KCP-330-005

A Phase II, Open-label Study of Efficacy and Safety of the Selective Inhibitor of Nuclear Export/SINE Compound KPT-330 (Selinexor) in Patients with Advanced Gynaecologic Malignancies

Short Title	SIGN (KCP-330-005)
Sponsor	Karyopharm Therapeutics Inc.
Coordinating Investigator	PPD , MD
Coordinating CRO	GSO Global Clinical Research BV
Data Monitoring	GSO Global Clinical Research BV
EudraCT Number	2013-003650-24
Protocol Identification Number	KCP-330-005
Protocol Version: Original – Version 1.0, 11 November 2013 Amendment 1 – Version 2.0 (09 September 2014) Amendment 2 – Version 3.0 (12 November 2014) Amendment 2.1 – Version 3.1 (08 January 2016) Amendment 2.2 – Version 3.2 (04 August 2016)	

Confidentiality

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APPROVAL OF THE PROTOCOL

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04 August 2016

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Karyopharm Therapeutics Inc.

Date

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04 August 2016

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Karyopharm Therapeutics Inc.

Date

Investigator's Agreement

I have read the attached protocol entitled:

"A Phase II, Open-label Study of Efficacy and Safety of the Selective Inhibitor of Nuclear Export/SINE Compound KPT-330 (Selinexor) in Patients with Advanced Gynaecologic Malignancies" and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice, all applicable national regulations as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee and any other institutional requirements.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the study sponsor.

Signature Date (dd mmm yyyy)

Investigator

Investigator's Institution

SYNOPSIS

Protocol no.	KCP-330-005
Protocol version (Date)	Amendment 2.2 – Version 3.2 (04 August 2016)
Short Title	SIGN (KCP-330-005)
Title	A Phase II, Open-label Study of Efficacy and Safety of the Selective Inhibitor of Nuclear Export/SINE Compound KPT-330 (Selinexor) in Patients with Advanced Gynaecologic Malignancies
EudraCT no.	2013-003650-24
Coordinating Investigator	PPD , PPD MD
Sponsor	Karyopharm Therapeutics Inc. 85 Wells Avenue Newton MA 02459 USA
Study design	This trial has been designed as a multi-center, open-label, two-stage phase II study in 3 separate gynaecological cancer cohorts, with an additional set of patients in the ovarian cohort randomized into two different treatment regimens. The study is divided between a Primary Treatment Phase and a Maintenance Phase with each phase supported by a separate database. Part 1 – Three parallel cohorts of patients with ovarian (Cohort A), endometrial (Cohort B), or cervical (Cohort C) carcinoma will be enrolled. Part 2 - Based on the observed tolerability and efficacy profile in the ongoing ovarian cohort (Cohort A), two additional treatment schedules will be explored to optimize the dosing schedule in a patient population with ovarian carcinoma. Clinical and radiological examinations for disease status as well as QoL assessments will be performed at baseline, after 6 and 12 weeks of treatment, and approximately every 8 weeks thereafter. Treatment will continue until progression of disease (PD) or unacceptable toxicity, death, withdrawal of consent by the patient, or discontinuation of the patient due to non-compliance with protocol requirements. Safety assessments will be performed at the baseline visit and during each cycle through the End-of-Treatment (EoT) visit. If a patient discontinues treatment due to any reason other than PD, death, or withdrawal of informed consent, the disease evaluations shall continue until disease progression. This includes patients who wish to discontinue treatment, but agree to have further data captured for the purpose of the study.

	After treatment discontinuation, a call will be made to the patient (or the patient's family) approximately every 3 months to inquire about the patient's survival status.
Start date	January 2014
Duration of study	End of study is defined as 30 days after the last patient experiences PD
Total number of sites	Approximately 4
Study population	Three parallel cohorts of patients will be enrolled: • Cohort A: Ovarian carcinoma (Part 1 and Part 2) • Cohort B: Endometrial carcinoma (Part 1) • Cohort C: Cervical carcinoma (Part 1)
Objectives	Primary Treatment Phase
Primary objective	• Determine the efficacy of selinexor in patients with advanced or metastatic gynaecological cancers by assessing disease control rate (DCR).
Secondary objectives	• Determine the efficacy of selinexor in patients with advanced or metastatic gynaecological cancers by ○ Objective response rate (ORR) ○ Progression-free survival (PFS) ○ Overall survival (OS), including OS rates at 12 and 24 months • Evaluate the safety and tolerability of selinexor in patients with advanced or metastatic gynaecological cancers • Evaluate quality of life (QoL) in patients with advanced or metastatic gynaecological cancers who are treated with selinexor
Exploratory objectives	CCI [redacted]
See Section 18 (Appendix 16) for the objectives for the Maintenance Phase of the study for the patients receiving treatment under version ≥3.2 of the protocol.	

Planned sample size	Part 1: Approximately 63 evaluable patients in three disease cohorts (ovarian, endometrial, and cervical carcinoma) are planned. CCI [redacted] For both parts of the study, an evaluable patient is defined as a patient who has received at least one dose of study medication and has at least one post-baseline efficacy follow-up assessment, unless the patient discontinued treatment prior to the first assessment due to death, toxicity, or PD.
Inclusion criteria	1. Female patients age ≥ 18 years 2. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. 3. Adequate hematologic function defined as: • platelets ≥ 125 x 10^9/L • hemoglobin ≥ 5.59 mmol/L or 9 g/dL • ANC ≥ 1.5 x 10^9/L • WBC ≥ 3.0 x 10^9/L Up to 5% deviation is tolerated. Transfusions and growth factors are allowed. 4. Adequate liver function, defined as adequate hepatic function within 14 days prior to Cycle 1 Day 1: total bilirubin < 2 times the upper limit of normal (ULN) (except patients with Gilbert's syndrome, who must have a total bilirubin of < 3 times ULN), aspartate aminotransferase (AST) < 2.0 times ULN, and alanine aminotransferase (ALT) < 2.0 times ULN. In the case of known (radiologically and/or biopsy-documented) liver metastasis, AST < 5.0 times ULN and ALT < 5.0 times ULN is acceptable. Up to 10% deviation is acceptable. 5. Renal function defined as a calculated or measured glomerular filtration rate ≥ 30 mL/min. 6. The patient has recovered to Grade ≤ 1 by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (NCI-CTCAE v4.03) from the effects of recent surgery, radiotherapy, chemotherapy, hormonal therapy, or other targeted therapies, with the exception of alopecia. The exceptions for such effects are allowed lab values of ≤ Grade 2 specified elsewhere in these inclusion criteria. 7. Life expectancy of at least 12 weeks.

	8. Able to swallow and retain oral medication. 9. Patients must give written informed consent according to the rules and regulations of the individual participating site. 10. Negative serum pregnancy test in women of childbearing potential within 14 days of first dose of treatment, and patients of childbearing potential must agree to use effective contraception during treatment up to 3 months from last dose. Fertile male partners must be willing and able to use effective non-hormonal means of contraception (barrier method of contraception in conjunction with spermicidal jelly, or surgical sterilization) during and for at least 6 months post-study treatment. 11. The patient must be recovered from any prior treatment/major operation. The treatment/major operation must be performed at least 4 weeks prior to start of study drug. Palliative radiotherapy is permitted until one week prior to the start of study drug. 12. Only incurable patients with histologically or cytologically proven primary tumor and objective documentation of disease progression on prior treatment by computed tomography (CT)/ magnetic resonance imaging (MRI) may be enrolled. 13. *Ovarian, fallopian tube, or peritoneal carcinoma:* both platinum refractory* and platinum resistant** patients, who have received ≥1 line of chemotherapy for relapsed disease (i.e., ≥ 2 lines of chemotherapy in total). * Platinum refractory is defined as progression during or within 4 weeks of last treatment with a platinum-containing therapy. ** Platinum resistant is defined as relapse 4 weeks to < 6 months after a platinum-containing therapy. 14. *Endometrial carcinoma:* patients must have received ≥ 1 line of chemotherapy for relapsed or advanced (stage IV, IIIc) disease. 15. *Cervical carcinoma:* patients must have received ≥ 1 line of chemotherapy for relapsed or advanced (stage IVb) disease. 16. Carcinosarcomas (Malignant Mixed Mullerian Tumor) are allowed, but all other non-epithelial cancers of the ovary, fallopian tube, endometrium, or cervix are excluded. 17. Patients must have either measurable disease (Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1]) or evaluable disease outside irradiated field on CT/MRI. For ovarian cancer: Patients must have disease that is measurable according to RECIST or assessable according to the Gynecologic Cancer Intergroup (GCIG) CA-125 criteria. A rise in CA-125 or other tumor marker alone is not sufficient.
Exclusion criteria	Patients with any of the following will not be eligible for participation: 1. Disease-Specific Exclusions: • Evidence of complete or partial bowel obstruction. • Need of Total Parenteral Nutrition. 2. Patients who are pregnant or breast feeding. 3. Radiation (except planned or on-going palliative radiation to bone outside of the region of measurable disease) ≤ 3 weeks prior to

	Cycle 1 Day 1. 4. Chemotherapy, immunotherapy or any other systemic anti-cancer therapy, (including investigational anti-cancer therapy) ≤ 3 weeks prior to Cycle 1 Day 1. 5. Diagnosis or recurrence of invasive cancer other than the present cancer within 3 years (except basal or squamous cell carcinoma of the skin that has been definitively treated). 6. Unstable cardiovascular function: o Symptomatic ischemia, or o Uncontrolled clinically significant conduction abnormalities (e.g., ventricular tachycardia on anti-arrhythmics are excluded and 1st degree AV block or asymptomatic LAFB/ RBBB will not be excluded), or o Congestive heart failure (CHF) of NYHA Class ≥ 3, or myocardial infarction (MI) within 3 months of Cycle 1 Day 1. 7. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to the first dose. Active infection with concurrent treatment is acceptable only if the patient is clinically stable. 8. Significantly diseased or obstructed gastrointestinal tract or uncontrolled vomiting or diarrhea. 9. Concurrent therapy with approved or investigational anti-cancer therapeutics. 10. Medical, psychological, or social conditions that may interfere with the patient's participation in the study or evaluation of the study results. 11. Known brain metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and glucocorticoids. 12. All non-epithelial cancers of the ovary, fallopian tube, peritoneum, endometrium or cervix as well as neuro-endocrine tumors are excluded.
Treatment scheme	**Primary Treatment Phase** Treatment will continue until PD or unacceptable toxicity, death, withdrawal of consent by the patient, or non-compliance by the patient with protocol requirements. Each cycle is 28 days (4 weeks) long. In twice-weekly dose schedules (i.e., Part 1 and Part 2, Schedule 1), 8 doses of selinexor will be administered per cycle. In the once-weekly dose schedule (i.e., Part 2 Schedule 2), 4 doses of selinexor will be administered per cycle. Twice-weekly doses of selinexor must be administered at least 36 hours apart; once-weekly doses of selinexor must be administered at least 5 days apart.

	Dose escalations and reductions/interruptions are permitted according to safety guidelines in this protocol or in consultation with a sponsor representative. Part 1: Patients will receive oral selinexor 50 mg/m² twice weekly (e.g., Monday and Wednesday, Tuesday and Thursday, Wednesday and Friday or Thursday and Saturday) in each week of a 4-week cycle. If the patient has not experienced a major toxicity after 12 weeks of treatment, a selinexor dose escalation to 60 mg/m^2 twice weekly will be allowed. Dose reductions (minimum dose: 35 mg/m^2 once weekly) and interruptions are permitted. Part 2: *Schedule 1* Patients will receive oral selinexor 35 mg/m² twice weekly (e.g., Monday and Wednesday, Tuesday and Thursday, Wednesday and Friday or Thursday and Saturday) in each week of a 4-week cycle. If there has been no major toxicity after 6 weeks, a dose escalation to 50 mg/m^2 twice weekly in each week of a 4-week cycle will be allowed. *Schedule 2* Patients will receive oral selinexor 50 mg/m² once weekly in each week of a 4-week cycle (e.g., Monday of each week). If the patient has not experienced a major toxicity after 6 weeks of treatment, a dose escalation to 60 mg/m^2 once weekly will be allowed. Dose reductions (minimum doses - Schedules 1 and 2: 35 mg/m^2 once a week) and interruptions are permitted. **Maintenance Phase** See Section 18 (Appendix 16) for the schedule of assessments for the Maintenance Phase of the study to continue treatment with selinexor and/or survival follow-up under Version ≥3.2 of the protocol.
Primary parameter	The analysis of DCR will be performed for each study cohort by calculating the point estimate of the percentage of patients in that cohort who have CR, PR, or SD for at least 12 weeks, assessed according to RECIST 1.1. Duration of SD will be calculated from the date of start of study therapy until the date of PD, or last disease assessment should progression not have occurred; for patients without at least one post-baseline disease assessment, duration will be censored at time 0.

