the lowest dose level than reduce dose level of Ganetespib.
Neutrophils < 1 x 10^9 /L	Carboplatin and Ganetespib must be interrupted until neutrophil counts are ≥ 1 x 10^9 /L with weekly blood counts for CBC monitored until recovery. If prophylaxis with G-CSF is *not* considered feasible, **Ganetespib** shall be resumed at a **reduced dose level**, while remaining the Carboplatin dose level. If prophylaxis can be given, Carboplatin and Ganetespib are resumed at the same dose level.
prolonged neutrophils count < 1 x 10^9 /L until day 35 (2 weeks from the last planned Ganetespib administration) or grade 4 neutropenia	Carboplatin and Ganetespib must be interrupted until neutrophil counts are ≥ 1 x 10^9 /L with weekly blood counts for CBC monitored until recovery. If prophylaxis with G-CSF is *not* considered feasible, **Ganetespib** and **Carboplatin** shall both be resumed at a **reduced dose level**, respectively. If prophylaxis can be given, Carboplatin and Ganetespib are resumed at the same dose level.
2nd occurrence of neutrophils count < 1 x 10^9 /L	Carboplatin and Ganetespib must be interrupted until neutrophil counts are ≥ 1 x 10^9 /L with weekly blood counts for CBC monitored until recovery. **Carboplatin** shall be resumed at **reduced dose level**, while remaining the Ganetespib dose level
3nd occurrence of neutrophils count < 1 x 10^9 /L	Carboplatin and Ganetespib must be interrupted until neutrophil counts are ≥ 1 x 10^9 /L with weekly blood counts for CBC monitored until recovery. **Ganetespib** shall be resumed at a **reduced dose level**, while remaining the Carboplatin dose level.
4th occurrence of neutrophils count < 1 x 10^9 /L	Carboplatin and Ganetespib must be interrupted until neutrophil counts are ≥ 1 x 10^9 /L with weekly blood counts for CBC monitored until recovery. **Carboplatin** shall be resumed at **reduced dose level**, while remaining the Ganetespib dose level
5th occurrence of neutrophils count < 1 x 10^9 /L	Carboplatin and Ganetespib must be interrupted until neutrophil counts are ≥ 1 x 10^9 /L with weekly blood counts for CBC monitored until recovery. **Ganetespib** shall be resumed at a **reduced dose level**, while remaining the Carboplatin dose level.
6th occurrence of neutrophils count < 1 x 10^9 /L	Discontinue Carboplatin and Ganetespib treatment

18.3.2 Non-haematologic Toxicity

Renal toxicity

The combination of Carboplatin and Ganetespib is not directly expected to cause renal toxicity. Therefore, no specific dose modifications are recommended for renal toxicity. Any concerns should be discussed with the Sponsor.

However, the administered dose of Carboplatin must be recalculated, based on a recalculated or remeasured GFR, for:

- renal toxicity (CTC Grade 2, serum creatinine >1.5 x ULN)
- changes in serum creatinine of ≥10%
- each dose modification of Carboplatin
- Cycle 2, if there has been significant doubt about the true GFR at Cycle 1 (e.g. due to significant ascites).

18.4 Dose Modification for Niraparib single agent in maintenance treatment (Arm A and B)

18.4.1 Dose modification of Niraparib for non-haematologic parameters

Dose reduction levels for Niraparib are given in Table 23.

Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient.For patients whose initial dose is 3 capsules daily (300 mg/day), dose reductions to 2 capsules daily (200 mg/day) and subsequently to 1 capsule daily (100 mg/day) will be allowed. No further dose reduction will be allowed.

For patients whose initial dose is 2 capsules (200 mg/day), dose reduction to 1 capsule once daily (100 mg/day) will be allowed. No further dose reduction will be allowed.

Table 23: Dose reduction levels of Niraparib

Recommended Niraparib Dose Modifications for Adverse Reactions

Dose level	**Initial Dose: 3 capsules per day**	**Initial Dose: 2 capsules per day**
Starting dose	3 capsules once daily (300 mg/day)	2 capsules once daily (200 mg/day)
First dose reduction	2 capsules once daily (200 mg/day)	1 capsule once daily (100 mg/day)
Second dose reduction	1 capsule once daily (100 mg/day)	NA

Treatment must be interrupted for any non-haematologic, non-hepatic National Cancer Institute (NCI)-CTCAE (v.5) Grade 3 or 4 AE which the Investigator considers to be related to administration of Niraparib. If toxicity is appropriately resolved to baseline or grade 1 or less within 28 days, the patient may restart treatment with Niraparib, but with a dose level reduction according to Table 23 if prophylaxis is not considered feasible. If the event recurs at similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose

reduction must be made. No more than 2 dose reductions will be permitted during single agent Niraparib maintenance treamtent (arms A and B).

If the toxicity requiring dose interruption has not resolved completely or to NCI-CTCAE Grade 1 during the maximum 4 week (28 day) dose interruption period, and/or the patient has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the patient must permanently discontinue treatment with Niraparib.

Dose interruption, reduction or permanent discontinuation may be implemented at any time depending on laboratory and/or clinical evidence of hepatic toxicity.

Dose modification for Other Non-haematologic Adverse Reactions for Niraparib single agent treatment in maintenance (arms A and B)

Table 24 Niraparib Dose modification for Other Non-haematologic Adverse Reactions

Abnormality	**Intervention**
Non-haematologic CTCAE ≥ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	Withhold Niraparib for a maximum of 28 days or until resolution of adverse reaction. Resume Niraparib at a reduced dose level.
CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered Niraparib 100 mg/day	Discontinue Niraparib.

Hepatic toxicity

Dose modification for liver function abnormalities are given in Table 28.

Table 25: Dose modification for hypertransaminasaemia (AST/ALT)

Finding	**Modification**
Grade 2* AST/ALT	Monitor liver enzymes and direct bilirubin initially within 24 hours and then at least weekly until abnormalities resolve to Grade ≤ 1. No interruption is necessary, unless ALT and/or AST worsens to > 5 × ULN (or > 5 × baseline, if baseline abnormal), or symptoms of liver injury or hypersensitivity develop.
Grade 3* AST/ALT (>5 x ULN, CTCAE v5.0) in the absence of other signs of liver dysfunction	Niraparib must be interrupted (for a maximum of up to 28 days) and monitor liver enzymes and direct bilirubin initially within 24 hours and then every 24 to 72 hours until clear signs of improvement, and then at least weekly until abnormalities resolve to Grade ≤ 1. **1st occurrence: Niraparib** shall be resumed at **reduced dose level** **2nd occurrence: Niraparib shall be permanently discontinued.**

Grade 4 AST/ALT (>20 x ULN, CTCAE v5.0)	Niraparib must be interrupted (for a maximum of up to 28 days) and monitor liver enzymes and direct bilirubin initially within 24 hours and then every 24 to 72 hours until clear signs of improvement, and then at least weekly until abnormalities resolve to Grade ≤ 1. **1st occurrence: Niraparib shall be permanently discontinued**

*In case of ALT or AST > 3 × ULN **AND** bilirubin > 2 × ULN (suspected DILI) Niraparib must be interrupted. The patient should be evaluated for the presence of confounding factors including malignant disease in the liver, coadministration of other suspect drugs, cholestasis, and viral or autoimmune hepatitis that could have caused the laboratory abnormalities. Other laboratory investigations of liver function such as international normalized ratio (INR) should be implemented as indicated. If no alternative cause is identified, Niraparib must be permanently discontinued. Patients should be followed until all abnormalities have returned to normal, returned to baseline levels, or an alternative cause is found to explain the combination of the increased transaminases and total bilirubin."

18.4.2 Dose modifications for haematologic parameters for Niraparib single agent treatment in maintenance (arms A and B)

The dose interruption/modification criteria for haematologic parameters will be based on blood counts and are outlined in Table 26.

Table 26: Dose modification/reduction for Haematologic toxicitities of Niraparib on day 28 (q4w)

Finding	Modification
Platelet count 75 -99.9 x 10^9 /L	Niraparib must be interrupted (for up to a maximum of 28 days) until platelet counts are ≥100.000/µl, with weekly blood counts for CBC monitored until recovery. **Niraparib** may then be resumed **at same dose level or at a reduced dose level** based on clinical judgement.
2nd and 3rd occurrence of platelet count 75 -99.9 x 10^9 /L	Niraparib must be interrupted (for up to a maximum of 28 days) until platelet counts are ≥100.000/µl, with weekly blood counts for CBC monitored until recovery. **Niraparib** may then be resumed at a **reduced dose level.** Discontinue Niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100mg QD.
Platelet count < 75 x 10^9 /L	Niraparib must be interrupted (for up to a maximum of 28 days) until platelet counts are ≥100.000/µl, with weekly blood counts for CBC monitored until recovery.

	Niraparib may then be resumed at a **reduced dose level**. Discontinue Niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Neutrophil < 1 x 10^9 /L	Niraparib must be interrupted (for up to a maximum of 28 days) until neutrophil counts ≥1.500/µl, with weekly blood counts for CBC monitored until recovery. **Niraparib** may then be resumed at a **reduced dose level**. Discontinue Niraparib if the neutrophil count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Hemoglobin <8 g/dL	Niraparib must be interrupted (for a maximum of up to 28 days) until hemoglobin is ≥ 9 g/dL, with weekly blood counts for CBC monitored until recovery. **Niraparib** may be resumed at a **reduced dose level**. Discontinue Niraparib if the hemoglobin has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD. Iron substitution and erythropoiesis-stimulating agents are allowed according to standard of care. Also bloed transfusions are allowed if indicated during the treatment period.
Haematologic adverse reaction requiring transfusion	For patients with platelet count ≤10,000/µL, platelet transfusion should be considered. If there are other risk factors such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count, such as ≤ 20.000/µl. Resume **Niraparib** at a **reduced dose level**. Discontinue Niraparib if the patient has already undergone dose reduction to 100 mg QD.
Confirmed diagnosis of MDS or AML	Permanently discontinue Niraparib.

Abbreviation: CBC = complete cell count

In the case of thrombocytopenia, following the first occurrence, resumption of therapy may occur at the same dose or 1 dose level lower when the haematologic toxicity has resolved. Subsequent occurrences should trigger dose reduction upon resumption of therapy. If the

platelet count has not reverted within 28 days of interruption to ≥ 100 x 10^9 /L, then study treatment should be discontinued.

If dose interruption or modification is required at any point on study because of haematologic toxicity, to ensure safety of the new dose, weekly blood draws for complete blood cell count (CBC) will be required for an additional 4 weeks after the AE has been resolved to the specified levels, after which monitoring every 4 weeks may resume. Weekly blood draws for CBC can be collected either at study site or local laboratories. If the haematologic toxicity has not recovered to the specified levels within 4 weeks (28 days) of the dose interruption period, and/or the patient has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the patient must permanently discontinue treatment with Niraparib.
Any patient requiring transfusion of platelets or red blood cells (1 or more units) or hematopoietic growth factor support must undergo a dose reduction upon recovery if study treatment is resumed.
The patient must be referred to a haematologist for further evaluation (1) if transfusions are required on more than 1 occasion or (2) if the treatment-related haematologic toxicities have not recovered to CTCAE grade 1 or less after 4 weeks. If a diagnosis of MDS/AML is confirmed by a haematologist, the patient must permanently discontinue study treatment.
For major surgery while on treatment, up to 28 days of drug interruption is allowed.
Once the dose of study treatment has been reduced, any re-escalation must be discussed with the Sponsor.
All dose interruptions and reductions (including any missed doses), and the reasons for the reductions/interruptions, are to be recorded in the electronic case report from (eCRF).

18.5 Dose Modification for Niraparib and Ganetespib in maintainance treatment (arm C)

18.5.1 Dose modifications for Niraparib plus Ganetespib combination treatment in maintenance (arm C)

Please consider, Niraparib starting dose is only 200 mg, Ganetespib starting dose is only 100 mg/m^2. Thus, only 1 dose reduction step of each of the two drugs is possible: If toxicity persists then one or both drugs should be discontinued, based on the toxicity observed (see Table 27).

For dose reduction levels please see Table 23 for Niraparib and see Table 21 for Ganetespib.

Dose modifications for **haematologic toxicity** with Niraparib and Ganetespib in maintenance treatment are given in Table 27.