Secondary parameters	1. Response to therapy per RECIST 1.1: response for patients in each cohort will be determined by the objective response rate (ORR), defined as either CR or PR using RECIST 1.1 calculated as a proportion and including a two-sided 95% CI for that cohort. 2. Response to therapy per GCIG response criteria (RECIST 1.1 and CA-125): response for patients in the ovarian cohort will also be assessed for DCR and ORR, as described above, using the GCIG response criteria. 3. Median Progression-free Survival (PFS): PFS for patients in each cohort will be calculated from the date of start of study therapy to the date of PD based on RECIST 1.1, or date of death if PD does not occur. 4. Overall Survival (OS): OS for patients in each cohort will be calculated from the date of start of study therapy to the date of death due to any cause. OS rate at 12 and 24 months will also be calculated. 5. Safety and tolerability of selinexor will be evaluated descriptively for all study patients combined, according to NCI CTCAE, v.4.03. Safety endpoints include AEs, clinical laboratory data, vital signs, ECGs, and physical examinations, further described below. 6. Quality of Life (QoL) will be evaluated for patients in each cohort, and for all study patients combined by EORTC QLQ-C30 after 6 and 12 weeks of treatment and approximately every 8 weeks thereafter.
Efficacy assessments	During the Primary Treatment Phase, clinical and radiological examinations will be performed at baseline, after 6 and 12 weeks of treatment, and every 8 weeks thereafter. If a patient discontinues treatment due to any reason other than PD, death, or withdrawal of informed consent, the disease evaluations shall continue until PD. This includes patients who wish to discontinue treatment, but agree that further data are captured for the purpose of the study. OS data will be collected approximately every 3 months.
Safety assessments	All serious adverse events (SAEs) and adverse events (AEs) for the Primary Treatment Phase and Maintenance Phase occurring from the signing of the ICF and from the start of treatment (i.e., Cycle 1 Day 1), respectively, and for up to 30 days after the last dose of study medication will be captured, documented, and reported, and graded according to CTCAE v.4.03. Safety blood samples include complete blood count, clinical chemistry, including liver function test, and coagulation.
Statistical considerations	<u>Pre-planned subgroup analyses:</u> Part 1 of the study will enroll three cohorts of ovarian (Cohort A), endometrial (Cohort B), and cervical (Cohort C) cancers which will be evaluated independently. Part 2 of the study will enroll additional ovarian patients to evaluate efficacy and safety of once-weekly versus twice-weekly dosing. Subtypes of each tumor (e.g., adenocarcinoma versus squamous

	carcinoma) will be evaluated both together and separately. All enrolled patients are eligible for the analyses of toxicity and compliance. The treated population (modified intention-to-treat [mITT]) will consist of all patients who receive at least one dose of study medication and have at least one post-baseline efficacy follow-up assessment, unless the patient discontinued treatment prior to the first assessment due to death, toxicity, or PD. This population will be used for primary analyses of efficacy.
Sample size calculation	CCI [redacted]

INFORMATION TO BE PROVIDED REGARDING SAES/PREGNANCY

In the case of a serious adverse event (SAE) or pregnancy, contact Karyopharm by fax or email within 24 hours of knowledge.

Pharmacovigilance Department
Karyopharm Therapeutics Inc.
Email: pharmacovigilance@karyopharm.com
Fax: +1-617-334-7617 (US)
+49-89-9218-5650 (Germany)

TABLE 1:SCHEDULE OF ASSESSMENTS FOR THE PRIMARY TREATMENT PHASE. See Section 18 (Appendix 16) for the Schedule of Assessments for the Maintenance Phase for the patients who continue treatment with selinexor and/or survival follow-up under version ≥3.2 of the protocol.

Assessment	Baseline (Within 14 days prior to C1 D1)	Day 1 of Each Cycle (-3 days)	Day 15 of Each Cycle (± 3 days)	After 6 Weeks of Treatment (± 7 days)	After 12 Weeks of Treatment Every 8 weeks (± 7 days) Until PD	End of Treatment (30 days ± 7 days post-last dose)	Survival Status (Every 3 months)
Informed consent[1]	X						
Inclusion and exclusion criteria	X						
Demographics	X						
Medical history[2]	X						
Pregnancy test (if applicable)[3]	X						
Physical exam and ECOG[4]	X	X				X	
Neurological exam[5]	X						
Body height and weight[6]	X	X	X			X	
BSA	X	X					
Vital signs[7]	X	X				X	
Ophthalmic exam[8]	X						
12-lead ECG[9]	X					X	
Pulse oximetry[10]	X					X	
Hematology[11]	X	X	X			X	
GFR calculation[12] (or measurement)	X						
Clinical chemistry[13]	X	X	X			X	
Urinalysis[14]	X					X	
Coagulation test[15]	X						

Assessment	Baseline (Within 14 days prior to C1 D1)	Day 1 of Each Cycle (-3 days)	Day 15 of Each Cycle (± 3 days)	After 6 Weeks of Treatment (± 7 days)	After 12 Weeks of Treatment Every 8 weeks (± 7 days) Until PD	End of Treatment (30 days ± 7 days post-last dose)	Survival Status (Every 3 months)
CA-125 (Cohort A only)	X	X					
Gynaecological exam	X			X (Optional)	X	X	
CT/MRI chest and abdomen[16]	X			X	X		
PET-CT[16]	X			X	X		
EORTC QLQ-C30[17]	X			X	X	X	
Adverse Events (AE)	X (SAEs beginning at ICF signing; AEs beginning at first dose)						
Concomitant medication	X	X	X	X	X	X	
Selinexor dosing[18]		X	X				
Required supportive care[19]	X	X	X				
CCI							
CCI							
CCI							
Blood draws for CTC[22]		X (Cycle 1 only)					
Telephone contact[23]							X

[1] Informed consent required prior to the first study-specific measures.
[2] Medical history includes baseline symptoms as well as a detailed history of prior cancer therapies including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.
[3] Pregnancy test for women of childbearing potential. Serum beta human chorionic gonadotropin (β-HCG) test within 7 days before the first dose of study drug. To be repeated by urine test, if date of first result exceeds the 7-day window. Urine pregnancy testing is to be performed as clinically indicated during the study. Any positive urine pregnancy test must be confirmed with a serum β-HCG test.

[4] Full physical examination and ECOG at baseline and End-of-Treatment (EoT) visit. All other physical examinations should be symptom directed.
[5] A standard neurological examination to assess motor, sensory, and balance functions to be performed.
[6] Body height will be measured at screening only.
[7] Vital signs include blood pressure, pulse, and temperature.
[8] Full ophthalmic exam: required at screening and if clinically indicated during the study (e.g., monitoring of pre-existing cataracts, visual disturbances). *Please note:* Patients enrolled under a prior version of the protocol who had detectable cataracts graded according to the LOCS III will continue to have their cataracts graded according to LOCS III and will not switch to the AOA scale. For new patients and patients for whom no cataracts have been detected to date, if cataracts are detected, they will be graded according to the AOA scale.
[9] 12-lead ECG performed at screening, EoT visit, and if clinically indicated during the study.
[10] Pulse oximetry is performed for patients at rest while breathing room air.
[11] Hematology: includes hemoglobin, white blood cell (WBC) count, neutrophils, and platelets. Blood draws may be done 3 days prior to visit.
[12] Calculated glomerular filtration rate (GFR) according to the formula of *Cockroft and Gault*.
[13] Clinical chemistry: includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphate, magnesium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), total protein, and albumin. Blood draws may be completed 3 days prior to the visit; testing may be repeated on the day of the visit if clinically indicated.
[14] Urinalysis will include urine bilirubin, glucose, hemoglobin, ketones, pH, and protein. Performed at screening, the EoT visit, and if clinically indicated. Urinalysis may be done up to 3 days prior to visit.
[15] Coagulation test includes prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT). This will be performed at baseline and if clinically indicated during the study. Blood draw may be done up to 3 days prior to visit.
[16] CT/MRI of abdomen must include pelvis. PET-CT is allowed, but ultrasound of the abdomen and x-ray of thorax is not allowed. CT/MRI or PET/CT scans to be performed within four weeks prior to registration. CT scan is required again if patient has relapse and if clinically justified during trial period. On-study tumor assessment should be performed after 6 (± 7 days) and 12 weeks (± 7 days) of treatment. Thereafter, tumor assessments will be performed every 8 weeks (± 7 days), thereafter independent of cycle delays until PD or death.
[17] Patients to complete the EORTC QLQ-C30 at baseline, with tumor assessment at Week 6, Week 12, and every 8 weeks thereafter, and at the EoT visit.
[18] Selinexor dosing for Part 1, and Part 2, Schedule 1: Twice weekly in each week of a 4-week cycle; Part 2, Schedule 2: Once weekly in each week of a 4-week cycle. For dosing details, including delayed doses and changes to the visit schedule, see Section 6.2.2 and Section 6.3).
[19] All patients will receive required supportive care to prevent nausea, as described in Section 6.5.1.
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CCI
[23] After treatment discontinuation, a call will be made to the patient (or the patient's family) approximately every 3 months to inquire about the patient's survival status.

GLOSSARY OF ABBREVIATIONS

β-HCG	Beta human chorionic gonadotropin
ADR	Adverse Drug reaction
AE	Adverse event
ALT (SGPT)	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-last}}$	Area under the concentration-time curve from time zero to last observed non-zero concentration
AV block	atrioventricular block
BID	Twice daily
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CA	Competent Authority
CHF	Congestive heart failure
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
C_{max}	maximum observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRM1	Chromosome region maintenance protein 1
CRO	Contract research organization
CSR	Clinical Study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CYP450	Cytochrome P450
D	Day
DCR	Disease Control Rate
DLBCL	Diffuse large B-Cell Lymphoma
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EOT	End of treatment

FIGO	International Federation of Gynecology and Obstetrics
FPI	First patient in
GCIG	Gynecological Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
GLP	Good laboratory practice
GRP	Growth regulatory protein
GSH	Glutathione
H	Hour
HPV	Human papillomavirus
HR	Hazard ratio
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalization ratio
IRB	Institutional review board
ITT	Intent to treat
IV	Intravenous
LAFB	Left anterior fascicular block
LDH	Lactate dehydrogenase
LLN	Lower Limit of Normal
m^2	Square meter (body surface area)
LMW	Low molecular weight
mg	Milligram
MCL	Mantle Cell Lymphoma
MI	Myocardial infarction
min	Minute
mL	Milliliter
MM	Multiple myeloma
MPA	Medroxyprogesterone acetate
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NES	Nuclear export sequences
NHL	Non-Hodgkin lymphoma
NK1R	Neurokinin-1 receptor
NPC	Nuclear pore complex
NYHA	New York Heart Association
ORR	Overall response rate

OS	Overall survival
PBMC	Peripheral Blood Mononuclear cells
PD	Progressive disease, Progression of disease
PDn	Pharmacodynamic(s)
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PLT	Platelets
po	By mouth
PPS	Per protocol set
PR	Partial response
PRN	as needed
PT	Prothrombin time
qd	every day
qhs	every night at bedtime
qid	Four times a day
QoL	Quality of life
qpm	every day after noon or every evening
qRT-PCR	Quantitative real time polymerase chain reaction
RBBB	Right bundle branch block
RBC	Red blood cell(s)
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
RR	Response Rate
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAM	S-Adenosyl methionine
SD	Stable disease
SINE	Selective inhibitor of nuclear export
SMC	Safety Monitoring Committee
SUSAR	Suspected unexpected serious adverse reaction
SUV	Standardized uptake value
$T_{1/2}$	Half-life
TGI	Tumor growth inhibition
T_{max}	Time of first observation of C_{max}
TSP	Tumor suppressor protein
ULN	Upper limit of normal
WBC	White blood cell(s)
WHO	World Health Organization
XPO1	Exportin 1

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

1 BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Gynaecological Malignancies

Gynaecological malignancies include all cancer types of the woman's reproductive organs. The main types are cervical, ovarian, uterine, vaginal, and vulvar cancer.

Ovarian Cancer

Ovarian cancer continues to be a leading cause of cancer-related deaths in women and is the leading cause of deaths attributed to gynaecological malignancies.

Ovarian cancer was the eighth most common cancer in women in 2008 worldwide with roughly 235,000 new diagnoses. Approximately 140,000 women died from ovarian cancer making it the seventh leading cause of cancer death in the world.[1] Approximately 90% of primary malignant ovarian tumors are epithelial carcinomas.[2]

The disease is classified into three grades depending on their percentage of solid growth on glandular and papillary component by the FIGO (International Federation of Gynecology and Obstetrics) system, whereas early disease is defined as FIGO stage I-IIa, and advanced disease includes FIGO stage IIb-IIIc. In stage IV, distant metastases are present.[2]

Primary cytoreductive surgery is the method of choice for the initial treatment of patients with advanced ovarian carcinoma. In a meta-analysis of 81 studies involving 6,885 patients, Bristow et al showed that patients with ≤ 25% maximal cytoreduction had a median overall survival of 22.7 months, whereas patients with ≥ 75% maximal cytoreduction achieved an increase in overall survival of 50%, to 33.9 months.[3] Even if optimal tumor debulking is not feasible, an interval debulking surgery performed after a short course of induction chemotherapy of 2-3 cycles may lengthen survival for the individual patient.[4]

Because ovarian cancer is usually asymptomatic in its early stages, the disease often has spread outside of the pelvic region at the time of diagnosis and requires debulking surgery followed by systemic chemotherapy. First-line chemotherapy involves platinum-based treatments, including the widely adopted regimens of cisplatin/paclitaxel, carboplatin/paclitaxel, and single-agent carboplatin. Although these regimens yield relatively satisfactory tumor response rates, the vast majority of patients experience disease recurrence and receive additional treatments. For such patients, a number of anti-tumor agents with distinct mechanisms of action (topotecan, gemcitabine, pegylated liposomal doxorubicin, docetaxel, etoposide) have been utilized, in addition to retreatment with platinum, with the goal of re-establishing remission or disease control, minimizing disease-related symptoms, improving quality of life, and extending patient survival.

Patients with progression during treatment with platinum are called "platinum-refractory", whereas patients who develop recurrence < 6 months after completion of first-line platinum chemotherapy have what is known as "platinum-resistant" disease.[5] While patients with "platinum-sensitive" disease, i.e. > 6 months without recurrence, may respond again to a platinum-based chemotherapy, patients with platinum-refractory or resistant ovarian carcinoma have a poor prognosis. Most trials suggest that median life

expectancy is < 12 months in these resistant/ refractory cases. In these situations, single agent treatment is usually recommended outside of the research setting, and the toxicity from the chemotherapy regimen should be a major consideration in choosing additional therapy.

It is difficult to justify the use of secondary cytoreductive surgery in women with platinum-resistant disease due to the significant morbidity of the surgery and the fact that platinum resistance is associated with a poor overall prognosis regardless of surgical intervention.[6]

Initial platinum-based chemotherapy will produce a response rate of approximately 70% in patients with epithelial ovarian cancer. The response rates to second-line therapy vary considerably based on the length of time from the completion of therapy to the time the recurrence is diagnosed.[5] However, when ovarian cancer recurs within 6 months of completing chemotherapy, the overall response to additional therapy is very poor. In this setting, the most active agents have shown an overall response rate (ORR) of about 10% to 30%, with a progression-free survival (PFS) of < 7 months and an OS of approximately < 16 months. See Table 6 (Appendix 1).[7-33]

Cervical Cancer

Cervical cancer is the second most common cancer affecting women worldwide, and it remains a major health problem in developing countries because of high oncogenic human papilloma virus (HPV) infection rates, the absence of screening programs and the lack of access to affordable vaccination programs.[34] The main cause is HPV infection. Although the HPV vaccine is expected to reduce its incidence over the next decades, for the present, cervical carcinoma is still a major public health concern.[35]

In economically developed countries, most women are diagnosed at early stages (associated with frequent Pap smears and/or HPV testing) of their disease and can be cured by surgery. However, the risk of recurrent disease is 10–20% for International Federation of Obstetrics and Gynecology (FIGO) stages I–IIa and 50–70% in locally advanced cases (stages IIb–IVa).[39]

Early cervical cancer (FIGO stage IA1 to IIA1) is treated with conization, hysterectomy or radical trachelectomy, depending on the stage.[36] For patients with locally advanced cervical cancer, concurrent platinum-based chemoradiation is the current treatment of choice. One meta-analysis with data from 18 randomized trials revealed a 5-year survival benefit of 8% for overall disease-free survival, 9% for locoregional disease-free survival, and 7% for metastases-free survival. If cisplatin is not tolerated, carboplatin or non-platinum chemoradiation schedules are options.[37] Adjuvant chemotherapy after chemoradiation with cisplatin-gemcitabine has demonstrated benefits, but is not yet recommended as standard treatment.[35-38]

Patients with distant metastases and/or with disease recurrence not amenable to loco-regional control have a poor prognosis.[39] In this setting, systemic chemotherapy is a palliative treatment aimed at prolonging survival and improving quality of life (QOL). The combination of cisplatin and paclitaxel is considered the standard of care, as it showed a higher response rate (RR) and longer progression-free survival (PFS) than single-agent cisplatin, although there were no significant differences in QOL.[40,41] No other cisplatin doublet has shown superiority in overall survival (OS) when compared with cisplatin–

paclitaxel.[42] Responses to platinum-based chemotherapy are short-lived and effective second-line options are lacking.[43]

The treatment of patients with metastatic or recurrent cervical carcinoma is palliative. cisplatin-based regimens are preferred, e.g., cisplatin plus paclitaxel or topotecan, but the response is poor especially in patients who have previously undergone chemotherapy.[44] In several clinical trials with women in advanced stage (IVB), which means recurrent or persistent cervical cancer, response rates of 3% to approximately 35% have been achieved. The median overall survival times ranged from 3.5 to 9.4 months and the median progression-free survival times lay between 3.5 months to 7.1 months. See Table 7 (Appendix 2).[45-51]

Endometrial Cancer

In 2008, endometrial cancer (uterine cancer) was the 6th leading malignancy in women worldwide, approximately 288,000 new cases were diagnosed.[1] In 2013, endometrial cancer was the most common gynaecological malignancy in the United States and other developed countries.[52]

The standard surgical therapy is total hysterectomy with or without lymphadenectomy, depending on the stage of the disease. In stage III-IV, maximal surgical cytoreduction is recommended for patients with a good performance status.[53] For patients with localized endometrial cancer, an optimal adjuvant treatment has not yet established. Options are radiotherapy, platinum-based chemotherapy or a combined radiochemotherapy.[53-55]

Endometrial cancer generally carries a favorable prognosis, mainly because the majority of women present with bleeding early on in the disease course. As a result, the disease is caught early and for most women the disease is curable by surgery; 5-year survival rates of 80% to 90% are generally reported.[56,57] However, for women with advanced stage disease or high-risk histologies, the prognosis is poor, with 5-year survival rates of 57% for regional disease (stage III) and 19% for distant spread (stage IV).[1]

The overall rate of recurrence for endometrial cancer is about 15%, with more than half occurring within 2 years of primary treatment. Recurrence rates for patients with early stage disease range from 2% to 15%, whereas it is up to 50% in women with advanced stage disease or in patients with aggressive histologies (grade 3 or non-endometrioid).[58,59,60]

In the setting of recurrent disease, certain clinico-pathologic factors are associated with a good prognosis, including a longer disease-free interval, low-grade and endometrioid histology, and isolated recurrence at the vaginal cuff. The disease in women with non-endometrioid histologies (uterine serous carcinoma and clear cell) behaves more aggressively and carries a significantly worse prognosis in regard to response to chemotherapy and overall survival.

Although non-endometrioid histologies, such as uterine serous cancer and clear cell, constitute < 10% of all cases of endometrial cancer, they account for a disproportionately high number of cancer-related deaths and cases of recurrence.[61-66] The poor prognosis associated with serous tumors, in particular, may be due to their advanced disease at the time of diagnosis.[64]

In addition to isolated vaginal recurrences, patients may present with disease isolated to the pelvis, which is considered a loco-regional recurrence. For these patients, treatment is similar to the management of metastatic disease.

Survival rates for women whose disease recurs outside of the pelvis are dramatically lower than those for women with a local, vaginal relapse. In fact, they are comparable to those of women with distant disease.[67]

For women with metastatic disease, the predominant modality of treatment is systemic therapy with either endocrine therapy or chemotherapy. However, the prognosis for these patients is poor. Cytotoxic chemotherapy has activity in endometrial cancer with response rates ranging from 7 to 25%. See Table 8 (Appendix 3)[68-83].

There is no single optimal treatment regimen. Rather, one must consider the patient's performance status and prior treatment history.

1.1.2 Selinexor

1.1.2.1 Mechanism of Action

Exportin-1 (XPO1, also called chromosomal region maintenance protein 1 [CRM1]) is a nuclear export protein that transports tumor suppressor proteins (TSPs) out of the nucleus, leading to their inactivation. XPO1 is overexpressed 2-4 fold in all cancers studied to date and overexpression is frequently correlated with poor prognosis and/or reduced survival, suggesting that XPO1 could have a direct role in the etiology of the malignant phenotype.

Selinexor (KPT-330) is a first-in-class Selective Inhibitor of XPO1-mediated Nuclear Export (SINE) compound that binds and inactivates XPO1. XPO1 inhibitors, including selinexor, have been shown to block the nuclear export of key TSPs (e.g., p53, IkB, FOXO and p21) into the cytoplasm, leading to their accumulation in the nucleus, as nuclear import proceeds unimpeded. Moreover, nuclear retention appears to prevent proteasome-mediated degradation (which is typically cytoplasmic) of these TSPs. Forced nuclear retention of TSPs leads to activation of their tumor suppressing functions and can counteract a multitude of oncogenic (and inflammatory) pathways that perpetuate the neoplastic phenotype. Forcing nuclear retention of proteins such as survivin[84] and $p21^{CIP}$[185] that can be anti-apoptotic when present in the cytoplasm can prevent their anti-apoptotic functions and, for p21, expose its antitumor activities.

In addition, XPO1 inhibition prevents the eIF4e-mediated messenger ribonucleic acid (mRNA) nuclear export of proteins with short half-lives, leading to down regulation of multiple oncogenic proteins including FLT3, c-KIT, cyclin D1, and c-MYC, further providing anticancer activity.

Inhibition of XPO1 activity by selinexor also reduces deoxyribonucleic acid (DNA) damage repair, enhancing the effect of DNA damaging agents (e.g., X-rays and alkylating agents) on cancer cells and promoting apoptosis[86,87].

More information about the mechanism of action, pharmacology, nonclinical, and ongoing clinical studies for selinexor are available in the *Selinexor/KPT-330 Investigator's Brochure (IB).*

1.1.2.2 Clinical Experience

1.1.2.2.1 Overview

Selinexor is currently in clinical development and has not been approved by any regulatory authority for commercial use.

Phase 1 and 2 studies with oral selinexor are being conducted in patients with advanced hematological malignancies and solid tumors (multiple indications for each). As of 01 June 2016, more than 1500 patients have received selinexor in Karyopharm Therapeutics Inc. (Karyopharm)-sponsored clinical studies, most with single-agent selinexor. (Additional patients have been treated in investigator-sponsored studies.) Based on preliminary, interim, unaudited safety for 1175 patients from Karyopharm-sponsored studies as of 31 May 2016, selinexor has been relatively well tolerated, with the most frequently reported treatment-emergent adverse events (TEAEs) being low-grade nausea, fatigue, anorexia, vomiting, and thrombocytopenia that were generally manageable with standard supportive care[88]. (Additional information is provided in the *Selinexor/KPT-330 IB*.) Selinexor treatment is not associated with significant major organ toxicity. Moreover, clinically-relevant cumulative toxicities have not been observed during long-term treatment, with more than 15 patients remaining on selinexor therapy for > 1 year, with the longest for > 2 years.

1.1.2.2.2 Potential Risks of Selinexor

Since selinexor is still being evaluated in ongoing clinical studies, the full safety profile for selinexor is not defined. A summary of safety results reported as of 31 May 2015 is provided in the *Selinexor/KPT-330 IB*.

In ongoing clinical studies, the most common AEs suspected to be related to selinexor (incidences in parentheses) have been low-grade nausea (55%), fatigue (54%), anorexia (43%), vomiting (35%), and mild/moderate thrombocytopenia (30%). Most of these effects can be managed effectively with dose modification and/or supportive care initiated prior to first dosing.

In a previous study, one patient who had been, heavily pre-treated for recurrent pancreatic cancer, developed acute cerebellar syndrome following 3 doses of selinexor at 85 mg/m^2 body surface area (BSA) twice weekly. The patient experienced abnormal speech, loss of coordination, and was unable to walk. Since the date of the initial reported event, this patient is recovering, with both speech and mobility recovered to near baseline over ~6 weeks. No other patients have reported similar symptoms to date.