Of note, if Niraparib maintenance treatment is stopped in arm C for any reason, then Ganetespib will be continued as single agent until 9 months of total Ganetespib treatment (including the time of Niraparib and Ganetespib combination treatment).

Table 27: Dose modification for Niraparib and Ganetespib in maintenance treatment on day 28 (q4w)

Finding	Modification
Platelet count 75-99.9 x 10^9 /L	Ganetespib and Niraparib must be interrupted (for up to a maximum of 28 days) until platelet counts are > 100 x 10^9 /L with weekly blood counts for CBC monitored until recovery. Niraparib and Ganetespib shall then be resumed at the same dose level, i.e. **Niraparib 200mg QD and Ganetespib 100mg/m²**. *Exception:* In case of prolonged platelet count <100 x 10^9 /L over >2 weeks, **Niraparib** shall be resumed at **100mg QD**, while retaining **Ganetespib at 100mg/m²**.
2nd or 3rd occurrence of platelet count 75-99.9 x 10^9 /L	Ganetespib and Niraparib must be interrupted (for up to a maximum of 28 days) until platelet counts are > 100 x 10^9 /L with weekly blood counts for CBC monitored until recovery. **Niraparib** shall then be resumed at a **100mg QD**, while retaining **Ganetespib at 100mg/m²**. Discontinue **Niraparib** if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone a dose reduction to 100mg QD. In case of discontinuation of Niraparib, then **Ganetespib** will be continued as single agent until 9 months of Ganetespib treatment
Platelet count <75 x 10^9 /L	Ganetespib and Nirarparib must be interrupted (for a maximum of up to 28 days) until platelet counts are > 100 x 10^9 /L with weekly blood counts for CBC monitored until recovery. **Niraparib** shall then be resumed at a **100mg QD**, while retaining **Ganetespib at 100mg/m²**. Discontinue **Niraparib** if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone a dose reduction to 100mg QD. In case of discontinuation of Niraparib, then **Ganetespib** will be continued as single agent until 9 months of Ganetespib treatment
1th or 2rd occurrence of neutrophils < 1 x 10^9 /L	Ganetespib and Niraparib must be interrupted (for a maximum of up to 28 days) until neutrophil counts are ≥ 1,500 /µL with weekly blood counts for CBC monitored until recovery.

	Niraparib shall then be resumed at **100mg QD** and **Ganetespib at 75mg/m^2.** Discontinue **Niraparib** if the neutrophil count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone a dose reduction to 100mg QD. In case of discontinuation of Niraparib, then **Ganetespib** will be continued as single agent until 9 months of Ganetespib treatment. G-CSF treatment is allowed but cannot be used as prophylaxis ahead of any event.
Hemoglobin < 8g/dL	Ganetespib and Niraparib must be interrupted (for a maximum of up to 28 days) until hemoglobin ≥ 9 g/dL with weekly blood counts for CBC monitored until recovery. Resume **Niraparib at 100mg QD**, while retaining **Ganetespib at 100mg/m^2**. Discontinue Niraparib if hemoglobin has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone a dose reduction to 100mg QD. In case of discontinuation of Niraparib, then **Ganetespib** will be continued as single agent until 9 months of Ganetespib treatment. Iron substitution and erythropoiesis-stimulating agents are allowed according to standard of care. Also bloed transfusions are allowed if indicated during the treatment period.
Haematologic adverse reaction requiring transfusion	For patients with platelet count ≤10,000/µL, platelet transfusion should be considered. If there are other risk factors such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count, such as ≤ 20.000/µl. Resume **Niraparib** at a **reduced dose level**. Discontinue Niraparib if the patient has already undergone dose reduction to 100 mg QD.
Confirmed diagnosis of MDS or AML	Permanently discontinue Niraparib.

Hepatic toxicity

Dose modification for liver function abnormalities are given in Table 28.

Table 28: Dose modification for hypertransaminasaemia (AST/ALT)

Finding	Modification
Grade 2* AST/ALT	Monitor liver enzymes and direct bilirubin initially within 24 hours and then at least weekly until abnormalities resolve to Grade ≤ 1. No interruption is necessary, unless ALT and/or AST worsens to > 5 × ULN (or > 5 × baseline, if baseline abnormal), or symptoms of liver injury or hypersensitivity develop.
Grade 3* AST/ALT (>5 x ULN, CTCAE v5.0) in the absence of other signs of liver dysfunction	Niraparib and Ganetespib must be interrupted (for a maximum of up to 28 days) and monitor liver enzymes and direct bilirubin) initially within 24 hours and then every 24 to 72 hours until clear signs of improvement, and then at least weekly until abnormalities resolve to Grade ≤ 1. **1st occurrence: Niraparib** shall be resumed at **reduced dose level**, while remaining the Ganetespib dose level **2nd occurrence: Niraparib shall be permanently discontinued.** In case of discontinuation of Niraparib, then **Ganetespib** will be continued as single agent until 9 months of Ganetespib treatment
Grade 4 AST/ALT (>20 x ULN, CTCAE v5.0)	Niraparib and Ganetespib must be interrupted (for a maximum of up to 28 days) and monitor liver enzymes and direct bilirubin initially within 24 hours and then every 24 to 72 hours until clear signs of improvement, and then at least weekly until abnormalities resolve to Grade ≤ 1. **1st occurrence: Niraparib and Ganetespib shall be permanently discontinued**

*In case of ALT or AST > 3 × ULN **AND** bilirubin > 2 × ULN and/or direct bilrubin >35% (suspected DILI) Niraparib and Ganetespib must be interrupted. The patient should be evaluated for the presence of confounding factors including malignant disease in the liver, coadministration of other suspect drugs, cholestasis, and viral or autoimmune hepatitis that could have caused the laboratory abnormalities. Other laboratory investigations of liver function such as international normalized ratio (INR) should be implemented as indicated. If no alternative cause is identified, Niraparib and Ganetespib must be permanently discontinued. Patients should be followed until all abnormalities have returned to normal, returned to baseline levels, or an alternative cause is found to explain the combination of the increased transaminases and total bilirubin."

Dose modification for hyperbilirubinaemia are given in Table 29.

Table 29: Dose modification for hyperbilirubinaemia

Finding	Modification
Grade 2* Hyperbilirubinaemie	Niraparib and Ganetespib must be interrupted (for a maximum of up to 28 days) and monitor liver enzymes and direct bilirubin initially within 72 hours and then at least weekly until bilirubin resolves to Grade ≤ 1. No interruption is necessary, unless bilirubin elevation worsens to > 3 × ULN (or > 3 × baseline, if baseline abnormal) and/or ALT to > 3 × ULN (or > 3 × baseline, if baseline abnormal). For a first occurrence, Niraparib and Ganetspib shall be resumed at the same dose level when recovered to ≤ grade 1. For a second occurrence, Niraparib shall be resumed at a reduced dose and Ganetspib shall be resumed at the same dose.
Grade 3* or 4 Hyperbilirubinaemie	Nirarparib and Ganetespib must be interrupted (for a maximum of up to 28 days). Patients who experience a grade ≥ 3 hepatic adverse event should have their liver enzymes and direct bilirubin checked initially within 24 hours and then every 24 to 72 hours until clear signs of improvement, and then twice per week until they are stable or recovered to ≤ grade 1. **Ganetespib** and **Niraparib** shall than be resumed at **reduced dose level for a first occurrence**. Niraparib shall be discontinued permanently for a second occurrence.
Simultaneous occurrence of: • > 3 × ULN ALT or AST and, • > 2 × ULN total bilirubin and, • < 2 × ULN alkaline phosphatase and, • Absence of other reasons than drug toxicity such as e.g. viral hepatitis, pre-existing or acute liver disease, or impaired bilirubin glucuronidation, to explain the laboratory constellation	Withhold both drugs and monitor liver tests initially within 24 hours and then every 24 to 72 hours until clear signs of improvement, and then at least weekly until liver test abnormalities resolve to Grade ≤ 1. Permanently discontinue both drugs.

Simultaneous occurrence of: • > 3 × ULN ALT or AST and, • INR > 2 in the absence of confounding factors, or • Symptoms suggestive of liver injury or hypersensitivity	Withhold both drugs and monitor liver tests initially within 24 hours and then every 24 to 72 hours until clear signs of improvement, and then at least weekly until liver test abnormalities resolve to Grade ≤ 1. Permanently discontinue both drugs.

*In case of ALT or AST > 3 × ULN **AND** bilirubin > 2 × ULN (suspected DILI) Niraparib and Ganetespib must be interrupted. The patient should be evaluated for the presence of confounding factors including malignant disease in the liver, coadministration of other suspect drugs, cholestasis, and viral or autoimmune hepatitis that could have caused the laboratory abnormalities. Other laboratory investigations of liver function such as international normalized ratio (INR) should be implemented as indicated. If no alternative cause is identified, Niraparib and Ganetespib must be permanently discontinued. Patients should be followed until all abnormalities have returned to normal, returned to baseline levels, or an alternative cause is found to explain the combination of the increased transaminases and total bilirubin."

Dose modification for Ganetespib-related gastrointestinal toxicity

Table 30: Dose modification for Ganetespib-related gastrointestinal toxicity

Finding	Modification
Grade 2 Gastrointestinal toxicity	Retreat with Ganetespib at same dose level
Grade 3 Gastrointestinal toxicity	**1st occurrence:** hold dose; retreat with Gantespib at same dose level when recovered to ≤ grade 2 **2nd occurrence:** consider one dose level reduction

Ensure that optimal prophylactic and therapeutic measures are taken (e.g. Loperamide).

Dose modification for Ganetespib-related QTc prolongation

Table 31: Dose modification for Ganetespib related QTc prolongation

Finding	Modification
Grade 2 QTc prolongation	Retreat with Ganetespib at same dose level
Grade 3 (> 500 ms on average of triplicate ECGs) *or* **repeated grade 3** QTc prolongation *or* **grade 4** QTc prolongation	Discontinue Ganetespib treatment

Patients with reported QTc > 500 ms (QTc prolongation Grade 3 severity) or with reported Grade 4 QTc prolongation (QTc > 500 ms or > 60 ms change from baseline and Torsades de Pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia) at any of the specified ECG time points (average of triplicate recordings) must discontinue treatment with Ganetespib.
Close cardiac monitoring should be ensured in case of a grade 3 QTc prolongation occurrence by:

- patient hospitalisation
- cardiac monitoring
- discharge of the patient after specialist review

Drugs which prolong QTc interval and have a known risk to cause Torsade de Pointes (TdP, see APPENDIX F), are to be avoided and drugs which prolong QTc interval and have a possible risk to cause TdP (see APPENDIX G) are to be used with caution in patients receiving Ganetespib.

18.5.2 Management guidelines of the most significant AE diarrhoea

For diarrhoea the postulated mechanism of action is inhibition of EGFR in enterocytes that line the GI tract, leading to transient secretory diarrhoea, limited to 24-48 hours following Ganetespib infusion.
This AE is **readily manageable** by antidiarrheal medication (Loperamide). Prophylactic use of Loperamide can reduce the occurrence of diarrhoea to approximately 40%.

In the EUDARIO prophylactic medication with Loperamide is highly recommended. Loperamide 2 mg should be given prophylactically to patients receiving Ganetespib before the onset of diarrhoea, starting approximately 1-2 hours before Ganetespib administration, to be repeated every 4 hours for the first 12 hours.

In the event of diarrhoea it is highly recommended to apply **therapeutic medication with Loperamide.**

Patients should take Loperamide at an initial 4 mg dose (irrespective of the timing of the last prophylactic dose), followed by 2 mg doses every 4 hours. In the presence of uncomplicated grade 1 or 2 diarrhoea,
Loperamide should be continued until the patient is free from diarrhoea for 12 hours. Total daily dose should not exceed 16 mg (eight capsules).

For grade 3 or 4 diarrhoea or complicated grade 1 or 2 (severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, grade 3 or 4 neutropenia, dehydration), i.v. fluids should be used as appropriate, as well as prophylactic antibiotics.

In addition, due to the potential for dehydration, patients will be advised to maintain appropriate hydration. Blood chemistries, including electrolytes, will be regularly monitored and corrected as appropriate.

18.6 Study drug interruption or discontinuation

The investigator must temporarily interrupt or permanently discontinue the study drug if continued administration of the study drug is believed to be contrary to the best interests of the patient.
The interruption or premature discontinuation of study drug might be triggered by an AE, a diagnostic or therapeutic procedure, an abnormal assessment (e.g., laboratory abnormalities; see chapter 19.6.4), or for administrative reasons, in particular withdrawal of the patient's consent.
The reason for study drug interruption or premature permanent discontinuation must be documented in the CRF.