Low-grade blurred vision was reported in 12% of patients treated with selinexor. In patients without pre-existing cataracts, blurred vision was not associated with objective findings of lens opacity (or other abnormalities) on expert ophthalmic examination. The cases have generally been self-limiting without progression, even when selinexor dosing was continued.

Overall, increased rates of infection associated with selinexor have not been reported, however greater incidences of sepsis were seen with selinexor versus physician's choice in patients with relapsed/refractory acute myeloid leukemia (AML) who were > 60 years of age and receiving higher doses of selinexor (most patients were receiving 100 mg) in

study KCP-330-008. This increased rate of sepsis has not been observed in any other studies conducted with selinexor to date.

Please refer to the *Selinexor/KPT-330 IB* for the most current safety information.

1.1.2.2.3 Reproductive Risks of Selinexor

Macroscopic and microscopic changes in reproductive organs were noted during rat and monkey toxicology studies, most of which partially or fully resolved during the recovery period. The long-term effects of these changes on reproductive potential are unknown. Secondary developmental effects due to reduced maternal body weights were also noted during a study on rat embryo/fetal development. It is unknown whether similar effects may occur in humans. As it is unknown whether selinexor might have reproductive toxicity in humans, patients must agree to use effective contraception (see Prevention of Pregnancy, Section 6.4.1.1) during the study and for 3 months after the end of treatment. Please refer to the *Selinexor/KPT-330 IB* for additional information.

1.2 Rationale

Selinexor is being evaluated in both hematologic and solid tumor indications as a chronic therapy with single agent antitumor activity. Clear evidence of antitumor activity has been demonstrated in Phase 1 trials. In particular, disease stabilization and tumor shrinkage has been observed in endometrial stromal tumors, Ewing's sarcoma, colon cancers, squamous cell cancers of the cervix and thymus, and cervical adenocarcinomas, as well as in multiple types of hematologic malignancies.

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1.2.1 XPO1 and Selinexor in Gynaecological cancer

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1.3 Study Rationale

Selinexor has demonstrated potent anti-cancer activity in models (in vitro and in vivo) hematologic and solid cancers including ovarian, endometrial and cervical cancers (see *Selinexor/KPT-330 IB*).

In an ongoing Phase 1 dose escalation study in patients with advanced solid tumors (KCP-330-002), a selinexor dose of 50 mg/m^2 twice weekly was tolerated and cleared DLT evaluation. Based on the Phase 1 results, the original doses and schedules for selinexor were chosen for the current study. During the conduct of the study, as a result of new findings regarding selinexor tolerability, and regulatory authority interactions regarding the overall selinexor development program, the recommended doses and schedules in Part 2 were revised to 35 mg/m² twice weekly or 50 mg/m^2 once weekly (depending on the patient population).

In KCP-330-002, selinexor has induced > 16-week disease control in several patients with R/R gynaecologic tumors. Patients with cervical adeno- and squamous carcinomas had stable disease for ≥ 6 cycles (24 weeks). Of six ovarian cancer patients treated to date, one has a 28% tumor reduction, another has stable disease with slight reduction in CA-125 levels, and a third has stable disease on first computed tomography (CT) scan. This data further supports the development of KPT-330 for the therapy of gynaecological cancers.

Ovarian, endometrial, and cervical cancers are sensitive to anti-neoplastic chemotherapy. Despite this fact, the majority of women with advanced ovarian, cervical and endometrial cancer will ultimately relapse. Altogether, in all three types of gynaecologic malignancies, the treatment of patients with advanced or relapsed disease remains difficult. Thus, new therapy options for women with these diseases are urgently needed.

In the current ongoing study, selinexor has shown promising results. An interim analysis of 12-week DCR data at the end of Stage 1 IA in evaluable patients (as of 29 April 2015) reported:

- 6 out of 8 patients for Cohort A (75%) (95% CI, 34.9 – 96.8)
- 5 out of 8 patients for Cohort B (62.5%) (95% CI, 24.5 – 91.5)
- 2 out of 8 patients for Cohort C (25%) (95% CI, 3.2 – 65.1)

1.4 Rationale for the Maintenance Phase (Continued Access to Treatment following termination of Primary Treatment Phase)

As of July 2016, 3 patients remain on treatment in the study, with additional patients in long-term survival follow-up. As of Version 3.2 of the protocol, Karyopharm will terminate the Primary Treatment Phase of the study and the existing patients will transfer to the Maintenance Phase of the study to continue treatment with selinexor and/or survival follow-up. These patients will be assessed primarily for safety. See Section 18 (Appendix 16) for objectives and treatment plan (including study treatment, schedule of assessments, dose modifications, and supportive care) for the Maintenance Phase of the study. The database for the Primary Treatment Phase will be reviewed and locked for analysis and the subjects in the Maintenance Phase will have their data entered into a separate database designed to collect data for extended treatment.

2 OBJECTIVES OF THE STUDY

2.1 Primary Treatment Phase

2.1.1 Objective

The primary objective is to determine the efficacy of selinexor in patients with advanced or metastatic gynaecological cancers by assessing DCR.

2.1.2 Secondary Objectives

- Determine the efficacy of selinexor in patients with advanced or metastatic gynaecological cancers by
  - Objective response rate (ORR)
  - Progression-free survival (PFS)
  - Overall Survival (OS), including OS rates at 12 and 24 months
- Evaluate safety and tolerability of selinexor in patients with advanced or metastatic gynaecological cancers.
- Evaluate Quality of Life (QoL) for patients with advanced or metastatic gynaecological cancers who are treated with selinexor.

2.1.3 Exploratory Objectives

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[redacted]

2.2 Maintenance Phase

See Section 18 (Appendix 16) for the objectives for the Maintenance Phase of the study for patients who continue treatment with selinexor and/or survival follow-up under version ≥3.2 of the protocol.

3 INVESTIGATIONAL PLAN

3.1 Overview of Study Design and Dosing Regimen

This trial has been designed as a multi-center, open-label, Simon two-stage, Phase 2 study with 3 parallel gynaecological cancer cohorts, with an additional set of patients in the ovarian cohort randomized into two different dosing regimens. This study will include a Primary Treatment Phase and a Maintenance Phase.

Primary Treatment Phase

Patients are informed, screened and enrolled in the study after PD on prior chemotherapy documented by CT/ MRI. Selinexor treatment should be started within two weeks after enrollment.

The cohorts to be enrolled in Parts 1 and 2 are:

- Part 1 – Three parallel cohorts of patients with ovarian (Cohort A), endometrial (Cohort B), or cervical (Cohort C) carcinoma will be enrolled.
- Part 2 - Based on the observed tolerability and efficacy profile in the ongoing ovarian cohort (Cohort A), two additional treatment schedules will be explored to optimize the dosing schedule in patients with ovarian carcinoma.

Clinical and radiological examinations for disease status as well as QoL assessments will be performed at baseline, after 6 and 12 weeks of treatment, and approximately every 8 weeks thereafter.

Treatment will continue until PD or unacceptable toxicity, death, withdrawal of consent by the patient, or patient discontinuation due to non-compliance with protocol requirements.

Safety assessments will be performed at the baseline visit and during each cycle through the EoT visit.

If a patient discontinues treatment due to any reason other than PD, death, or withdrawal of informed consent, the disease evaluations shall continue until PD. This includes patients who wish to discontinue treatment, but agree to have further data captured for the purpose of the study.

After treatment discontinuation, a call will be made to the patient (or the patient's family) approximately every 3 months to inquire about the patient's survival status.

Maintenance Phase (Continued Access to Treatment and Survival Follow-up Following Termination of the Primary Treatment Phase)

See Section 18 (Appendix 16) for a description of the investigational plan (including the schedule of assessments) for the Maintenance Phase of the study (protocol version ≥3.2).

3.1.1 Definition of Treatment Cycle and Duration

Each cycle is 28 days (4 weeks) long. In twice-weekly dose schedules (i.e., Part 1 and Part 2, Schedule 1), 8 doses of selinexor will be administered per cycle. In the once-weekly dose schedule (i.e., Part 2 Schedule 2), 4 doses of selinexor will be administered per cycle. Twice-weekly doses of selinexor must be administered at least 36 hours apart; once weekly doses of selinexor must be administered at least 5 days apart.

Dose escalations and reductions/interruptions are permitted according to safety guidelines in this protocol or in consultation with a sponsor representative (see Section 6.3).

Dose schedules in Parts 1 and 2 are as follows:

- Part 1: Patients will receive oral selinexor 50 mg/m² twice weekly (e.g., Monday and Wednesday, Tuesday and Thursday, Wednesday and Friday or Thursday and Saturday) in each week of a 4-week cycle.

- Part 2:
  - *Schedule 1* – Patients will receive oral selinexor 35 mg/m² twice weekly (e.g., Monday and Wednesday, Tuesday and Thursday, Wednesday and Friday or Thursday and Saturday) in each week of a 4-week cycle.
  - *Schedule 2* – Patients will receive oral selinexor 50 mg/m² once weekly in each week of a 4-week cycle (e.g., Monday of each week).

3.2 Registration of Patients

Patients to be enrolled are as follows:

- Part 1: As described in Section 8.2, approximately 21 evaluable patients will be enrolled in each cohort (Cohorts A, B, and C).
- Part 2: Approximately 32 additional patients (16 per schedule) with ovarian cancer will be enrolled in Cohort A. Each patient enrolled into this part of the study will be randomized into two treatment groups (Schedule 1 and Schedule 2) using centralized randomization via an interactive web-response system (IWRS). Randomization will be performed within the ovarian cohort and will not be specific to the study site.

Study drug administration may be delayed for toxicity as described in Section 6.3.

Patient eligibility will be confirmed by GSO once all screening procedures are completed. There will be no exceptions. Any questions should be addressed to GSO prior to registration. The eligibility check form/ Patient Registration Form will be sent from the site to GSO either by fax or email for evaluation. Upon confirmation of eligibility, GSO will assign a patient number and return the signed eligibility check form/ Patient Registration Form via fax or email to the site. The Patient Registration Form will confirm the treatment arm in which the patient will participate.

GSO
Fax: 0049-40-44 19 54 78
UMS Fax: 0049- 32 12 14 88 842
Email: sign@gso-hamburg.com

3.2.1 Treatment Phase

Treatment will be continued until PD is demonstrated by CT/MRI, unacceptable toxicities occur in individual patients, death, consent is withdrawn, or discontinuation due to non-compliance by the patient. Details of the study schedule are illustrated in the Table 1.

3.2.2 End of Treatment Visit

Patients that discontinue from treatment will undergo an EoT visit, regardless of the reason of discontinuation, 30 days (± 7 days) after the last dose of study medication.

3.2.3 Follow-Up Phase

Investigators should continue to collect survival data for patients after PD unless the patient withdraws consent to participate in the study.

After treatment discontinuation, a call will be made to the patient (or the patient's family) approximately every 3 months to inquire about the patient's survival status. If the patient has died, the patient's date of death will be collected, together with the reason for death, if possible.

3.3 Study Duration

Patients will be followed as outlined in Section 3.2 until the End of Study (EoS). End of study will be defined as 30 days after the last patient has PD, an unacceptable toxicity, withdrawn consent or died.

4 SELECTION OF THE STUDY POPULATION

4.1 Target Population

Three cohorts of patients will be enrolled in parallel:

- Cohort A: patients with ovarian, fallopian tube, or peritoneal carcinoma who are platinum refractory or platinum resistant and have received at least one line of chemotherapy for relapsed disease will be enrolled. (Part 1 and Part 2)
- Cohort B: patients with endometrial carcinoma who have received at least one line of chemotherapy for relapsed or advanced (stage IVb, IIIc) disease will be enrolled. (Part 1)
- Cohort C: patients with cervical carcinoma who have received at least one line of chemotherapy for relapsed or advanced (stage IV) disease will be enrolled. (Part 1)

Progression of disease (PD) on prior treatment must be documented by CT/MRI. Baseline tumor assessment must have taken place within 4 weeks prior to start of treatment. Under no circumstances are patients, who were previously enrolled in this study, permitted to re-enroll.

4.2 Eligibility Criteria

4.2.1 Inclusion criteria

To be eligible for enrollment, patients must fulfill the following criteria:

1. Female patients aged ≥18 years
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
3. Adequate hematologic function defined as:
   - platelets ≥ 125 x 10^9/L
   - hemoglobin ≥ 5.59 mmol/L or 9 g/dL
   - ANC ≥ 1.5 x 10^9/L
   - WBC ≥ 3.0 x 10^9/L
   - Up to 5% deviation is tolerated. Transfusions and growth factors are allowed.
4. Adequate liver function defined as adequate hepatic function within 14 days prior to Cycle 1 Day 1: total bilirubin < 2 times the upper limit of normal (ULN) (except patients with Gilbert's syndrome, who must have a total bilirubin of < 3 times ULN), aspartate aminotransferase (AST) < 2.0 times ULN, and alanine aminotransferase (ALT) < 2.0 times ULN. In the case of known (radiologically and/or biopsy- documented) liver metastasis, AST < 5.0 times ULN and ALT < 5.0 times ULN is acceptable. Up to 10% deviation is acceptable.
5. Renal function defined as a calculated or measured glomerular filtration rate ≥ 30 mL/min.
6. The patient has recovered to Grade ≤ 1 by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (NCI-CTCAE v4.03) from the effects of recent surgery, radiotherapy, chemotherapy, hormonal therapy, or other targeted therapies, with the exception of alopecia. The exceptions for such effects are allowed lab values of ≤ Grade 2 specified elsewhere in these inclusion criteria.
7. Life expectancy of at least 12 weeks.

8. Able to swallow and retain oral medication.
9. Patients must give informed consent according to the rules and regulations of the individual participating sites.
10. Negative serum pregnancy test in women of childbearing potential within 14 days of first dose of treatment, and patients of childbearing potential must agree to use effective contraception during treatment up to 3 months from last dose. Fertile male partners must be willing and able to use effective non-hormonal means of contraception (barrier method of contraception in conjunction with spermicidal jelly, or surgical sterilization) during and for at least 6 months post-study treatment.
11. The patient must be recovered from any prior treatment/major operation. The treatment/major operation must be performed at least 4 weeks prior to start of study drug. Palliative radiotherapy is permitted until one week prior to the start of study drug.
12. Only incurable patients with histologically or cytologically proven primary tumor and objective documentation of disease progression on prior treatment by CT/MRI may be enrolled.
13. *Ovarian, fallopian tube, or peritoneal carcinoma:* both platinum refractory* and platinum resistant** patients, who have received ≥1 line of chemotherapy for relapsed disease (i.e., ≥ 2 lines of chemotherapy in total).
    * Platinum refractory is defined as progression during or within 4 weeks of last treatment with a platinum-containing therapy.
    ** Platinum resistant is defined as relapse 4 weeks to < 6 months after a platinum-containing therapy.
14. *Endometrial carcinoma:* patients must have received ≥ 1 line of chemotherapy for relapsed or advanced (stage IV, IIIc) disease.
15. *Cervical carcinoma:* patients must have received ≥ 1 line of chemotherapy for relapsed or advanced (stage IVb) disease.
16. Carcinosarcomas (Malignant Mixed Mullerian Tumor) are allowed, but all other non-epithelial cancers of the ovary, fallopian tube, endometrium, or cervix are excluded.
17. Patients must have either measurable disease per RECIST 1.1 or evaluable disease outside irradiated field on CT/MRI. For *ovarian cancer*: Patients must have disease that is measurable according to RECIST or assessable according to the GCIG CA-125 criterion. A rise in CA-125 or other tumor marker alone is not sufficient.

4.2.2 Exclusion criteria

Patients who meet any of the following exclusion criteria will not be eligible for the study:

Patients with any of the following will not be eligible for participation:

1. Disease-Specific Exclusions:
   - Evidence of complete or partial bowel obstruction.
   - Need of Total Parenteral Nutrition.
2. Patients who are pregnant or breast feeding.
3. Radiation (except planned or on-going palliative radiation to bone outside of the region of measurable disease) ≤ 3 weeks prior to Cycle 1 Day 1.
4. Chemotherapy, endocrine therapy, immunotherapy or any other systemic anti-cancer therapy (including investigational anti-cancer therapy) ≤ 3 weeks prior to Cycle 1 Day 1.
5. Diagnosis or recurrence of invasive cancer other than the present cancer within

3 years (except basal or squamous cell carcinoma of the skin that has been definitively treated).

6. Unstable cardiovascular function:
    - Symptomatic ischemia, or
    - Uncontrolled clinically significant conduction abnormalities (e.g. ventricular tachycardia on anti-arrhythmics are excluded and 1st degree AV block or asymptomatic LAFB/ RBBB will not be excluded), or
    - Congestive heart failure (CHF) of NYHA Class ≥ 3, or myocardial infarction (MI) within 3 months of Cycle 1 Day 1.
7. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to the first dose. Active infection with concurrent treatment is acceptable only if the patient is clinically stable.
8. Significantly diseased or obstructed gastrointestinal tract or uncontrolled vomiting or diarrhea.
9. Concurrent therapy with approved or investigational anti-cancer therapeutics.
10. Medical, psychological, or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.
11. Known brain metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and glucocorticoids.
12. All non-epithelial cancers of the ovary, fallopian tube, peritoneum, endometrium or cervix as well as neuro-endocrine tumors are excluded.

5 SCHEDULE OF ASSESSMENT AND PROCEDURES

5.1 Primary Treatment Phase Study Assessments

5.1.1 Tumor Assessments

Objective response will be evaluated based on RECIST v. 1.1 using CT or MRI[101]. For patients with multiple measurable lesions, up to 5 lesions in total and 2 lesions per organ should be identified.

The imaging modality (i.e., either CT or MRI) used for measurement of lesions will be left to the discretion of the Investigator, however, for each patient the same technique must be used throughout the study, assessed whenever possible by the same person.

The CT/MRI scan of the abdomen must include the pelvis. A PET-CT is allowed for all patients, but ultrasound and x-ray of thorax for patients with is not sufficient for protocol requirements. If optional PET-CT scan is employed at baseline and first evaluation, standardized uptake value (SUV) should be reported for each of the target lesions determined in the assessment according to RECIST v.1.1 and for any new lesions.

All lesions identified at screening must be assessed at each scheduled tumor measurement. Patients with measurable lesions will be eligible for inclusion. Measurable lesions must have at least one diameter of 10 mm by CT scan (CT slice thickness no greater than 5 mm. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness). Where there are several lesions, assessment is based on the sum of the longest diameters of the individual target lesions. Lymph nodes with a short axis of $\geq$ 15 mm are considered measurable and assessable as target lesions. The short axis measurement should be included in the sum of lesions in calculation of tumor response. Nodes that shrink to < 10 mm short axis are considered normal. All other pathological nodes (those with short axis $\geq$ 10 mm but < 15 mm) should be considered as non-target lesions.

A CT/MRI scan must be performed if there is clinical suspicion of relapse in order to document PD; in cases where there is suspicion of PD before the next scheduled assessment, an unscheduled tumor assessment should be performed.

If a detected increase in tumor size is below the resolution limit of the CT/MRI scanner, it is acceptable to continue with treatment until a second assessment at a later time point unequivocally confirms PD. Partial response (PR) requires confirmation with a follow-up scan at least 4 weeks apart.

The following are defined as non-target lesions: bone lesions, leptomeningeal disease, pleural/ pericardial effusion, ascites, inflammatory breast disease, lymphangitis, cystic lesions and lesions not measurable by CT/MRI. All non-target lesions are described over time and need not be measured.

The tumor assessment for inclusion must be recorded and measured within 28 days prior to treatment start.

A first evaluation of disease status by imaging will be done after 6 weeks of treatment. The second tumor assessment will be performed after 12 weeks. Thereafter, tumor assessments will be performed every 8 weeks during treatment, independent of cycle delays.

Patients will also be eligible for the study if their disease is evaluable outside irradiated field on CT/MRI.

CA-125 will be measured for patients with ovarian cancer. A rise in CA-125 alone is not sufficient for inclusion of patients in Cohort A.

In case palliative radiation becomes necessary during the treatment within the study, there must be at least two target lesions left outside the irradiated filed for continuous assessment for response.

5.1.2 Exploratory Assessments

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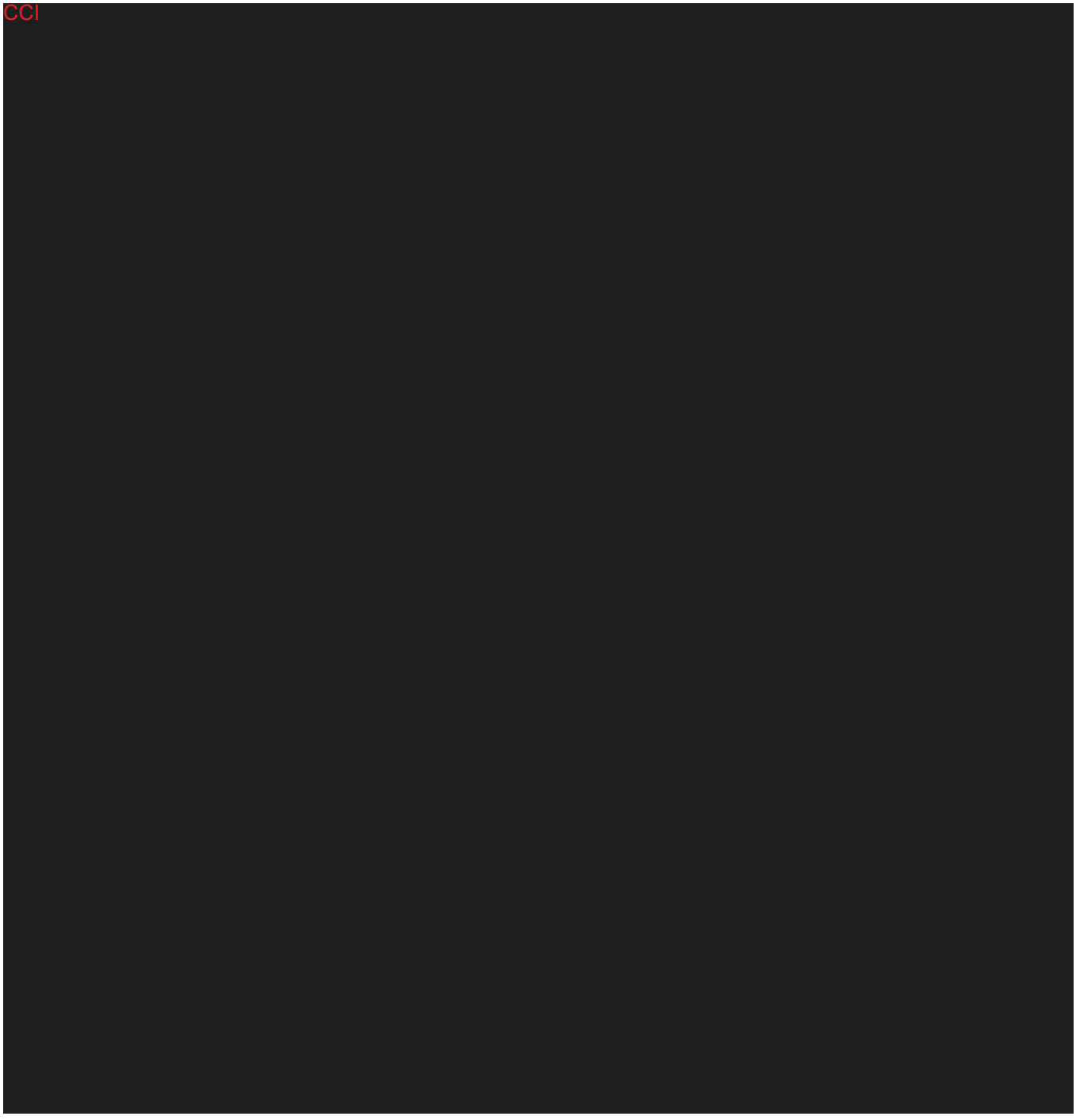

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5.1.3 Safety Assessments

Throughout the treatment period until 30 days (± 7 days) after the last dose of study medication, safety will be assessed per CTCAE v.4.03 (see Appendix 8). If necessary, a patient may be withdrawn from the study treatment.

- *Medical history* including baseline symptoms as well as a detailed history of the patient's disease, prior cancer therapies (including start and stop dates), PD during or after prior therapy, as well as discontinuations due to intolerability.
- *Concomitant medications* will be documented throughout the treatment phase until the EOT visit.
- *Adverse events* (see also Section 7.1.1): All patients will be closely monitored for SAEs from the signing of the ICF and for AEs from the start of treatment, i.e., Cycle 1 Day 1, until 30 days (± 7 days) after the last dose of study medication. Adverse events for which the relationship to test drug is considered to be "not related" should be followed up until they have returned to baseline status or stabilized. Adverse events will be recorded at each visit.

5.1.4 Laboratory Assessments

Blood samples will be collected as noted in Table 1 and will include the analytes listed below; samples may be collected up to 3 days prior to a visit and may be repeated if clinically indicated.