The patient has to be taken off study drug permanently if interruption (time between two study drug applications) is longer than 4 weeks during maintenance therapy. It is permitted to omit 1 cycle during Ganetespib maintenance therapy in case of patients wish (e.g. because of vacation). An interruption of more than 1 cycle during Ganetespib maintenance must be discussed with the sponsor.

Study drug premature permanent discontinuation

In case of premature permanent discontinuation of study treatment for any reason, the patient should have an EOT/safety follow-up visit with all the assessments performed 28 days (+/- 7 days) after last administration of IMP or, if the decision was reached after this time frame, on day of decision for discontinuation.

18.7 Summary of known and potential risks of the study drug Ganetespib

For the most up-to-date information on the safety profile of Ganetespib, the list of expected AEs and those considered listed for regulatory purposes, please refer to the current version of the Investigator's Brochure. The safety information in the Investigator's Brochure is continually updated as the toxicity profile of Ganetespib is refined.
Ganetespib is **well tolerated** with most reported adverse events (AEs) being mild or moderate and readily manageable. In addition, there has been no observed pattern of specific target organ severe toxicity.

The *most frequently* reported AEs (taking as reference the **largest pooled data set of single agent studies, n = 402 patients**) were related to gastrointestinal (GI) toxicity and included **diarrhoea (80.1 %)**, nausea (44.5 %), decreased appetite (31.6 %), vomiting (27.4 %), constipation (21.9 %), and abdominal pain (20.9 %).
Non-GI-related events that occurred frequently included fatigue (53.5 %), anemia (21.1 %), headache (20.4 %), insomnia (21.1 %), dyspnoea (17.4 %), back pain (15.7 %), blood alkaline phosphatase (AP) increase (15.9 %), aspartate aminotransferase (AST) increase (16.2 %), alanine aminotransferase (ALT) increase (15.4 %), hypokalaemia (13.7 %), and hyponatraemia (13.7 %).

AEs of g*rade 3 or higher* [National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE)], were seen in 275 patients (68 %), and 126 patients (31 %) had an AE deemed *related* to treatment (defined as possibly, probably, or definitely related to treatment). The most common treatment-related ≥ grade 3 AEs were diarrhoea (10 %), fatigue (6 %), increased lipase and hyponatraemia (3 %), and hypophosphatemia, nausea, increased ALT and increased AST (2 % each).

160 patients (40 %) experienced a treatment-emergent AE that was assessed as *serious* (SAE). 33 (8 %) patients had an SAE deemed *related* to treatment. The most common treatment-related SAE was diarrhoea, which occurred in 7 (2 %) patients. All other treatment-related SAEs occurred in <1 % of study patients.

Note new safety information GIP (gastrointestinal perforation):
GIP is a hole that for example develops through the wall of the oesophagus, stomach, small intestine, large bowel, rectum, or gallbladder. According to the Ganetespib Safety Update letter (dated 28-Sep-2015) 11 cases out of 1.509 patients (0.7 %) exposed to Ganetespib were identified with GIP overall. In the GANNET53 trial, which is including patients with platinum-resistant ovarian cancer, GIP has been observed in 2 of 65 patients (1.3 %; cut-off date 15-Jan-2016).
GIP was therefore identified as a new safety finding and as such has been added to the reference safety information of the Investigators Brochure (edition 11, dated 13-Nov-2015).

Medications used with caution

1. **Inhibitors of P-glycoprotein efflux Transporters**

Concomitant medications that are strong inhibitors of P-glycoprotein efflux transporters should be used with caution during the study; examples of these medications include ritonavir, cyclosporine, verapamil, erythromycin, ketoconazole, itraconazole, quinidine, and elacridar.

2. **Medications associated with QTc interval prolongation**

Drugs which prolong QTc interval and have a *known* risk to cause Torsade de Pointes (TdP, see APPENDIX F), are to be avoided in patients receiving Ganetespib.
Medications that have the potential of prolonging the QTc interval but that are not linked to the occurrence of Torsades de Pointes (i.e. drugs with *possible* Torsades de Pointes risk) should also be avoided or used with caution (see APPENDIX G) in patients receiving Ganetespib. The decision whether or not such a medication with possible Torsades de Pointes risk may be used

will be made by the investigator, taking into consideration the patient's medical history and current QTc values.

3. Substrates of CYP3A4 or CYP2C19

Preliminary results of a clinical drug-drug interaction study, examining the effect of Ganetespib on the pharmacokinetics of the CYP2C19-sensitive probe omeprazole, show a modest (20 %) increase in omeprazole exposure when co-administered with Ganetespib. In vitro data implies expectation of greater interaction with CYP2C19 substrates than with CYP3A4 substrates. Caution is advised when sensitive narrow therapeutic range CYP3A4 or CYP2C19 substrates are concomitantly administered.

Examples of compounds frequently used in oncology and metabolised predominantly by CYP3A4 or CYP2C19 are provided in Table 32.

Table 32: List of medications frequently used in oncology treatment that are substrates of CYP3A4 or CYP2C19

Drug Class	Drug	Washout
CYP3A4 substrate examples		
antibiotics (macrolide)	clarithromycin	17 hours
	erythromycin	8 hours
antifungals	ketoconazole	16 hours
	itraconazole	4 days
antiretrovirals	amprenavir	2 days
	indinavir	16 hours
	lopinavir	1 day
	nevirapine	9 days
	ritonavir	1 day
	saquinavir	2 ½ days
	nelfinavir	1 day
Benzodiazepines	midazolam	10 hours
	alprazolam	2 ½ days
	triazolam	15 hours
calcium channel blockers	diltiazem	1 day
	felodipine	3 days
	nifedipine	9 hours
	verapamil	1 day
Gastrointestinal (GI) Agents	aprepitant	1 week
CYP2C19 substrate examples		
anticonvulsants	phenytoin	5 days
antifungals	voriconazole	1 day
antiretrovirals	nelfinavir	1 day

Breast Feeding

Participants must not breast-feed while receiving protocol therapy and for 180 days following the last dose of protocol therapy

Blood Donation

Participants must not donate blood during the study or for 90 days after the last dose of protocol therapy.

18.8 Summary of known and potential risks of the study drug Niraparib

The following adverse reactions (all CTCAE grades) have been reported in ≥ 20 % of patients who received Niraparib: anemia, thrombocytopenia, nausea, constipation, vomiting, fatigue, platelet count decreased, decreased appetite, headache, and insomnia. The median exposure to Niraparib in these patients was 250 days.

The following adverse reactions and laboratory abnormalities have been identified in ≥ 10 to < 20 % of the 367 patients receiving Niraparib: neutropenia, palpitations, asthenia, neutrophil count decreased, dizziness, dysgeusia, dyspnea, cough and hypertension. The following adverse reactions and laboratory abnormalities have been identified in ≥ 1 to < 10 % of the 367 patients receiving Niraparib: tachycardia, dry mouth, mucosal inflammation, white blood cell count decreased, aspartate aminotransferase increased, alanine aminotransferase increased and photosensitivity reaction

Breast Feeding

Participants must not breast-feed while receiving protocol therapy and for 180 days following the last dose of protocol therapy

Blood Donation

Participants must not donate blood during the study or for 90 days after the last dose of protocol therapy.

18.9 Summary of known and potential risks of non IMPs

18.9.1 Paclitaxel, Gemcitabin, Carboplatin

Current information on the safety profile of Paclitaxel, Carboplatin and Gemcitabine is provided in detail in the Summary of Product Characteristics (SmPC). Investigators should refer to the SmPC for warnings and precautions particular to Paclitaxel therapy.

Premedication
Due to the known potential for allergic reaction to Paclitaxel and/or the cremophor vehicle, premedications should be administered in accordance with **local standard of care** in order to prevent severe hypersensitivity reactions.

Of note, drugs which prolong QTc interval and have a *known* risk to cause Torsade de Pointes (TdP, see APPENDIX F) are to be avoided and drugs which prolong QTc interval and have a *possible* risk to cause TdP (see APPENDIX G) are to be used with caution in patients receiving Ganetespib.

Investigators may use their discretion in determining the regimen to be used according to institutional guidelines or practice.

Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available.
Significant hypersensitivity reactions as characterised by dyspnoea and hypotension requiring treatment, angiooedema, and generalised urticaria have occurred in < 1 % of patients receiving Paclitaxel after adequate premedication.
These reactions are probably histamine-mediated.

In the case of severe hypersensitivity reactions, Paclitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be rechallenged with Paclitaxel.

34 % of patients receiving Paclitaxel (17 % of all courses) experienced minor hypersensitivity reactions. These minor reactions, mainly flushing and rash, did not require therapeutic intervention nor did they prevent continuation of Paclitaxel therapy.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Frequent monitoring of blood counts should be instituted during Paclitaxel treatment. Patients should not be treated with Paclitaxel in case neutrophil count is < 1,000 cells/mm^3 and platelet count is < 100,000 cells/mm^3.

Severe conduction abnormalities have been documented in < 1 % of patients during Paclitaxel therapy and in some cases requiring pacemaker placement. If patients develop significant conduction abnormalities during Paclitaxel infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with Paclitaxel.

18.9.2 Study drug delivery & drug storage conditions

The IMP Ganetespib will be provided by Aldeyra Therapeutics (Lexington, MA, USA) at no charge. Niraparib will be provided by TESARO (Waltham, MA, USA).
Paclitaxel, Gemcitabine and Carboplatin are considered an NIMP and will be supplied and covered by the local hospital/health insurer.

The IMP Ganetespib is a concentrate for solution for infusion provided in a single-use vial.

The IMP is supplied as Ganetespib drug product, 25 mg/mL, 300 mg/vial (identified with a dark blue colour cap and applicable product label): Each vial contains 12 mL of deliverable volume (12.84 mL total including an overage per USP requirements) equivalent to 300 mg of Ganetespib at a concentration of 25 mg/mL in a PEG 300, polysorbate 80, and dehydrated alcohol non-aqueous solvent system. The drug product, as noted, is a clear, colourless-to-pale-yellow solution essentially free of visible particles.

The 300 mg/vial drug products are shipped at ambient temperatures. No temperature monitoring devices are utilized during the shipping of this drug product.
Storage of the 300 mg/vial drug product should be at 20-25 °C (68 °F to 77 °F) with excursions allowed between 15 °C and 30 °C (59 °F and 86 °F). Alternatively, Ganetespib drug product may be stored in a cool place between 8 °C (46 °F) and 20 °C (68 °F). DO NOT FREEZE. Infusion solutions must be stored at room temperature and exposure to direct light should be avoided.
Please refer to the Pharmacy Manual for detailed information.

The IMP Niraparib drug product is formulated as a dry blend of Niraparib tosylate monohydrate and lactose monohydrate lubricated with magnesium stearate. The active potency is 100 mg in size 0 purple/white hard gelatin capsule shell.

Niraparib will be administered as a flat-fixed (100 mg, 200 mg or 300 mg), continuous daily dose. Niraparib should be swallowed whole and not opened, crushed or chewed. Food does not significantly affect the absorption of Niraparib; therefore, Niraparib may be taken without regard to meals. Participants should take doses at approximately the same times each day. Bedtime administration may be a potential method for managing nausea.

Vomited doses should not be made up.

If a participant misses a dose (greater than 12 hours from normal dosing time) of Niraparib, they should skip that dose and take their next dose at its regularly scheduled time.

If Niraparib is dose reduced, participants should be instructed to continue using their current supply at their new dose until their supply has been exhausted.

Participants must be instructed to return unused study drugs to the site at discontinuation or completion of treatment. The site personnel must ensure that the appropriate dose of each study drug is administered and that the drug accountability is performed and documented.

Niraparib 100 mg capsules are packaged in a high-density polyethylene (HDPE) white bottle with a two-piece, pulp-backed, heat-induction-foil inner seal, tamper-evident cap. The label text of the study treatment will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries.
All study treatment supplies must be stored in accordance with the Pharmacy Manual instructions and package labeling. Until dispensed to the patients, the study treatment will be stored in a securely locked area, accessible to authorized personnel only.
All investigational study drug supplies in the US must be stored at 20 °C to 25 °C (68 °F to 77 ° F); excursions are permitted between 15 °C to 30 °C (59 °F to 86 °F) (see US Pharmacopoeia [USP] Controlled Room Temperature) and investigation study drug supplies in the European Union (EU) must be stored below 30 °C. Refer to the Pharmacy Manual for further details.