- *Hematology*: hemoglobin, white blood cell (WBC) count, neutrophils, and platelets.
- *Clinical chemistry*: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphate, magnesium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), total protein, and albumin.

- *Urinalysis*: urine bilirubin, glucose, hemoglobin, ketones, pH, and protein.
- *Coagulation test*: prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT).
- *CA-125* (Ovarian cancer patients only)

5.2 Maintenance Phase (Continued Access to Treatment and Survival Follow-up following Termination of the Primary Treatment Phase)

See Section 18 (Appendix 16) for a description of the investigational plan (including the schedule of assessments) for the Maintenance Phase of the study (protocol version ≥3.2).

5.3 Primary Treatment Phase Study Procedures

5.3.1 Baseline

All patients will be screened and baseline procedures performed within 14 days prior to the start of treatment on Cycle 1 Day 1, unless specified otherwise below:

Procedure	Notes
Signed written informed consent	Obtained prior to any study-specific assessments
Demographics and medical history	• Age, gender, ethnic background • Details on tumor diagnosis • Details on prior cancer therapy, including start and stop dates, disease progression during or after therapy, as well as discontinuation due to toxicities • Previous and concurrent relevant diseases • Current symptoms and/or residual toxicities from prior therapies
Pregnancy test (if applicable)	A serum pregnancy test will be performed in pre-menopausal women and women who are post-menopausal for < 2 years. In case the sampling date for the serum pregnancy test exceeds 7 days before treatment start, a urine test is required for confirmation.
Physical examination and vital signs	• Body height and weight • BSA • Blood pressure, pulse, temperature • Pulse oximetry • Physical examination
ECOG performance status	Please refer to Appendix 6
Standard clinical neurological examination	A neurological exam will be performed to assess motor, sensory and balance functions.
Ophthalmic exam	An ophthalmic examination by an optometrist or ophthalmologist is required at screening and if clinically indicated during the study (e.g., monitoring of pre-existing cataracts, visual disturbances). *Please note:* patients enrolled under a prior version of the protocol who had detectable cataracts graded according to the LOCS III will continue to have their cataracts graded according to LOCS III and will not

	switch to American Optometric Association (AOA) Grade 1-4 cataract scale. For new patients or patients for whom no cataracts have been detected to date, if cataracts are detected, they will be graded according to the AOA scale.
Gynaecological examination	A gynaecological examination will be performed.
Cardiac evaluation	12-lead ECG
Calculation (or measurement) of GFR	Please refer to Appendix 7
Urinalysis	Urine bilirubin, glucose, hemoglobin, ketones, pH, protein
Hematology	Hemoglobin, white blood cell (WBC) count, neutrophils, and platelets
Clinical chemistry	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, and LDH
Coagulation tests	prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT)
Tumor marker (ovarian cancer patients only)	Ovarian cancer patients only: CA-125 (see Appendix 12)
CCI	
Assessment of disease status (Day -28 to 0)	Disease status will be measured by CT/MRI or optional PET-CT evaluated according to RECIST v1.1 criteria (see Section 5.1.2)
QoL	EORTC QLQ-C30
SAEs	Assessed on an ongoing basis
Concomitant medication	Concomitant medication currently used
Required supportive care	Initiated prior to first selinexor dose (see Section 6.5.1).

5.3.2 Treatment Phase

During the treatment phase, the following assessments are to be performed according to the study schedule of assessments within the allowed visit windows:

Procedure	**Notes**
Physical examination and vital signs	• Body weight • BSA • Blood pressure, pulse, temperature • Physical examination (symptom directed)
ECOG performance status	Please refer to Appendix 6
Hematology	Hemoglobin, white blood cell (WBC) count, neutrophils, and platelets
Clinical chemistry	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, and LDH.

Tumor marker (ovarian cancer patients only, every 4 weeks)	Ovarian cancer patients only: CA-125 (see Appendix 12)
CCI CCI	
QoL	EORTC QLQ-C30 (disease specific)
Gynaecological examination	A full gynaecological examination will be performed
Assessment of disease status	CT/MRI scans will be obtained. Optional PET-CT may be obtained. (see Section 5.1.1)
AEs and concomitant medication	Assessed on an ongoing basis
Required supportive care	Received prior to selinexor dose (see Section 6.5.1).
Selinexor dosing	See Section 6.2.2

5.3.3 End of Treatment

Patients who discontinue therapy for any reason must have an End of Treatment (EOT) visit completed 30 days (± 7 days) after the last administration of study drug.

At the EOT visit, the patients will undergo the following assessments:

Procedure	**Notes**
Physical examination and vital signs	• Body weight • Blood pressure, pulse, temperature • Physical examination • Pulse oximetry
ECOG performance status	Please refer to Appendix 6
Gynaecological examination	A gynaecological examination will be performed.
Cardiac evaluation	12-lead ECG
Urinalysis	Urine bilirubin, glucose, hemoglobin, ketones, pH, protein
Hematology	Hemoglobin, WBC count, neutrophils, and platelets
Clinical chemistry	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, and LDH
QoL	EORTC QLQ-C30 and the disease specific indications
AEs and concomitant medication	Assessed on an ongoing basis

5.3.4 Follow-Up

Investigators should continue to collect survival data for patients after progression of disease unless patient withdraws consent to participate in the study.

After treatment discontinuation, a call will be made to the patient (or the patient's family) approximately every 3 months to inquire about the patient's survival status. If the patient has died, the patient's date of death will be collected, together with the reason for death, if possible.

5.3.5 End of Study

The primary statistical analysis will be performed after all patients have discontinued treatment with study medication.

5.4 Planned Treatment of the Patient after End of Treatment Phase

After receiving their final dose of study drug, patients will generally be treated at the discretion of the Investigator according to medical routine.

5.5 Removal of Patients from Treatment

Patients will be free to discontinue treatment or withdraw from the study at any time, for any reason, or they may be withdrawn/ removed, if necessary, in order to protect their health (see reasons for withdrawal below). It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable, therefore unnecessary withdrawal of patients should be avoided. Patients who are withdrawn from the study will not be replaced.

Patients will be removed from further treatment for the following reasons:

- Disease progression (PD)
- Adverse event (unacceptable toxicity)
- Non-compliance
- Need of treatment with medications not allowed by the study protocol
- Patient no longer consents to participate in the study
- Intercurrent illness that interferes with study assessments
- Incidence or severity of AEs in this study indicates a potential health hazard to the patient
- Investigator discretion
- Pregnancy
- Termination of the study by the Sponsor

If there is a medical reason for withdrawal of treatment, the patient will remain under the supervision of the Investigator until AEs (if relevant) have resolved or declined to baseline values.

If a patient fails to attend scheduled assessments or withdraws consent to participate in the study, every effort will be made to determine the reasons and circumstances as completely and accurately as possible.

When a patient discontinues study treatment, the EoT visit should be performed, if possible. The eCRF section entitled “End of Treatment” must be completed in all cases. If the reason for removal of a patient from the study is an AE or abnormal laboratory test result, the principal specific event or test will be recorded on the eCRF.

If a patient is discontinued from study treatment, the patient should still be followed for PD and survival. If a patient withdraws consent for further participation in the study, follow-up assessments will be discontinued.

5.6 Study Discontinuation

The study may be discontinued at the sole discretion of the Sponsor for any reason, including medical or ethical reasons affecting the continued performance of the study, or difficulties in the recruitment of patients. Medical reasons may include, but are not limited to, such features as deemed by the Safety Monitoring Committee (SMC) to constitute an unacceptable risk to the patients in the study, such as lack of efficacy or SAEs, such as Grade 4 anorexia and fatigue unresponsive to medical treatment.

The sponsor (Karyopharm), in conjunction with appropriate regulatory authorities, will determine if the trial should be modified or terminated. If this occurs, the sponsor will notify IRBs and Investigators.

5.7 Maintenance Phase (Continued Access to Treatment following Termination of the Primary Treatment Phase)

See Section 18 (Appendix 16) for a description of the investigational plan (including the schedule of assessments) for the Maintenance Phase of the study (protocol version ≥3.2).

6 INVESTIGATIONAL PRODUCT

6.1 Investigational medicinal product (IMP)

An investigational medicinal product (IMP) is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

The IMP in this study is selinexor (KPT-330).

The Investigator or other appropriate individual, who is designated by the local principal Investigator, should maintain records of the inventory at the site, the use for each patient and delivery, storage and destruction. Investigators should maintain records that adequately document that patients were provided the doses specified in the protocol and reconcile all investigational product(s) received from the sponsor.

6.2 Preparation and Administration of Selinexor

The Investigator or responsible site personnel must instruct the patient or caregiver to take the study drug as described in this protocol. Study drug will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Selinexor tablets, with instructions for administration, will be dispensed by study personnel on an outpatient basis.

Patients will be provided with an adequate supply of study drug for self-administration at home until at least their next scheduled study visit.

6.2.1 Drug Name, Formulation and Storage

Recommended INN:	Selinexor
Company´s Drug ID:	KPT-330
Chemical name:	(Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-1-yl)-*N*′-(pyrazin-2-yl)acrylohydrazide
Classification:	Cell biological modifier: Apoptosis-inducing agent
Mechanism of action:	Selinexor is a **S**elective **I**nhibitor of **N**uclear **E**xport/SINE compound that specifically blocks nuclear export by reversible covalent binding to XPO1 protein.
Molecular formula:	$C_{17}H_{11}F_6N_7O$
Molecular weight:	443.31
Approx. solubility:	< 0.03 mg/mL in water (pH 2-8)
	> 10 mg/mL in dimethylsulfoxide
	< 2 mg/mL in 40% v/v PEG-400/ H_2O
	< 2 mg/mL in 15% v/v EtOH/ H_2O

Tablets:

Selinexor (KPT-330) for oral administration will be supplied in up to three (3) tablet strengths: 10 mg, 20 mg, and 25 mg. Bulk bottles of 50 tablets per bottle will be supplied to the pharmacies for both the 10 mg and 25 mg strength tablets. The 20 mg tablets will be provided in blister packs when available.

Labeling:

Each bottle or blister pack of selinexor tablets will be labeled in accordance with current ICH guidelines and specific national requirements.

Storage:

10 mg and 25 mg Tablets

Selinexor tablets will be supplied in white high-density polyethylene (HDPE) bottles with induction seals and desiccant. They will be stored at ambient temperatures between 5–30 °C in a locked and secured area with restricted access to study staff. Do not freeze.

20 mg Tablets

Selinexor tablet blister packs can be stored at room temperature or refrigerated, at or below 86 ˚F or 30 ˚C, but not frozen. Room temperature storage is recommended. The study site will be required to maintain documentation of the temperature and/or temperature excisions where the study medication is stored.

6.2.2 Administration of Study Drug

The dose of selinexor to be administered will be determined, by patient, on a mg/m² basis, based on the patient's actual calculated body surface area (BSA) at baseline. Patients with a BSA > 2.5 m² will receive a dose based upon a 2.5 m² BSA.

Primary Treatment Phase

Dose Schedules in Parts 1 and 2:

- Part 1: Selinexor tablets will be dosed at 50 mg/m^2 orally twice weekly (e.g., Monday and Wednesday, Tuesday and Thursday, Wednesday and Friday or Thursday and Saturday) in each week of a 4-week cycle.
- Part 2:
  - *Schedule 1* – Selinexor tablets will be dosed orally at 35 mg/m² twice weekly (e.g., Monday and Wednesday, Tuesday and Thursday, Wednesday and Friday or Thursday and Saturday) in each week of a 4-week cycle.
  - *Schedule 2* - selinexor will be dosed orally at 50 mg/m² once weekly (e.g., Monday of each week) in each week of a 4-week cycle.

Once- and Twice-weekly Dose Schedules:

- Twice-weekly dose schedules (Part 1 and Part 2 Schedule 1): Eight (8) doses of selinexor will be administered, ≥ 36 hours apart, during each 28-day (4-week) cycle.
- Once-weekly dose schedules (Part 2 Schedule 2): Four (4) doses of selinexor will be administered, ≥ 5 days apart, in each 28-day (4-week) cycle.

Selinexor should be taken with a light meal (to optimize tolerability) together with 120 mL (4 ounces) of water.

Maintenance Phase: See Section 18 (Appendix 16) for study treatment during the Maintenance Phase of the study (Version ≥ 3.2).

6.2.3 Compliance

The Investigator should ensure that the investigational product is used only in accordance with the protocol. All doses given are to be documented in the eCRF, including exact dose, number of tablets, time and date administered. The principal Investigator or the designee will account for the number of tablets dispensed against those stored at the site. Any deviations and missed doses will be recorded in the eCRF and drug accountability logs for verification with the reasons for missed doses. The Investigator/ designee will try to ensure complete compliance with the dosing schedule by providing timely instructions to the patients. It will be requested from patients to document intake of selinexor in a patient diary.