18.9.3 Study drug packaging and labelling

Drug labelling, storage and distribution to the patient-recruiting sites will be done in accordance with all local legal requirements and conducted according to Good Manufacturing Practice.

Participating sites will maintain records of the receipt, storage, and administration or dispensing of the study drugs, identifying (but not necessarily by name) each patient to whom the drug is administered or dispensed, with the patient details redacted so as to preserve the patient's anonymity. Participating sites shall ensure that any shipment of study drugs is inspected upon receipt. Participating sites shall ensure that any notice of defect or non-conformity is sent to the company providing the drugs within ten (10) days from receipt of the drugs. Latent defects which are detected later shall be immediately reported to the company providing the drugs for further processing within the company. Shipment of study drugs may be withheld at any time for failure to promptly respond to requests for production of the study drug records. Upon completion or termination of the study, participating sites shall follow the instructions of the company providing the study drugs regarding the return or disposal of all unused study drugs. Participating sites shall be responsible for compliance with all laws and regulations applicable to any destruction or disposal of study drugs at their participating site, if applicable. Participating sites will inform the company providing the study drug should the participating site determine that a recall of the study drug is required.

Participating sites shall not use the study drugs except as specified in this protocol and shall return any unused study drug following completion of the study, giving account for any discrepancies and signing certificates of delivery and of returns.

18.10 Concomitant medications

Throughout the study, investigators are permitted to use their clinical judgement when prescribing concomitant medications and treatments for trial patients. Local prescribing information and institutional guidelines should be followed as applicable. In all cases, concomitant medications and treatments should only be used with the intention of either maintaining existing medical conditions, or controlling cancer-related symptoms or treatment-related complications. Caution should be exercised when using treatments that could potentially interfere with any of the study medications or the interpretation of the study results. For specific information, please refer to the Ganetespib Investigators' Brochure and the local prescribing information for whichever chemotherapy is being used.

- The use of Erythropoietin or other specific red blood cell growth factors and red blood cell transfusions will be permitted as clinically indicated during the study after documentation of anemia secondary to the study treatment. These agents cannot be used prior to this occurrence.
- The use of bone marrow colony-stimulating factors (such as granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) is permitted as clinically indicated after documentation of neutropenia secondary to the study treatment. These agents cannot be used prior to this occurrence.
- Other concomitant medications may be given as clinically indicated
- A standard 3-5 day course of dexamethasone following the institutional standard of care for the prevention of chemotherapy-induced nausea and vomiting is allowed; steroids (inhaled, topical, or for physiologic replacement, or for short-term treatment of conditions

such as allergic reactions and asthma flares, or for appetite stimulation) and glucocorticoid daily doses (oral) ≤ 1.5 mg dexamethasone (or equivalent) are allowed.
- Also see section “Medications Used with Caution” (section 18.7).

Not allowed are:

- Use of medications associated with a high incidence of QTc prolongation and *known* risk of TdP in subjects receiving Ganetespib should not be administered during the course of this trial and drugs with QTc prolongation and *possible* risk of TdP should also be avoided or used with caution. See Appendix F and Appendix G, respectively.
- Treatment with other systemic anticancer agents (e.g., chemotherapy, hormonal therapy, and immunotherapy) or other treatments not part of protocol-specified anticancer therapy.
- Any oral, injected or implanted hormonal methods of contraception. The use of non-hormonal contraceptives is required for WOCBP, as per the inclusion criteria
- Concurrent investigational agents of any type.
- Use of herbal remedies for cancer treatment.

Chronic daily treatment with corticosteroids (dose >10 mg/day methylprednisolone equivalent), excluding inhaled steroids.
- Tumour necrosis factor-α inhibitors.
- Anti-T cell antibodies.

19 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

Safety assessments will consist of monitoring and recording AEs, including SAEs; measurement of protocol-specified vital signs deemed critical to the safety evaluation of the study.

19.1 Adverse events

It is the responsibility of the investigator(s) to report all adverse events in the eCRF.

An AE is any untoward adverse change from the subject's baseline condition, i.e. any unfavourable and unintended sign including an abnormal laboratory finding, symptom or disease which is considered to be clinically relevant by the physician that occurs during the course of the study, whether or not considered related to the study drug.

Adverse events include:
- Worsening or increase in frequency or intensity of a pre-existing disease or medical condition occurring at any time after the time of randomisation and/or treatment assignment, including baseline or washout periods, even if no study treatment has been administered.
- Abnormal laboratory tests (see section 19.6.4).

Adverse events do not include:
- Pre-planned interventions/hospitalisations (see also section 19.2.1)

- Medical or surgical procedures, e.g. surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Overdose of either study drug or concomitant medication without any signs or symptoms.

19.2 Serious adverse events (SAEs)

A serious adverse event (SAE) is defined by the International Conference on Harmonisation (ICH) guidelines and WHO GCP guidelines as any AE fulfilling at least one of the following criteria:

- Results in death.
- Life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring subject's hospitalisation or prolongation of existing hospitalisation – inpatient hospitalisation refers to any inpatient admission, regardless of length of stay.
- Resulting in persistent or significant disability or incapacity (i.e. a substantial disruption of a person’s ability to conduct normal life functions).
- Congenital anomaly or birth defect.
- Is medically significant or requires intervention to prevent at least one of the outcomes listed above.

Important medical events that may not immediately result in death, be life-threatening, or require hospitalisation may be considered as SAEs when, based upon appropriate medical judgement, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above. Examples of such events are allergic bronchospasm, blood dyscrasias, or convulsions that may require intensive treatment in an emergency room or at home but do not result in hospitalization, development of drug dependency or drug abuse, and transmission of disease associated with the administration of the study drug.

19.2.1 Hospitalisation – Prolongation of existing hospitalisation

Hospitalisation is defined as an overnight stay in a hospital unit and/or emergency room.
An additional overnight stay defines a prolongation of existing hospitalisation.

The following is not considered a SAE and should be reported as an AE only:

- Treatment on an emergency or outpatient basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalisation.

The following reasons for hospitalisation are not considered AEs or SAEs:

- Hospitalisation for cosmetic elective surgery, social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g. hospitalisation for coronary angiography in a subject with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g. hospitalisation for chemotherapy for cancer, elective hip replacement for arthritis.
- Placement of a central venous catheter (e.g. port-a-cath) as a routine intervention

19.2.2 Treatment-Emergent Adverse Event (TEAE)

Any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.

19.2.3 Adverse Events of Special Interest

Selected nonserious AEs and SAEs are also known as Adverse Events of Special Interest (AESI).

Any AE (serious or non-serious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is approproiate.

AESI for Niraparib are the following:

- Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)
- Secondary cancers (new malignancies other than MDS or AML)
- Pneumonitis
- Embryo-fetal toxicity

AESI should be collected and reported as follows:

- MDS and AML along with other secondary cancers should be reported to the Sponsor and TESARO upon awareness for any patient who has received niraparib (regardless of the timeframe since the last dose), throughout the Follow-up Assessment Period
- Pneumonitis should be reported to the Sponsor through 90 days after the last dose of study drug (or until the start of alternate anticancer therapy, whichever occurs first).
- Embryo-fetal toxicity should be reported as outlined in the pregnancy reporting section.

19.2.4 Suspected unexpected serious adverse reactions (SUSARs)

SUSARs are serious adverse reactions with a suspected causal relationship to the study drug that is unexpected (not previously described in the SmPC - Summary of Product Characteristics or Investigator's Brochure) and serious.

Per regulatory requirements, if an event is assessed by the Sponsor Institution as a Serious Unexpected Adverse Reaction (SUSAR), it is the responsibility of the Sponsor Institution to submit the SUSAR to the Regulatory Authorities according to applicable regulations.
In addition, the SUSAR will be distributed to the Investigators/sites, utilizing a Council for International Organizations of Medical Sciences (CIOMS) report form, or the MedWatch 3500A form). The Investigator/site will submit a copy of the report to their respective Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and TESARO per the governing institutional requirements and in compliance with local laws and guidelines.

19.2.5 Pregnancy

Any pregnancy that occurs during study participation must be reported to the KKS Marburg immediately. If a pregnancy is confirmed during the study, the continued use of the study drug must be immediately evaluated. If a pregnancy should be confirmed after informed consent has been obtained, but prior to the initiation of the study drug, the patient must be excluded

from the trial. KKS Marburg has the responsibility to monitor the outcome of all pregnancies reported during the clinical study.

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications (including spontaneous abortions) and elective terminations must be reported as an AE or SAE.

Each pregnancy must be reported by the Investigator to the KKS Marburg on an Initial Pregnancy Report Form within 24 hours of becoming aware of the pregnancy. Pregnancy is not an AE, and therefore does not need to be reported as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. The Investigator must follow-up all pregnancies, document the course and the outcome, and report this information to KKS Marburg on a Pregnancy Outcome Report Form within 24 hours of becoming aware - even if the patient was withdrawn from the study or the study has finished.

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

Any SAE that occurs during pregnancy must be recorded on the Pregnancy Outcome Report Form, reported as an SAE on the SAE Report Form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported to the KKS Marburg within 24 hours. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

All information, either initial or follow-up, received by KKS Marburg will be forwarded to the Sponsor and TESARO/Aldeyra Therapeutics.

19.3 Severity of adverse events/Grading

Intensity of all adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version v5.0 on a five-point scale (grade 1 to 5) and reported in detail on the eCRF.

Please note that there is a distinction between **serious** and **severe** AEs: Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 18.2. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe.

Adverse events not listed in the CTCAE v5.0 should be graded as follows:

Table 33 Grading AEs not listed in the CTCAE v5.0

CTC grade	Equivalent to	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall wellbeing or symptoms of the patient.
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall wellbeing or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.
Grade 4	Life threatening/ disabling	An immediate threat to life or leading to a permanent mental or physical condition that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death

19.4 Relationship to study drug

Medical judgment should be used to determine the cause of the AE, considering all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication.

Is there a reasonable possibility that the study drug caused the event?
Answer **YES** (possibly, probably or definitely related) if one or more of the following criteria apply:

- The event follows a reasonable temporal sequence from administration of study drug.
- The event could not be reasonably attributed to the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient.
- The event follows a known pattern of response to study drug.
  The event disappears or decreases on cessation or reduction in dose of the study drug. (It should be noted that in some situations an AE will not disappear or decrease in intensity upon discontinuation of study drug despite other clear indications of relatedness).

Otherwise answer **NO** (unlikely, probably not related or definitely not related).

19.5 Expectedness

The Sponsor will be responsible for determining whether an adverse event is 'expected' or 'unexpected'. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information provided in the Reference Safety Information of the effective Niraparib and Ganetespib Investigator Brochures (IB).

19.6 Collection and recording of adverse events

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

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

All SAEs will be collected from the signing of the ICF for this study through the Safety Follow-up Visit described in Section 14.3 and reported accordingly. SAEs considered by the Investigator to be related to study medication are reported throughout the Follow-up Assessment Period.

All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, or reported by patient), will be documented for each patient from the time of randomisation and/or treatment assignment through the Safety Follow-up Visit described in Section 14.3.

Concomitant illnesses that existed before entry into the study will not be considered AEs unless the illness worsens during the Treatment Period. Pre-existing conditions will be recorded as Medical History on any future SAE Report Forms.

Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal). Disease progression should be documented. If AEs/SAEs occur in relation to disease progression that are not consistent with the natural progression of the patient's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements.

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event eCRF. Avoid lay terminology and abbreviations.
Only one AE term should be recorded in the event field on the Adverse Event eCRF. See section 19.1 for the definition of an AE.

19.6.1 Follow-Up of Adverse Events

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

If an Investigator becomes aware of an SAE after the specified follow up period and considers the SAE related to the study drug, the Investigator should report the SAE to the Sponsor according to timelines for reporting SAEs.

19.6.2 Diagnosis versus signs and symptoms

Infusion-associated reactions
Adverse events that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction.