The investigational product should be stored as specified by the sponsor and in accordance with applicable regulatory requirements.

6.3 Dose Modifications for Selinexor

See Section 18 (Appendix 16) for supportive care and dose modification recommendations during the Maintenance Phase of the study (Version ≥3.2).

Toxicity will be graded according to NCI CTCAE, v.4.03; the therapy modifications described below are applied according to this severity grading.

If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification.

Re-escalation of the study drug is only allowed as outlined in the sections that apply for the specific toxicity. If toxicity requires a treatment delay of more than 4 weeks the patient is taken off protocol treatment.

Each dose modification or treatment delay has to be documented in the eCR, including the respective reason.

Based on observations from the ongoing Phase 1 studies in patients with advanced hematological and solid tumors, selinexor (KPT-330) shows a wide therapeutic range, with documented anti-cancer activity from ~ 12 mg/m^2 to ≥ 50 mg/m^2 orally twice weekly. At the time of Part 1 it could not be predicted which patient's tumors would respond to lower doses, nor could tolerability be predicted. Therefore, in order to individualize and optimize therapeutic benefit with selinexor, initiation of study therapy occurred at a dose just below the MTD (50 mg/m^2 twice weekly by mouth). To optimize specific anti-tumor activity and the patient's tolerability, dose and/or schedule modifications were allowed. Based on preliminary findings from this study and other studies, the dosing in Part 2 was modified as follows: Part 2 Schedule 1 to 35 mg/m² twice weekly, Part 2 Schedule 1 to 50 mg/m^2 once weekly. Dose modifications are allowed as described in Table 2 and Table 3.

Patients should also be treated aggressively with supportive care to reduce toxicities.

Patients will continue to receive selinexor until they need to have their dose reduced below the 35 mg/m^2 once weekly (reduced) dose in Part 1 and Part 2 (Schedules 1 and 2), at which time treatment will be discontinued.

Table 2: Pre-specified Dose/Schedule Modifications for AEs Related to Study Drug in Part 1

Dose Level	Dose of Selinexor
Dose level 0	50 mg/m^2 twice weekly (D1, D3)
Dose level -1	35 mg/m^2 twice weekly (D1, D3)
Dose level -2	50 mg/m^2 once weekly (D1)
Dose level -3	35 mg/m^2 once weekly (D1)
Dose level -4	Discontinue dosing[a]

[a] Patient discontinues treatment, but continues to be assessed.

Table 3: Pre-specified Dose/Schedule Modifications for AEs Related to Study Drug in Part 2

Dose Level	Schedule 1	Schedule 2
Dose level 0 (Starting dose)	35 mg/m^2 twice weekly	50 mg/m^2 once weekly
Dose level -1	50 mg/m^2 once weekly	35 mg/m^2 once weekly
Dose level -2	35 mg/m^2 once weekly	Discontinue dosing[a]
Dose level -3	Discontinue dosing[a]	Not applicable

[a] Patient discontinues treatment, but continues to be assessed.

6.3.1 Intrapatient Dose Escalation:

Intrapatient dose escalation can be considered after 12 weeks for patients in Part 1 and after 6 weeks for patients in Part 2 if the patient has not experienced a major toxicity; this requires approval of the Sponsor. Intrapatient dose escalations will be permitted as follows:

Part 1: Dose increase to 60 mg/m^2 twice weekly in each week of a 4-week cycle.

Part 2 Schedule 1: Dose increase to 50 mg/m^2 twice weekly in each week of a 4-week cycle (8 doses total).

Part 2 Schedule 2: Dose increase to 60 mg/m^2 once weekly in each week of a 4-week cycle (4 doses total).

6.3.2 Dose Adjustment Guidelines for Selinexor-Related Toxicities

Table 4: Criteria for Dose Adjustments for Selinexor-related Toxicities

Toxicity and Intensity	Dose Modification		
	Part 1: 50 mg/m^2 twice weekly	**Part 2, Schedule 1: 35 mg/m^2 twice weekly – Ovarian only**	**Part 2, Schedule 2: 50 mg/m^2 once weekly – Ovarian only**
Fatigue (common)			
Grade 1	Ensure adequate caloric intake and assess volume status. Adjust other medications. Rule out other causes of fatigue such as electrolyte imbalance, hyperglycemia.	Ensure adequate caloric intake and assess volume status. Adjust other medications. Rule out other causes of fatigue such as electrolyte imbalance, hyperglycemia.	Ensure adequate caloric intake and assess volume status. Adjust other medications. Rule out other causes of fatigue such as electrolyte imbalance, hyperglycemia.
Grade 2	1. As in grade 1 2. Consider patient diary to evaluate fluid and food intake. 3. Add medroxyprogesterone acetate (MPA) (ovarian and cervical only) or 4 mg dexamethasone (or equivalent) on day after selinexor dosing. 4. In case of dehydration add IV fluids on the dosing day. 5. If fatigue does not resolve to grade 1 or baseline, reduce one dose level of selinexor 6. For additional support see NCCN guidelines[a].	1. As in grade 1 2. Consider patient diary to evaluate fluid and food intake. 3. Add MPA or 4 mg dexamethasone (or equivalent) on day after selinexor dosing. 4. In case of dehydration add IV fluids on the dosing day. 5. If fatigue does not resolve to grade 1 or baseline, reduce one dose level of selinexor 6. For additional support see NCCN guidelines[a].	1. As in grade 1 2. Consider patient diary to evaluate fluid and food intake. 3. Add MPA or 4 mg dexamethasone (or equivalent) 3 days post dosing of selinexor. 4. In case of dehydration add IV fluids on the dosing day. 5. If fatigue does not resolve to grade 1 or baseline, reduce one dose level of selinexor 6. For additional support see NCCN guidelines[a].
Grade 3 mm^3	As in grade 2; if symptoms not resolved within 7 days, interrupt selinexor dosing until symptoms return to grade 1 or baseline and restart treatment with one dose reduction of selinexor	As in grade 2; if symptoms not resolved within 7 days, interrupt selinexor dosing until symptoms return to grade 1 or baseline and restart treatment with one dose reduction of selinexor	As in grade 2; if symptoms not resolved within 7 days, interrupt selinexor dosing until symptoms return to grade 1 or baseline and restart treatment with one dose reduction of selinexor

Toxicity and Intensity	Dose Modification		
	Part 1: 50 mg/m^2 twice weekly	**Part 2, Schedule 1: 35 mg/m^2 twice weekly – Ovarian only**	**Part 2, Schedule 2: 50 mg/m^2 once weekly – Ovarian only**
Anorexia/Weight Loss (common)			
Grade 1	Ensure adequate caloric intake and assess volume status. Adjust other medications. Rule out other causes of anorexia/weight loss such as electrolyte imbalance, hyperglycemia	Ensure adequate caloric intake and assess volume status. Adjust other medications. Rule out other causes of anorexia/weight loss such as electrolyte imbalance, hyperglycemia	Ensure adequate caloric intake and assess volume status. Adjust other medications. Rule out other causes of anorexia/weight loss such as electrolyte imbalance, hyperglycemia
Grade 2	1. As grade 1 2. Consider patient diary to evaluate fluid and food intake. 3. Add MPA (ovarian and cervical only) or 4 mg dexamethasone (or equivalent) on day after selinexor dosing. 4. In case of dehydration add IV fluids on the dosing day. 5. If anorexia dose not resolve to Grade 1 or baseline, reduce one dose level of selinexor 6. For additional supportive care see NCCN guidelines[b]	1. As grade 1 2. Consider patient diary to evaluate fluid and food intake. 3. Add MPA or 4 mg dexamethasone (or equivalent) on day after selinexor dosing. 4. In case of dehydration add IV fluids on the dosing day. 5. If anorexia dose not resolve to Grade 1 or baseline, reduce one dose level of selinexor 6. For additional supportive care see NCCN guidelines[b]	1. As grade 1 2. Consider patient diary to evaluate fluid and food intake. 3. Add MPA or 4 mg dexamethasone (or equivalent) 3 days post dosing of selinexor. 4. In case of dehydration add IV fluids on the dosing day. 5. If anorexia dose not resolve to Grade 1 or baseline, reduce one dose level of selinexor 6. For additional supportive care see NCCN guidelines[b]
Grade ≥ 3 (Grade 4 for anorexia only)	1. As in grade 2 2. Add MPA (ovarian and cervical only) or megestrol acetate 3. If symptoms not resolved within 7 days, interrupt selinexor dosing until resolved to grade 1 or baseline and restart treatment with one dose reduction of selinexor	1. As in grade 2 2. Add MPA or megestrol acetate 3. If symptoms not resolved within 7 days, interrupt selinexor dosing until resolved to grade 1 or baseline and restart treatment with one dose reduction of selinexor	1. As in grade 2 2. Add MPA or megestrol acetate 3. If symptoms not resolved within 7 days, interrupt selinexor dosing until resolved to grade 1 or baseline and restart treatment with one dose reduction of selinexor
Nausea/Emesis (common)			
Grade 1	5-HT3 antagonists, D2 antagonists as needed. Consider adding 4 mg dexamethasone (or equivalent) on day after selinexor dosing.	5-HT3 antagonists, D2 antagonists as needed. Consider adding 4 mg dexamethasone (or equivalent) on day after selinexor dosing.	5-HT3 antagonists, D2 antagonists as needed. Consider adding 4 mg dexamethasone (or equivalent) on day after selinexor dosing.

Grade 2	Implement one or more combinations of anti-nausea medications. Next dose add neurokinin-1 receptor (NK1R) antagonist (e.g., aprepitant) prophylactic. If nausea does not resolve to Grade ≤ 1 or baseline, reduce one dose level of selinexor. Consider NK1R antagonist as prophylaxis next cycle. For additional options see NCCN guidelines for antiemesis.[c]	Implement one or more combinations of anti-nausea medications. Next dose add NK1R antagonist (e.g., aprepitant) prophylactic. If nausea does not resolve to Grade ≤ 1 or baseline, reduce one dose level of selinexor. Consider NK1R antagonist as prophylaxis next cycle. For additional options see NCCN guidelines for antiemesis.[c]	Implement one or more combinations of anti-nausea medications. Next dose add NK1R antagonist (e.g., aprepitant) prophylactic. If nausea does not resolve to Grade ≤ 1 or baseline, reduce one dose level of selinexor. Consider NK1R antagonist as prophylaxis next cycle. For additional options see NCCN guidelines for antiemesis.[c]
Grade ≥ 3 (Grade 4 for emesis only)	As in grade 2; if symptoms persist hold dose until nausea and vomiting resolve to grade 1 or baseline. Restart dose of selinexor, one dose below. Start NK1R antagonist as prophylaxis next cycle.	As in grade 2; if symptoms persist hold dose until nausea and vomiting resolve to grade 1 or baseline. Restart dose of selinexor, one dose below. Start NK1R antagonist as prophylaxis next cycle.	As in grade 2; if symptoms persist hold dose until nausea and vomiting resolved to grade 1 or baseline. Restart dose of selinexor, one dose below. Start NK1R antagonist as prophylaxis next cycle.
Hematologic			
Neutropenia			
Grade ≤ 3	1. Maintain dose level 2. The use of growth factors during selinexor treatment is permitted and in patients with poor marrow function, encouraged. If ANC drops to < 1000/mm^3, growth factors are encouraged to reduce dose interruptions.	1. Maintain dose level 2. The use of growth factors during selinexor treatment is permitted and in patients with poor marrow function, encouraged. If ANC drops to < 1000/mm^3, growth factors are encouraged to reduce dose interruptions.	1. Maintain dose level 2. The use of growth factors during selinexor treatment is permitted and in patients with poor marrow function, encouraged. If ANC drops to < 1000/mm^3, growth factors are encouraged to reduce dose interruptions.
Grade 4 (ANC < 500/mm^3)	1. Delay study treatment until ANC returns to > 800/mm^3, then: 2. If increased to > 800/mm^3 by ≤ 7 days after suspending selinexor, maintain dose level 3. If increased to > 800/mm^3 by > 7 days after suspending selinexor, then reduce one dose level. 4. The use of growth factors during selinexor treatment is encouraged.	1. Delay study treatment until ANC returns to > 800/mm3, then: 2. If increased to > 800/mm^3 by ≤ 7 days after suspending selinexor, maintain dose level 3. If increased to > 800/mm^3 by > 7 days after suspending selinexor, then reduce one dose level. 4. The use of growth factors during selinexor treatment is encouraged.	1. Delay study treatment until ANC returns to > 800/mm^3, then: 2. If increased to > 800/mm^3 by ≤ 7 days after suspending selinexor, maintain dose level 3. If increased to > 800/mm^3 by > 7 days after suspending selinexor, then reduce one dose level 4. The use of growth factors during selinexor treatment is encouraged.