Other adverse events
For AEs other than infusion-associated reactions, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g. record only liver failure or hepatitis rather than jaundice and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterised as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

19.6.3 Persistent or recurrent adverse events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (mild, moderate, severe, life-threatening/disabling) of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.
A recurrent AE is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

19.6.4 Abnormal laboratory values or vital signs

Not every laboratory abnormality qualifies as an AE. A laboratory test result/vital sign should be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g. dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention (e.g. potassium supplementation for hypokalaemia) or a change in concomitant therapy.
- Clinically significant in the investigator's judgment.

It is the investigator's responsibility to review all laboratory findings/vital signs. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality or vital sign should be classified as an AE.
If a clinically significant laboratory abnormality or vital sign is a sign of a disease or syndrome (e.g. alkaline phosphatase and bilirubin 5 times the ULN associated with cholecystitis), only the diagnosis (i.e. cholecystitis) should be recorded on the Adverse Event eCRF. The supporting laboratory abnormalities should be included in the event description if the event qualifies as a SAE.

19.6.5 Progression of underlying malignancy

Progression of underlying malignancy and clinical symptoms of progression (e.g. ileus, sub-ileus, vomiting) are not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST 1.1 criteria or GCIG criteria for CA-125. Clinical symptoms of disease progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under trial. Hospitalisation due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event.
If there is any uncertainty about an adverse event being due only to the disease under the clinical trial it should be reported as an AE or SAE.

19.7 Reporting procedures

A special section is designated to adverse events in the case report form where the following details must be entered:

- Type of adverse event (diagnosis or syndrome; if not known signs or symptoms)
- Start (date)
- End (date)
- Severity (mild, moderate, severe, life-threatening/disabling, death)
- Serious (no / yes)
- Unexpected (no / yes)
- Outcome (recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, unkown, fatal)
- Action taken (none, study medication dose reduced, study medication interrupted, study medication discontinued, medication therapy, surgical procedure, hospitalisation, other)
- Relation to study drug (possibly, probably or definitely related or unlikely, probably not related or definitely not related)

Certain events require immediate reporting to allow the sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events.
- Pregnancies.

- Adverse Events of Special Interest (AESIs, see Section 18.2.3).

The investigator must report new significant follow-up information for these events to the sponsor immediately (i.e. no more than 24 hours after becoming aware of the information). New significant information includes, but is not limited to, the following:

- New signs or symptoms or a change in the diagnosis.
- Significant new diagnostic test results.
- Change in causality based on new information.
- Change in the event's outcome, including recovery.
- Additional narrative information on the clinical course of the event.

Investigators must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

19.7.1 Reporting procedures for SAEs and SUSARs

In the event of a serious adverse event, the investigator has to use all supportive measures for best patient treatment. All SAEs and AESIs must be reported to the KKS Marburg within 24 hours of becoming aware of the initial SAE/AESI or any follow-up information regarding the SAE/AESI. The SAE form must be completed by the investigator and reported no more than 24 hours after awareness of the event.

The following details should be available with the initial report:

- Patient number
- Patient: age, height, weight
- Name of investigator and investigating site
- Period of administration
- The suspected investigational medicinal product (IMP)
- The adverse event assessed as serious
- Concomitant disease and medication
- Relevant medical history
- Short description of the event and outcome
    - Description
    - Onset and if applicable, end
    - Therapeutic intervention
    - Causal relationship to each of the study drugs
    - Hospitalisation or prolongation of hospitalisation
    - Death, life-threatening, persistent or significant disability or incapacity

If applicable, the initial report should be followed by the follow-up report, indicating the outcome of the SAE.

For SAEs, SUSARs and pregnancies, KKS Marburg or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g. from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case. A follow-up SAE form must also be completed and reported appropriately.

SUSARs will be reported to the required regulatory authorities, investigators and ethical committees in compliance with all reporting requirements according to local regulations and good clinical practice by the sponsor and/or its designees. Additionally, CIOMS reports will be immediately forwarded to Aldeyra and TESARO, the IDMC, the sponsor and the coordinating investigator.

On a quarterly basis, KKS Marburg will create line listings of all serious adverse events, which will be distributed to the Sponsor, IDMC, coordinating investigator, TESARO, Aldeyra Therapeutics. On at least an annual basis, KKS Marburg will prepare the Development Safety Update Report (DSUR) which will be distributed to the Sponsor, TESARO and Aldeyra, the IDMC and the coordinating investigator. The Sponsor will forward this document to the NTGs for submission to the local Ethic committees.

For detailed reporting procedures please refer to the SAE reporting manual.

19.7.2 Reporting to TESARO and Aldeyra Therapeutics

The Investigator must report all SAEs, and all follow up information to KKS Marburg on an SAE Report Form within 24 hours of becoming aware of the initial event or follow-up information. KKS Marburg will relay this SAE information to TESARO and Aldeyra Therapeutics within one business day and no more than three calendar days after receiving the SAE Report Form.

The Investigator must provide a causality assessment and must sign and date all SAE Report Forms.

It is the responsibility of the Investigator to review source documentation and describe pertinent information on the SAE Report Form. If supporting documentation is requested (e.g., hospital reports, consultant reports, death certificates, autopsy reports, etc.), the Investigator should highlight all relevant and pertinent information within such documents, ensure that any patient's personal identifiers (including Medical Record number) are removed, and submit the documents with the SAE Form to KKS Marburg, which will forward all documents to TESARO and Aldeyra Therapeutics

After receipt of the initial report, KKS Marburg will review the information and, if necessary, contact the Investigator to obtain further information. The Investigator must respond within 24 hours in urgent cases and within 72 hours in all other cases to queries from KKS Marburg. All additional information retrieved will be forwarded by KKS Marburg to TESARO and Aldeyra Therapeutics.

KKS Marburg SAE, Pregnancy and AESI Reporting Information
KKS Marburg Fax-No.: +49 6421 28 66 559

The information forwarded by KKS Marburg to TESARO and Aldeyra Therapeutics will be acknowledged according to their standard practice:

The practice of TESARO and Aldeyra Therapeutics is to acknowledge receipt of all safety information with 72 hours. KKS Marburg should resend any materials that are not acknowledged within this time period.

19.7.3 Adverse event reporting period

Investigators will seek information on AEs at each patient contact throughout the trial. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of the study drug**, only SAEs considered to be related to a protocol-mandated intervention should be reported (e.g. SAEs related to invasive procedures such as biopsies).

After initiation of study drug, all AEs and SAEs regardless of relationship to the study drug, will be reported until safety follow-up at 28 days after the last dose of IMP or EOT or until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent.
After the safety follow-up, investigators should report any deaths, SAEs, or other AEs of concern that are believed to be related to prior treatment with the study drug.

Any Serious Adverse Event (SAE) that is ongoing at the time of safety follow-up should be followed-up until resolved. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

19.8 Handling of safety parameters

19.8.1 Treatment and follow-up of adverse events

Adverse events, especially those for which a relationship to study drug is suspected, should be followed up until they have stabilised or returned to baseline status. If a clear explanation is established it should be recorded on the eCRF.

19.8.2 Follow-up of abnormal laboratory test value

In the event of unexplained and clinically significant laboratory test values, the tests should be repeated immediately if possible and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

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

- **Abuse:** is the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.
- **Misuse:** medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.

- **Medication error:** is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.
- **Overdose:** is a deliberate or accidental administration of study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol and under the direction of the Investigator. If an overdose occurs, the Investigator and the Sponsor should be notified immediately, and the patient should be observed closely for AEs. Associated AEs should be treated and monitored by the Investigator. The dosage of study drug administered, any associated AEs, and/or treatment provided to the patient because of the overdose, should be documented on the applicable sections within the eCRF. An overdose (including an AE or SAE resulting from the overdose, if any) will be reported as an SAE.
- **Accidental /Occupational exposure:** is the unintentional exposure to a study treatment as a result of one's professional or non-professional occupation, or accidental exposure to a non-professional to whom exposure was not intended (i.e., study product given to wrong patient).

Reporting Special Situations: All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure with any study treatment must be reported on an SAE Report Form [or designated Special Form] to the Sponsor regardless of whether or not an AE or SAE has occurred. If the abuse, misuse, medication error, overdose, or accidental / occupational exposure is associated with an SAE, an SAE report form must be submitted to the Sponsor within 24 hours of awareness. If there is no AE or SAE, the occurrence must be submitted on the designated Special Form (indicate 'no AE has occurred') as soon as possible.

19.10 Reporting Product Complaints for Niraparib

Any written, electronic or oral communication that alleges dissatisfaction related to manufactured clinical drug product with regards to its manufacturing, testing, labeling, packaging, or shipping, must be reported by the sponsor-investigator or qualified designee to TESARO Call Center: (EU Call Center: Tesaro@EU.ProPharmaGroup.com) within 1 working day of first becoming aware of the possible defect. This report to TESARO may also be made by telephone to the designated TESARO representative (1-844-4TESARO) or by fax to the Call Center (EU Call Center: +44 (0) 1748 828801). The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

20 DOCUMENTATION AND DATA MANAGEMENT

20.1 Retention of documents/Investigator site file

The sponsor must keep all essential documents of the clinical study after completion or discontinuation of the study for a minimum of 15 years. The sponsor must archive all study-relevant documents in accordance with the legal regulation.

The clinical trial centre is provided with an Investigator Site File (ISF). This contains all documents which are required for the clinical study. It is the responsibility of the investigator to file all documents in the ISF. During monitoring visits the ISF will be reviewed to verify accuracy and completeness in accordance with the regulations. After completion or discontinuation of the study this ISF has to be stored in a safe place for 15 years.

The investigators must keep all records and documents, which are related to the study or the allocation of investigational medicinal products (e.g. data entry form, consent form, list of the allocations of investigational medicinal products and further relevant documents), for a minimum of 15 years.
Medical records and other original data have to be kept for the longest possible duration, which the hospital, the institution or the private practice permits.

20.1.1 Case report form (CRF)

For each patient enrolled, an eCRF must be completed and electronically signed by the principal investigator or authorised delegate from the study staff. This also applies to records for those patients who fail to complete the study (even during a pre-enrolment screening period if an eCRF was initiated). If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.
The investigator should ensure the accuracy, completeness and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

20.2 Independent Data and Monitoring committee (IDMC)

The IDMC will be responsible for independently evaluating the safety of the patients participating in the trial. All captured adverse events and safety reports will be reported to the IDMC for assessment. All SAEs will be forwarded to the IDMC immediately after knowledge of it. The IDMC can, if required, suggest to amend the protocol and in case the risk to the patients outweighs the potential benefit, suggest to end the study prematurely.
The IDMC will meet (e.g. via teleconference) on a regular basis over the course of the study and may also meet on an unscheduled basis if any unexpected safety concerns arise. Pre-defined timepoints of safety evaluation by IDMC are after 6 and 12 patients, respectively, have received one cycle of Ganetespib plus Carboplatin treatment (in arms B and C; without recruitment stop), after 6 and 12 patients, respectively, have received one cycle of Ganetespib plus Nirarparib treatment (maintenance treatment in arm C; with stop of entering maintenance treatment for new patients in arm C until positive safety evaluation by IDMC).
To allow for close follow-up of the trial by the IDMC they will also be provided on a continuous basis with the CIOMS reports for all SUSARs, the SAE line listings on a quarterly basis and the DSUR on a yearly basis.

20.3 Quality control and quality assurance

Monitorings and audits are performed for the quality assurance within the clinical study and the A-AGO trial centre and the project management team will continuously monitor the recruitment process.

20.3.1 Periodic monitoring

It is understood that the responsible sponsor-assigned monitor (or designee) will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial (eCRFs, source notes, and other pertinent data), provided that patient confidentiality is maintained in accord with local requirements.
Monitoring and auditing procedures developed or endorsed by the sponsor will be adhered to, in order to comply with ICH-GCP guidelines and local legal requirements to ensure acceptability of the study data.

It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them, evaluation of the SAEs reports according to the regulations, evaluation of compliance. The monitor should have access to laboratory test reports and other patient records needed to verify the entries in the eCRF. The investigator (or his/her deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

20.3.2 Audit and inspections

Upon request, the investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the sponsor or to competent authority inspectors. The main purposes of an audit or inspection are to confirm that the rights and wellbeing of the subjects have been adequately protected, and that all data relevant for assessment of safety and efficacy of the investigational product have appropriately been reported to the sponsor.

At mutually agreeable times, investigator will give an independent auditor (at TESARO‘s and/or Aldeyra‘s sole expense) access to all records and documentation (however stored) relating to the study or to the care of study subjects in order to determine whether the evaluated study related activities were conducted, and the data were recorded, analyzed and accurately reported according to this protocol, Good Clinical Practices (GCP), and the applicable regulatory requirement (s).

20.4 Reporting and publications

20.4.1 Reports

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs within 24 hours after knowledge of which to the sponsor. Investigators may receive written safety reports or other safety-related communications from the sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

20.4.2 Publication of study results

The data from the whole trial will be reported together. Positive and inconclusive as well as negative results will be published or otherwise made publicly available.
The results of this trial may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor and the coordinating investigator (KULeuven/BGOG, Nicole Concin) prior to submission.
The rights of the investigator and of the KULeuven/BGOG with regard to publication and dissemination of the results of this trial are described in the Consortium Agreement.

Any publication shall be subject to prior review by Aldeyra and TESARO. A copy of any proposed disclosure, including any publication, abstract, oral presentation, or poster that reports all or parts (interim or final) of the results of the study or study progress, is given to TESARO and Aldeyra for review at least thirty (30) days prior to the date of submission for publication (including abstracts) or of public disclosure; if required by TESARO or Aldeyra, any reference to TESARO‘s and/or Aldeyra‘s confidential information is deleted; and if an Invention (as defined hereunder) is contained in the disclosure, investigator shall defer publication or disclosure for up to an additional sixty (60) days from the time TESARO and/or Aldeyra notifies investigator that TESARO and/or Aldeyra desires patent application(s) to be filed on the Invention.

21 ETHICAL AND LEGAL ASPECTS

21.1 Informed consent of subjects

Following comprehensive instruction regarding the nature, significance, impact and risks of this clinical trial, the patient must give written consent to participation in the study.
During the instruction the trial participants are to be made aware of the fact that they can withdraw their consent – without giving any reasons – at any time without their further medical care being influenced in any way.
In addition to the comprehensive instructions given to the trial participants by the investigator, the trial participants also receive a written patient information sheet in comprehensible language, explaining the nature and purpose of the study and its progress.
The patients must agree to the possibility of study-related data being passed on to relevant authorities.
The patients must be informed in detail of their obligations in relation to the trial participants insurance in order not to jeopardise insurance cover. The informed consent form has to be signed and dated by the patient and the investigator and stored in the Investigator Site File. One copy of the informed consent form has to be handed over to the patient.
No study specific procedures are allowed to be carried out prior to signing of the informed consent form.

21.2 Acknowledgement/Approval of the study

The study groups will submit this protocol and any related document provided to the subject (such as subject information used to obtain informed consent) to the responsible Independent Competent Authority (ICA) and Independent Ethics Committee (IEC) or Institutional Review Board (IRB) in their respective country according to legal requirements. Approval from the committee must be obtained before starting the study.
The clinical trial shall be performed in full compliance with the legal regulations according to applicable local laws and regulatory requirements.

Changes in the conduct of the study
Protocol amendments

Proposed amendments must be submitted to the appropriate competent authorities (CAs) and ECs. Substantial amendments may be implemented only after CA/EC approval has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving CA/EC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Study termination

If the sponsor, investigator, or a supporter decides to terminate the study before it is completed, they will notify each other in writing stating the reasons of early termination. In terminating the study, the sponsor and the investigator will ensure the adequate consideration is given to the protection of the subject interests. The investigator/trial group or sponsor will notify the relevant CA and EC. Documentation will be filed in the Trial Master and Investigator Site Files.

Clinical study report (CSR)

Within one year after the final completion of the study, a full CSR will be prepared by the sponsor and submitted to the EC and the competent authority.
The investigator will be asked to review and sign the final study report.

21.3 Insurance

In accordance with the Belgian Law relating to experiments on human persons dated May 7th, 2004, sponsor shall be liable, even without fault, for any damages incurred by a trial participant and linked directly or indirectly to the participation to the trial, and shall provide compensation therefore through its insurance.

The terms or the amount of cover of any insurance shall not relieve the sponsor of any liabilities under the clinical trial agreement.

If an insurance coverage is required by local laws of participating site outside Belgium, the participating site shall have and maintain in full force and effect during the term of the trial (and following termination of the trial to cover any claims arising from the trial) adequate insurance coverage for possible damages linked directly or indirectly to the patients' participation to the trial at participating site.

21.4 Study Data

Any inventions, methods, developments, and discoveries, whether patentable or not, relating to or arising from the study or made in the performance of work under the study ("Inventions") shall vest in the sponsor. The participating site, its employees and investigator(s) shall promptly disclose to sponsor any such Inventions.

Any and all study data as collected and prepared in the context of the study shall be the property of the sponsor. The sponsor hereby grants to the participating site a right to use the study data for educational purposes and patient care and in accordance with the obtained ICF.

Participating site expressly agrees that notwithstanding anything herein to the contrary, any inventions, discoveries or innovations, whether patentable or not, shall be the property of sponsor in case the inventions, discoveries or innovations, whether patentable or not, are related to the study. Raw data such as medical records of study subjects shall be and remain the sole property of the participating site.

21.5 Collection of investigator's personal data

Both prior to and during the conduct of the study, the investigator and study personnel of each participating site may provide Tesaro and/or Aldeyra and/or their respective designees with their personal data (as that term is defined under applicable law) (the "**Personal Data**"). The processing (including use, disclosure and/or transfer) of his/her Personal Data by Tesaro, Tesaro's designee(s), Aldeyra, Aldeyra's designee(s) and each of their respective agents and affiliates as well as all governmental and regulatory agencies (of any jurisdiction) shall be done for the following purposes (the "**Purposes**"): (a) TESARO and ALDEYRA's respective exercise of rights and performance of obligations under the Investigator-Initiated Research Agreement between UZ Leuven and TESARO and ALDEYRA; (b) review by governmental or regulatory agencies; and (c) satisfying legal or regulatory requirements. The Personal Data may also be transferred abroad for the Purposes, even if such Personal Data is transferred to countries that do not ensure an equivalent level of protection as in the country where the study is taking place, including to the United States of America (U.S.A.). The processing of the Personal Data shall be lawful under article 6, subparagraph (b), (c) and (f) of the Regulation (EU) 2016/679 (General Data Protection Regulation (GDPR)).

21.6 Ethics and Good Clinical Practice (GCP)

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended at the 64th WMA General Assembly, Fortaleza, Brasil, 2013) and with the laws and regulations of the country in which the clinical research is conducted.
The investigator of the clinical trial shall guarantee that only appropriately trained personnel will be involved in the study. All studies must follow the ICH-GCP Guidelines (November 2016).

22 REFERENCES

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23 APPENDICES

Appendix A – ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	ECOG
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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. (21)

Also see: http://www.ecog.org/general/perf_stat.html (last accessed: 05.09.2013)

Appendix B – CTCAE (version 5.0)

The NCI Common Terminology Criteria for Adverse Events version 5.0, instituted 27Nov2017, is available at:
https://www.eortc.be/services/doc/ctc/CTCAE_v5_Quick_Reference_5x7.pdf

Appendix C – Patient-reported outcome questionnaire, additional items

These are the questionnaires in German. Questionnaires will be provided for each national language.

GERMAN

EORTC QLQ-C30 (version 3.0)

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

Bitte tragen Sie Ihre Initialen ein: _____
Ihr Geburtstag (Tag, Monat, Jahr): _____
Das heutige Datum (Tag, Monat, Jahr): 31 _____

	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

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

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

Appendix D – Tumour assessment (RECIST) 1.1 (Eisenhauer et al. 2009 (22)**)**

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

Measurable tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum of:

1. 10 mm by CT scan (CT scan slice thickness no >5 mm).
2. 10 mm calliper measurement by clinical exam (lesions which cannot accurately be measured with callipers should be recorded as non-measurable).
3. 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no >5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable lesions: All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with P10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam and is not measurable by reproducible imaging techniques.

Method of Assessment
The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumour markers are disease-specific, instructions for their measurement should be incorporated into protocols on a disease-specific basis.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or SD in order to differentiate between response (or SD) and PD.

Tumour response evaluation

Assessment of overall tumour burden and measurable disease: To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint.
Measurable disease is defined by the presence of at least one measurable lesion (as detailed above). In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline documentation of 'target' and 'non-target' lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm·to 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.
A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.
All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline.
Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Response criteria
Evaluation of target lesions:

- Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable disease (SD): Neither sufficient reduction to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of best overall response
The best overall response is the best response recorded from randomisation into the trial until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if

post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation.

The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-~D	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Reference

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47. (20)

Appendix F – List of drugs with known Torsades de Pointes risk

This list was obtained from the Arizona Center for Education and Research on Therapeutics (AZCERT) website, accessed 16 December 2017.
https://www.crediblemeds.org

Substantial evidence supports the conclusion that these drugs, when used as directed in labelling, can prolong the QT interval and can have a risk of Torsades de pointes (TdP) in some patients.

Therefore Drugs that prolong QTc interval and have a known risk to cause TdP should not be administered during the course of the trial.

Generic Name	Brand Names	Drug Class	Therapeutic Use	Route
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Anti-arrhythmic	Abnormal heart rhythm	oral, injection
Anagrelide	Agrylin®, Xagrid®	Phosphodiesterase 3 inhibitor	Thrombocythemia	oral
Arsenic trioxide	Trisenox®	Anti-cancer	Leukemia	injection
Astemizole *	Hismanal®	Antihistamine	Allergic rhinitis	oral
Azithromycin	Zithromax®, Zmax®	Antibiotic	Bacterial infection	oral, injection
Bepridil *	Vascor®	Anti-anginal	Angina Pectoris (heart pain)	oral
Chloroquine	Aralen®	Anti-malarial	Malaria infection	oral
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Anti-psychotic / Anti-emetic	Schizophrenia/ nausea, many others	oral, injection, suppository
Cilostazol	Pletal®	Phospodiesterase 3 inhibitor	Intermittent claudication	oral
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	Antibiotic	Bacterial infection	oral, injection
Cisapride *	Propulsid®	GI stimulant	Heartburn	oral
Citalopram	Celexa®, Cipramil®	Anti-depressant, SSRI	Depression	oral
Clarithromycin	Biaxin®, Prevpac®	Antibiotic	Bacterial infection	oral
Cocaine	Cocaine	Local anesthetic	Topical anesthetic	oral, nasal
Disopyramide	Norpace®	Anti-arrhythmic	Abnormal heart rhythm	oral, injection
Dofetilide	Tikosyn®	Anti-arrhythmic	Abnormal heart rhythm	oral
Domperidone	Motilium®, Motillium®, Motinorm Costi®, Nomit®	Anti-nausea	Nausea, vomiting	oral, injection, suppository

Donepezil	Aricept®	Cholinesterase inhibitor	Dementia (Alzheimer's disease)	oral
Dronedarone	Multaq®	Anti-arrhythmic	Atrial Fibrillation	oral
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Anti-psychotic / Anti-emetic	Anesthesia adjunct, nausea	injection
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®	Antibiotic	Bacterial infection; increase GI motility	oral, injection
Escitalopram	Cipralex®, Lexapro®, Nexito®, Seroplex®, Elicea®, Lexamil®, Lexam®	Anti-depressant, SSRI	Major depression/ Anxiety disorders	oral
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Anti-arrhythmic	Abnormal heart rhythm	oral
Fluconazole	Diflucan®, Trican®	Antifungal	Fungal infection	oral, injection
Gatifloxacin *	Tequin®	Antibiotic	Bacterial infection	oral, injection
Grepafloxacin	Raxar®	Antibiotic	Bacterial infection	oral
Halofantrine	Halfan®	Anti-malarial	Malaria infection	oral
Haloperidol	Haldol®, Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol®, Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®	Anti-psychotic	Schizophrenia, agitation	oral, injection
Ibogaine	None	Psychedelic	Narcotic addiction, unproven	oral
Ibutilide	Corvert®	Anti-arrhythmic	Abnormal heart rhythm	injection
Levofloxacin	Levaquin®, Tavanic®	Antibiotic	Bacterial Infection	oral, injection
Levomepromazine	Nosnan®, Nozinan®, Levoprome®	Antipsychotic	Schizophrenia	oral, injection

Levomethadyl	Orlaam®	Opiate	Pain control, narcotic dependence	oral
Levosulpride	Lesuride®, Levazeo®, Enliva® (with rabeprazole)	Antipsychotic	Schizophrenia	Oral, injection
Mesoridazine*	Serentil®	Anti-psychotic	Schizophrenia	oral
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®	Opiate	Pain control, narcotic dependence	oral, injection
Moxifloxacin	Avelox®, Avalox®, Avelon®	Antibiotic	Bacterial infection	oral, injection
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®	Anti-emetic	Nausea, vomiting	oral, injection, suppository
Oxaliplatin	Eloxatin®	Antineoplastic Agent	Cancer	injection
Papaverine HCl	none	Vasodilator, Coronary	Diagnostic adjunct	injection
Pentamidine	Pentam®	Antibiotic	Pneumocystis pneumonia	Injection, inhaled
Pimozide	Orap®	Anti-psychotic	Tourette's tics	oral
Probucol *	Lorelco®	Antilipemic	Hypercholesterolemia	oral
Procainamide	Pronestyl®, Procan®	Anti-arrhythmic	Abnormal heart rhythm	injection
Propofol	Diprivan®, Propoven®	Anesthetic, general	Anesthesia	injection
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Anti-arrhythmic	Abnormal heart rhythm	oral, injection
Roxithromycin	Rulide®, Xthrocin®, Roxl-150®, Roxo®, Surlid®, Rulide®, Biaxsig®, Roxar®, Roximycinv®, Roxomycin®, Rulid®, Tirabicin®, Coroxin®	Antibiotic	Bacterial infection	oral
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general	Anesthesia	inhaled
Sotalol	Betapace®, Sotalex®, Sotacor®	Anti-arrhythmic	Abnormal heart rhythm	oral
Sparfloxacin *	Zagam®	Antibiotic	Bacterial infection	oral
Sulpiride	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®	Anti-psychotic, atypical	Schizophrenia	Oral, inhaled

Sultopride	Barnetil®, Barnotil®, Topral®	Antipsychotic, atypical	Schizophrenia	oral, injection
Terfenadine *	Seldane®	Antihistamine	Allergic rhinitis	oral
Terlipressin	Teripress®, Glypressin®, Terlipin®, Remestyp®, Tresil®, Teriss® and others	Vasoconstrictor	Septic shock	injection
Terodiline	Micturin®, Mictrol® (non bethanechol)	Muscle relaxant	Bladder spasm	oral
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Anti-psychotic	Schizophrenia	oral
Vandetanib	Caprelsa®	Anti-cancer	Thyroid cancer	oral

***** removed from market

Appendix G – List of drugs with possible Torsades de Pointes risk

This list was obtained from the Arizona Center for Education and Research on Therapeutics (AZCERT) website, accessed 16 December 2017.
https://www.crediblemeds.org

Substantial evidence supports the conclusion that these drugs, when used as directed in labelling, can prolong the QT interval and can possibly have a risk of Torsades de pointes (TdP) in some patients.

Therefore Drugs that prolong QTc interval and have a possible risk to cause TdP should be used with caution.

Generic Name	Brand Names	Drug Class	Therapeutic Use	Route
Alfuzosin	Uroxatral®	Alpha1-blocker	Benign prostatic hyperplasia	oral
Apomorphine	Apokyn®, Ixense®, Spontane®, Uprima®	Dopamine agonist	Parkinson's disease	oral, injection
Aripiprazole	Abilify®, Aripiprex®	Anti-psychotic, atypical	Schizophrenia, Adjunct for Depression	oral, injection
Artenimol + piperaquine	Eurartesim®	Animalarial	Malaria	oral
Asenapine	Saphris®, Syscrest®	Antipsychotics, atypical	Schizophrenia	sublingual
Atazanavir	Reyataz®	Anti-viral	HIV/AIDS	oral
Atomoxetine	Strattera®	Norepinephrine reuptake inhibitor	ADHD	oral
Bedaquiline	Sirturo®	Antibiotic	Tuberculosis, drug resistant	oral
Bendamustine	Treanda®, Treakisym®, Ribomustin®, Levact®	Alkylating agent	Leukemia, lymphoma	injection
Benperidol	Anquil®, Glianimon®	Anti-psychotic	Antipsychotic	oral
Betrixaban	Bevyxxa®	Anticoagulant	Anticoagulant	oral
Bortezomib	Velcade®, Bortecad®	Proteasome inhibitor	Multiple Myeloma,lymphoma	injection
Bosutinib	Bosulif®	Tyrosine kinase inhibitor	Leukemia	oral
Buprenorphine	Butrans®, Belbuca®, Bunavail®, Buprenex®	Opioid receptor modulator	Narcotic addiction and pain	Sublingual, topical, injection
Cabozantinib	Cometriq®	Anti-cancer	Renal cell carcinoma	oral
Capecitabine	Xeloda®	Anti-cancer	Cancer (GI, Breast)	oral
Ceritinib	Zykadia®	Kinase Inhibitor	Cancer (Lung)	oral
Clofazimine	Lamprene®	Antimycobacterial	Leprosy	oral
Clomipramine	Anafranil®	Antidepressant, Tricyclic	Depression	oral, injection

Clozapine	Clozaril®, Fazaclo®, Versacloz®	Anti-psychotic, atypical	Schizophrenia	oral
Crizotinib	Xalkori®	Kinase inhibitor	Anti-cancer	oral
Cyamemazine	Tercian®	Antipsychotic	Schizophrenia, sedation	oral, injection
Dabrafenib	Tafinlar®	Anti-cancer	Melanoma	oral
Dasatinib	Sprycel®	Tyrosine kinase inhibitor	Leukemia	oral
Delamanid	Deltyba®	Antibiotic	Tuberculosis, drug resistant	oral
Desipramine	Pertofrane®, Norpramine®	Antidepressant, Tricyclic	Depression	oral
Deutetrabenazine	Austedo®	Vesicular monamine transporter 2 inhibitor	Chorea (Huntington's disease)	oral
Dexmedetomidine	Precedex®, Dexdor®, Dexdomitor®	Sedative	Sedation	injection
Dolasetron	Anzemet®	Anti-nausea	Nausea, vomiting	oral, injection
Efavirenz	Sustiva® and others	Antiretroviral	HIV	oral
Eliglustat	Cerdelga®	Glucosylceramide synthase inhibitor	Gaucher's disease	oral
Epirubicin	Ellence®, Pharmorubicin®, Epirubicin Ebewe®	Anti-cancer	Cancer	injection
Eribulin mesylate	Halaven®	Anti-cancer	Metastatic breast neoplasias	injection
Ezogabine (Retigabine)	Potiga®, trobalt®	Anticonvulsant	Seizures, Partial	oral
Felbamate	Felbatol®	Anti-convulsant	Seizure	oral
Fingolimod	Gilenya®	Sphingosine phospate receptor modulator	Multiple Sclerosis	oral
Fluorouracil (5-FU)	Adrucil®, Carac®, Efudex®, Efudix®, others	Anticancer	Cancer	injection
Flupentixol	Depixol®, Fluanxol®	Dopamine 2 and 5HT2a antagonist	Schizophrenia	oral, injection
Gemifloxacin	Factive®	Antibiotic	Bacterial infection	oral
Granisetron	Kytril®, Sancuso®, Granisol®	Anti-nausea	Nausea, vomiting	oral, injection, topical
Hydrocodone - ER	Hysingla™ ER, Zohydro ER	Analgesic	Pain, severe	oral, suppository
Iloperidone	Fanapt®, Fanapta®, Zomaril®	Anti-psychotic, atypical	Schizophrenia	oral, injection
Imipramine (melipramine)	Tofranil®	Antidepressant, Tricyclic	Depression	oral

Inotuzumab ozogamicin	Besponsa®	Antineoplastic agent	Acute Lymphocytic Leukemia	injection
Isradipine	Dynacirc®	Anti-hypertensive	High blood pressure	oral
Ketanserin	Sufrexal®	Antihypertensive	Hypertension	oral
Lapatinib	Tykerb®, Tyverb®	Anti-cancer	Breast cancer, metastatic	oral
Levantinib	Lenvima®	Anticancer	Cancer	oral
Lithium	Eskalith®, Lithobid®	Anti-mania	Bipolar disorder	oral, injection
Lopinavir and ritonavir	Kaletra®, Lithobid®	Viral protease inhibitor	HIV/AIDS	oral
Melperone	Bunil®, Buronil®, Eunerpan®	Antipsychotic, atypical	Schizophrenia	oral, injection
Midostaurin	Rydapt®	Anti-cancer	Acute myeloid leukemia	oral
Mifepristone	Korlym®, Mifeprex®	Progesterone antagonist	Pregnancy Termination	oral
Mirabegron	Myrbetriq®	Beta3 adrenergic antagonist	Overactive bladder	oral
Mirtazapine	Remeron	Anti-depressant, Tetracyclic	Depression	oral
Moexipril/HCTZ	Uniretic®, Univasc®	Anti-hypertensive	High blood pressure	oral
Necitumumab	Potrazza®	Antipcancer	Lung cancer	injection
Nicardipine	Cardene®	Anti-hypertensive	High blood pressure	oral, injection
Nilotinib	Tasigna®	Anti-cancer	Leukemia	oral
Norfloxacin	Noroxin®, Ambigram®	Antibiotic	Bacterial infection	oral
Nortiptyline	Pamelor®, Sensoval®, Aventyl®, Norpress®, Allegron®, Noritren®, Nortrilen®	Antidepressant, Tricyclic	Depression	oral
Nusinersen	Spinraza®	Antisense oligonucleotide	Spinal muscular atrophy	injection
Ofloxacin	Floxin®	Antibiotic	Bacterial infection	oral, injection
Osimertinib	Tagrisso®	Tyrosine kinase inhibitor	Cancer	oral
Olanzapine	Zyprexa®, Zydis®, Relprevv®	Anti-psychotic, atypical	Schizophrenia, bipolar	oral, injection
Oxytocin	Pitocin®, Syntocinon®	Oxytocic	Labor stimulation	injection
Paliperidone	Invega®, Xepilon®	Anti-psychotic, atypical	Schizophrenia	oral, injection
Palonosetron	Aloxi®	Antiemetic	Nausea	injection
Panobinostat	Farydak®	Antineoplastic agent	Multiple myeloma	oral
Pasireotide	Signifor®	Somatostatin analog	Cushings Disease	injection, topical
Pazopanib	Votrient®	Tyrosine kinase inhibitor	Anti-cancer	oral
Perflutren lipid microspheres	Definity®	Imaging contrast agent	Echocardiography	injection
Perphenazine	trilafon®, Etrafon/Triavil, Decentan®	Antipsychotic	Schizophrenia	oral, injection

Pilsicainide	Sunrythm®	Anti-arrhythmic	Arrhythmia	oral, injection
Pimavanserin	Nuplzaid®	Antipsychotic, atypical	Psychosis, Parkinson's disease	oral
Pipamperone	Dipiperon (E.U)	Antipsychotic	Schizophrenia	oral
Primaquine phosphate		Anti-malarial	Malaria	oral
Promethazine	Phenergan®	Anti-psychotic / Anti-emetic	Nausea	oral, injection, suppository
Prothipendyl	Dominal®, Largophren®, Timoval®, Timovan®, Tumovan®	Antipsychotic	Schizophrenia	oral, injection
Ribociclib	Kisqali®	Cyclin dependent kinase inhibitor	Breast cancer	oral
Ranolazine	Ranexa®, Ranozex®	Anti-anginal	Chronic angina	oral
Rilpivirine	Edurant®, Complera®, Eviplera®	Anti-viral	HIV/AIDS	oral
Risperidone	Risperdal®	Anti-psychotic, atypical	Schizophrenia	oral, injection
Saquinavir	Invirase®(combo)	Anti-viral	HIV/AIDS	oral
Sertindole	Serdolect®, Serlect®	Anti-psychotic, atypical	Anxiety, Schizophrenia	oral
Sorafenib	Nexavar®	Tyrosine kinase inhibitor	Anti-cancer	oral
Sunitinib	Sutent®	Anti-cancer	Renal cell cancer, GIST	oral
Tacrolimus	Prograf®, Prograf®, Advagraf®, Protopic®	Immunosuppressant	Immune suppression	oral, injection
Tamoxifen	Nolvadex®(discontinued 6/13), Istubal®, Valodex®	Anti-cancer	Breast cancer	oral
Telavancin	Vibativ®	Antibiotic	Bacterial infection	injection
Telithromycin	Ketek®	Antibiotic	Bacterial infection	oral
Tetrabenazine	Nitoman®, Xenazine®	Monoamine Transporter Inhibitor	Chorea (Huntington's disease)	oral
Tiapride	Tiapridal®, Italprid®, Sereprile®, Tialaread®, Tiaryl®, Tiaprim®, Tiaprizal®, Sereprid®, Tiapridex®	Selective D2, D3 dopamine antagonist	Alcoholism, withdrawal	oral, injection
Tipiracil and Trifluridine	Lonsurf®	Anti-cancer	Metastatic colorectal cancer	oral
Tizanidine	Zanaflex®, Sirdalud®	Muscle relaxant	Spasticity	oral
Tolterodine	Detrol®, Detrusitol®	Muscle relaxant	Bladder spasm	oral
Toremifene	Fareston®	Estrogen agonist/antagonist	Anti-cancer	oral
Trimipramine	Surmontil®, Rhotrimine®, Stangyl®	Antidepressant, Tricyclic	Depression	oral
Tropisetron	Navoban®, Setrovel®	Antiemetic	Nausea, vomiting	oral, injection

Valbenazine	Ingrezza®	Vesicular monamine transporter 2 inhibitor	Tardive dyskinesia	oral
Vardenafil	Levitra®	Phosphodiesterase inhibitor	Vasodilator	oral
Vemurafenib	Zelboraf®	Kinase inhibitor	Anti-cancer	oral
Venlafaxine	Effexor®, Efexor®	Anti-depressant, SNRI	Depression	oral
Vorinostat	Zolinza®	Anti-cancer	Lymphoma	oral
Zotepine	Losizopilon®, Lodopin®, Setous® and Zoleptil®	Antipsychotic, atypical	Schizophrenia	oral

Appendix H – Unpublished data of preclinical data: Combination of Ganetespib with PARP-inhibitor Niraparib

To assay for a possible cooperation of Ganetespib with PARP inhibitors, we treated cells derived from ovarian cancer with Ganetespib and Olaparib, alone or in combination. In these assays, the cells were seeded as follows in 6-well plates: per well, we seeded 25000 Ovcar5 cells, 40000 Ovcar3 cells, 60000 Kuramochi cells, and 60000 Cov362 cells. Ovcar5 and Cov362 cells were cultured in DMEM, Ovcar3 and Kuramochi cells were cultured in RPMI , each with 10% FCS and antibiotics

The following drug concentrations were used.

- Ovcar3: 10 µM Olaparib, 30 nM Ganetespib
- Ovcar5 : 10 µM Olaparib, 12 nM Ganetespib
- Cov362: 6 µM Olaparib, 50 nM Ganetespib
- Kuramochi: 10 µM Olaparib, 40 nM Ganetespib

The cells were first incubated with Olaparib for 24 h, and then with Olaparib and Ganetespib simultaneously for an additional 48 h. In controls, either or both of the drugs were omitted and replaced by the DMSO solvent. The cells were then analyzed by visual inspection (Figure 5). In the cells treated by the drug combinations, we observed extensive morphological changes that were at least compatible with cell death. This was not observed to the same extent with single drugs or control treatment.

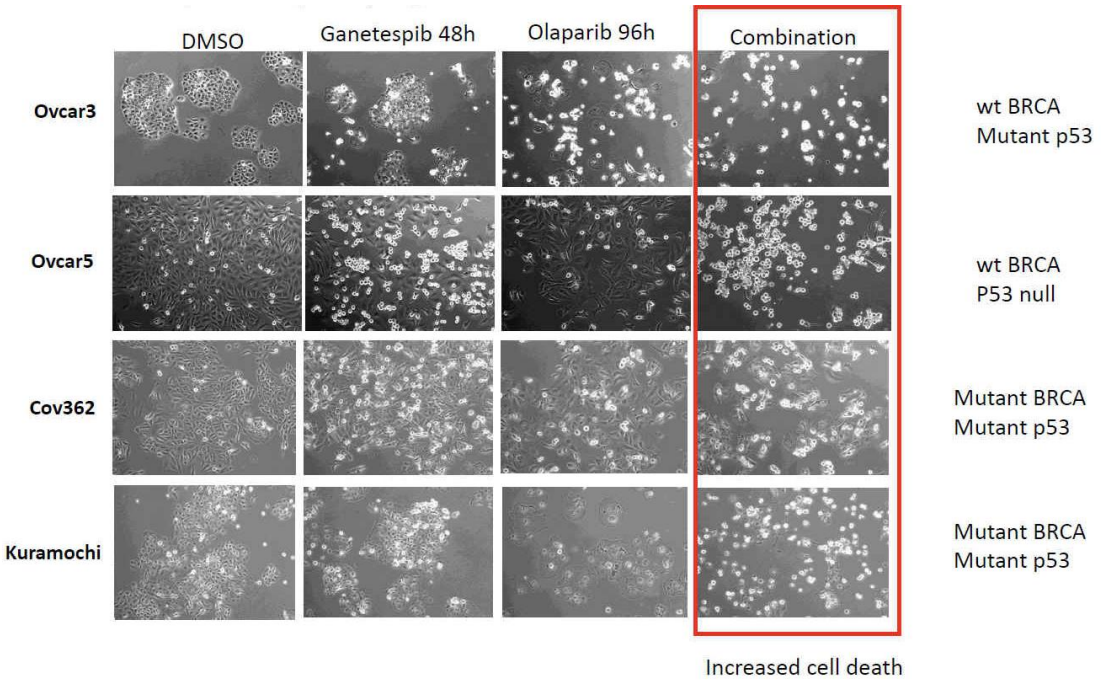

Figure 5: Combination of Ganetespib and Olaparib synergize in OvCa cells

Subsequently, the accumulation of phospho-H2AX, a marker of DNA damage and cell death, was evaluated by immunoblot analysis (Figure 6). Here again, the combination yielded a far stronger accumulation of the Phosphoprotein than the single treatments.

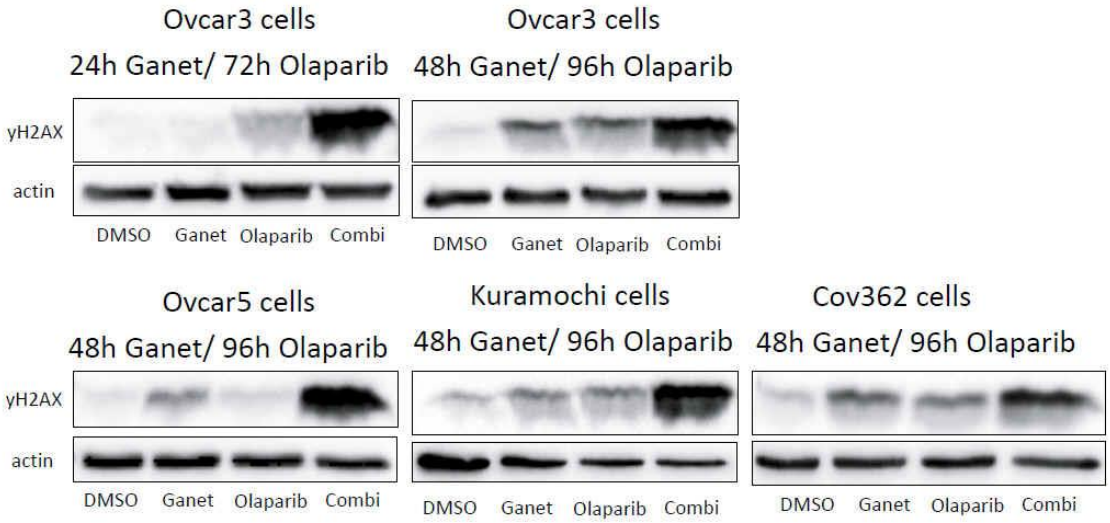

Figure 6: Combination treatment with Ganetespib and Olaparib leads to accumulation of DNA damage

Finally, we investigated the appearance of cell death by a combined staining with annexin V (binding phosphatidylserine to indicate apoptose) and 7AAD to indicated death-induced membrane permeability (Figure 7). Again, the drug combination strongly increased the appearance of dead cells, mostly by apoptosis, and to a markedly greater extent than the single drugs.

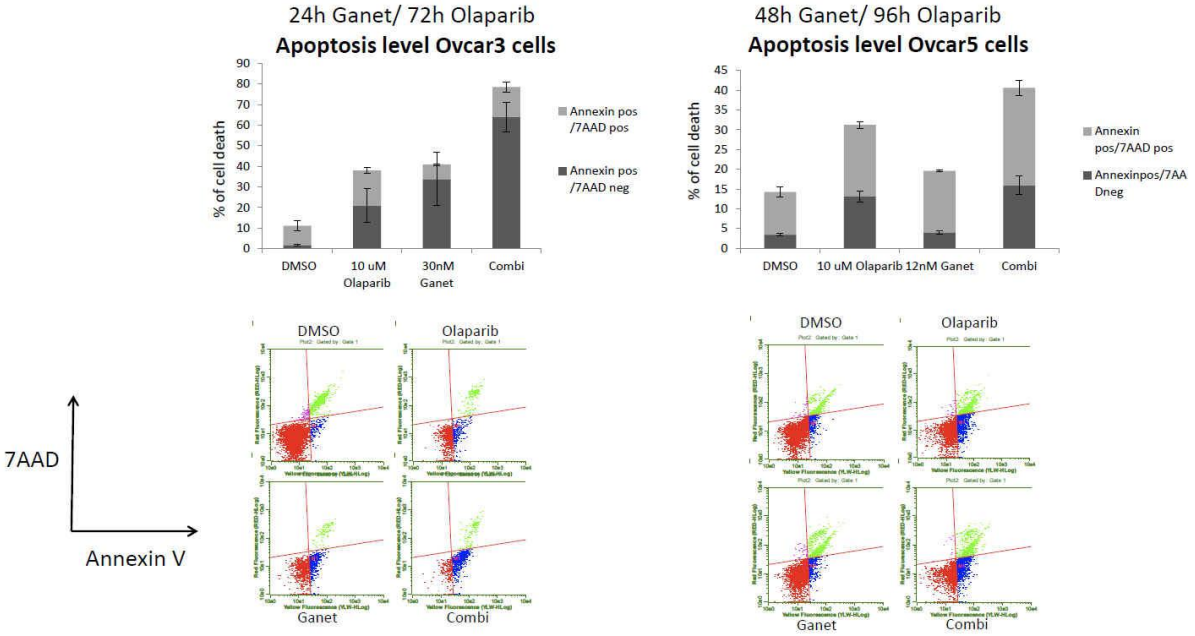

Figure 7: Combination treatment with Ganetespib and Olaparib leads to increased induction of apoptosis

In addition, we evaluated the accumulation of phospho- (gamma) H2AX by quantitative immunofluorescence, obtaining comparable results as by immunoblot analysis (Figure 8, cf. Figure 6)

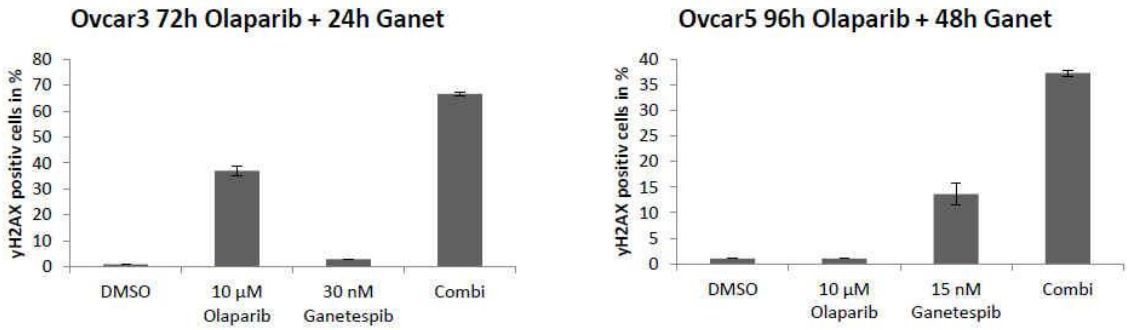

Figure 8: IF-Analysis, gammaH2AX, 96 well format

All these results indicate a cooperation between Olaparib and Ganetespib in cell killing. Correspondingly, we and others have previously observed that BRCA1 levels depend on HSP90 activity, suggesting that Ganetespib, through decreasing BRCA1 stability, might sensitize the cells towards Olaparib (much like BRCA1 mutations). Regardless of the mechanism, however, the data are indicative of drug cooperation.