Febrile neutropenia, or fever of unknown origin without clinically or microbiologically documented infection (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	1. Delay study treatment until patient has stabilized, then reduce selinexor one dose level. 2. Selinexor may be re-initiated at the reduced dose when patient's condition has stabilized following initiation of antibiotic therapy. 3. Selinexor dose may be re-escalated after ≥ 1 cycle at the reduced dose provided ANC is adequate.	1. Delay study treatment until patient has stabilized, then reduce selinexor one dose level. 2. Selinexor may be re-initiated at the reduced dose when patient's condition has stabilized following initiation of antibiotic therapy. 3. Selinexor dose may be re-escalated after ≥ 1 cycle at the reduced dose provided ANC is adequate.	1. Delay study treatment until patient has stabilized, then reduce selinexor one dose level. 2. Selinexor may be re-initiated at the reduced dose when patient's condition has stabilized following initiation of antibiotic therapy. 3. Selinexor dose may be re-escalated after ≥ 1 cycle at the reduced dose provided ANC is adequate.
Thrombocytopenia (Platelets)			
Grade ≤ 2	Maintain dose level	Maintain dose level	Maintain dose level
Grade ≥ 3 without bleeding	**First occurrence:** Delay selinexor treatment until resolved to ≤ grade 1 or baseline (max 4 weeks), and restart at 50 mg/m^2 once a week. Thrombocyte growth factors (e.g., romiplostim, eltrombopag, oprelvekin) are recommended. **Second occurrence:** Delay selinexor treatment until resolved to ≤ grade 1 or baseline (max 4 weeks), and restart 35 mg/m^2 once a week. Start treatment with thrombocyte growth factors. **Third occurrence:** stop treatment	**First occurrence:** Delay selinexor treatment until resolved to ≤ grade 1 or baseline (max 4 weeks), and restart at 50 mg/m^2 once a week. Thrombocyte growth factors (e.g., romiplostim, eltrombopag, oprelvekin) are recommended. **Second occurrence:** Delay selinexor treatment until resolved to ≤ grade 1 or baseline (max 4 weeks), and restart at 35 mg/m^2 once a week. Start treatment with thrombocyte growth factors. **Third occurrence:** stop treatment	**First occurrence:** Delay selinexor treatment until resolved to ≤ grade 1 or baseline (max 4 weeks), and restart at 35 mg/m^2 once a week Thrombocyte growth factors (e.g., romiplostim, eltrombopag, oprelvekin) are recommended. **Second occurrence:** Delay selinexor treatment until resolved to ≤ grade 1 or baseline (max 4 weeks), and restart at 35 mg/m^2 once a week. Start treatment with thrombocyte growth factors. **Third occurrence:** stop treatment

≥ Grade 3 Thrombocytopenia associated with purpura or bleeding	1. Delay selinexor treatment until resolved to ≤ grade 1 or baseline (max 4 weeks), and restart at 35 mg/m^2 once a week. 2. Transfuse platelets per institutional guidelines. If medically indicated, discontinue any anti-platelet agents. Implement platelet growth factors and/or transfusions. Platelet growth factors may require 2-4 weeks to take effect, and should be maintained until platelets are consistently > 100,000/mm^3.	1. Delay selinexor treatment until resolved to ≤ grade 1 or baseline (max 4 weeks), and restart at 35 mg/m2 once a week. Transfuse platelets per institutional guidelines. If medically indicated, discontinue any anti-platelet agents. Implement platelet growth factors and/or transfusions. Platelet growth factors may require 2-4 weeks to take effect, and should be maintained until platelets are consistently > 100,000/mm^3. 2. When purpura or bruising resolves, restart selinexor at level -1.	1. Delay selinexor treatment until resolved to ≤ grade 1 or baseline (max 4 weeks), and restart at 35 mg/m2 once a week Transfuse platelets per institutional guidelines. If medically indicated, discontinue any anti-platelet agents. Implement platelet growth factors and/or transfusions. Platelet growth factors may require 2-4 weeks to take effect, and should be maintained until platelets are consistently > 100,000/mm^3. 2. When purpura or bruising resolves, restart selinexor at level -1.
Platelet Stimulators	The use of platelet stimulators is encouraged in patients with a history of thrombocytopenia or compromised marrow function, or in patients in whom selinexor is having demonstrable disease control. IL-11 (oprelvekin), eltrombopag, or romiplastin should be considered.	The use of platelet stimulators is encouraged in patients with a history of thrombocytopenia or compromised marrow function, or in patients in whom selinexor is having demonstrable disease control. IL-11 (oprelvekin), eltrombopag, or romiplastin should be considered.	The use of platelet stimulators is encouraged in patients with a history of thrombocytopenia or compromised marrow function, or in patients in whom selinexor is having demonstrable disease control. IL-11 (oprelvekin), eltrombopag, or romiplastin should be considered.
Hyponatremia (common)			
Grade 1 (Lower Limit of Normal to 130 nM)	Maintain dose level, assure adequate fluid, electrolyte and caloric intake, adjust other medications, consider salt supplementation, rule out other causes.	Maintain dose level, assure adequate fluid, electrolyte and caloric intake, adjust other medications, consider salt supplementation, rule out other causes.	Maintain dose level, assure adequate fluid, electrolyte and caloric intake, adjust other medications, consider salt supplementation, rule out other causes.
Grade ≥ 3 (120-130 nM)	Discontinue selinexor until resolved to grade ≤ 1, then reduce dose by 1 level. Check renal function, serum, and urinary electrolytes, and rule out other causes.	Discontinue selinexor until resolved to grade ≤ 1, then reduce dose by 1 level. Check renal function, serum, and urinary electrolytes, and rule out other causes.	Discontinue selinexor until resolved to grade ≤ 1, then reduce dose by 1 level. Check renal function, serum, and urinary electrolytes, and rule out other causes.
AST or ALT (rare)			
Grade 1 (> ULN - 2.5 x ULN)	Maintain dose level	Maintain dose level	Maintain dose level

Grade 2 (> 2.5 - 5.0 x ULN)	Delay selinexor until resolved to grade ≤ 1 or baseline, then maintain dose level. Consider addition of S-adenosylmethionine (SAM) 400 mg qd-bid.	Delay selinexor until resolved to grade ≤ 1 or baseline, then maintain dose level. Consider addition of S-adenosylmethionine (SAM) 400 mg qd-bid.	Delay selinexor until resolved to grade ≤ 1 or baseline, then maintain dose level. Consider addition of S-adenosylmethionine (SAM) 400 mg qd-bid.
Grade 3 (> 5.0 - 20.0 x ULN)	1. Delay selinexor until resolved to ≤ grade 2 or baseline, then reduce by 1 dose level (Table 2 & Table 3) 2. Consider addition of S-adenosylmethionine (SAM) 400 mg qd-qid. 3. If no further AST or ALT elevations occur during one cycle (4 weeks) at the reduced dose level, then dose may be continued at the reduced dose. 4. Discontinuation of selinexor is required if concurrent elevations of direct bilirubin > 2.0 X upper limit of normal (ULN) and ALT or AST > 3.0 X ULN are observed. 5. In order to characterize hepatic toxicity more precisely, fractionation of bilirubin and alkaline phosphatases will be required for elevated values > 2.0 X ULN and ≥ CTCAE grade 2, respectively.	1. Delay selinexor until resolved to ≤ grade 2 or baseline, then reduce by 1 dose level (Table 2 & Table 3) 2. Consider addition of S-adenosylmethionine (SAM) 400 mg qd-qid. 3. If no further AST or ALT elevations occur during one cycle (4 weeks) at the reduced dose level, then dose may be continued at the reduced dose. 4. Discontinuation of selinexor is required if concurrent elevations of direct bilirubin > 2.0 X upper limit of normal (ULN) and ALT or AST > 3.0 X ULN are observed. 5. In order to characterize hepatic toxicity more precisely, fractionation of bilirubin and alkaline phosphatases will be required for elevated values > 2.0 X ULN and ≥ CTCAE grade 2, respectively.	1. Delay selinexor until resolved to ≤ grade 2 or baseline, then reduce by 1 dose level (Table 2 & Table 3) 2. Consider addition of S-adenosylmethionine (SAM) 400 mg qd-qid. 3. If no further AST or ALT elevations occur during one cycle (4 weeks) at the reduced dose level, then dose may be continued at the reduced dose. 4. Discontinuation of selinexor is required if concurrent elevations of direct bilirubin > 2.0 X upper limit of normal (ULN) and ALT or AST > 3.0 X ULN are observed. In order to characterize hepatic toxicity more precisely, fractionation of bilirubin and alkaline phosphatases will be required for elevated values > 2.0 X ULN and ≥ CTCAE grade 2, respectively.
Grade 4 (> 20.0 x ULN)	Delay selinexor until resolved to ≤ grade 2, then reduce by 2 dose levels.	Delay selinexor until resolved to ≤ grade 2, then reduce by 2 dose levels.	N/A
Diarrhea (common)			
Grade 1 (despite maximal anti-diarrheal medication)	At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated according to institutional standard of care. Maintain dose level of selinexor.	At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated according to institutional standard of care. Maintain dose level of selinexor.	At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated according to institutional standard of care. Maintain dose level of selinexor.

Grade 2 (despite maximal anti-diarrheal medication)	**First occurrence**: reduce selinexor to once weekly until resolved to ≤ grade 1, then re-start twice weekly at the current dose level. **Second occurrence:** reduce selinexor dose by one dose level and dose once weekly until resolved to ≤ grade 1, then re-start twice weekly at reduced dose level	**First occurrence:** reduce to selinexor to once weekly until resolved to ≤ grade 1, then re-start twice weekly at the current dose level. **Second occurrence**: reduce selinexor dose by one dose level and dose once weekly until resolved to ≤ grade 1, then re-start twice weekly at reduced dose level	**First occurrence:** reduce selinexor to 35 mg/m^2 until resolved to ≤ grade 1 or baseline, then re-start at the Dose level 0. **Second occurrence:** reduce one dose level
Grade 3/4 (despite maximal anti-diarrheal medication)	Delay selinexor until resolved to ≤ grade 2 or baseline, then follow guidelines above.	Delay selinexor until resolved to ≤ grade 2 or baseline, then follow guidelines above.	Delay selinexor until resolved to ≤ grade 2 or baseline then reduce one dose level.
Other selinexor-related adverse events			
Grade 1 or 2	Maintain dose level and initiate standard supportive care.	Maintain dose level and initiate standard supportive care.	Maintain dose level and initiate standard supportive care.
Grade 3	Delay dose until resolved to ≤ grade 1 or baseline, then reduce by one dose level.	Delay dose until resolved to ≤ grade 1 or baseline, then reduce by one dose level.	Delay dose until resolved to ≤ grade 1 or baseline, then reduce to Dose level -1.
Grade 4	Discontinue selinexor and rule out other causes. If other causes of grade 4 adverse event are uncovered, selinexor may be re-started at a reduced dose level	Discontinue selinexor and rule out other causes. If other causes of grade 4 adverse event are uncovered, selinexor may reduce in 2 dose level	Discontinue selinexor and rule out other causes. If other causes of grade 4 adverse event are uncovered, selinexor may be re-started at a reduced dose level.

All dose modifications should be based on the worst preceding toxicity.
Isolated values of ≥ grade 3 alkaline phosphatase values will NOT require dose interruption. Determination of liver vs bone etiology should be made, and evaluation of gamma-glutamyl transferase (GGT), 5'-nucleotidase (5'NT), or other liver enzymes should be performed.
≥ Grade 3 anemia judged to be a hemolytic process secondary to study drug will require interruption of study treatment until resolved to ≤ grade 1. Selinexor may then be re-instituted at 1 level below original dose (Table 2 and Table 3.
≥ Grade 3 lymphopenia considered clinically significant will require dose interruption until resolved to ≤ grade 2, then reduce by 1 dose level.
Patients are allowed dose reductions to a minimum dose of 35 mg/m^2 once weekly for Part 1 and Part 2 (Schedules 1 and 2) as described in Table 2 and Table 3, respectively.
If a patient requires a dose interruption of > 28 days, then the patient must be discontinued from the study. Patients who discontinue the study for a study-related adverse event or abnormal laboratory value must be followed at least once a week for 28 days and subsequently at 28-day intervals until resolution or stabilization of the event, whichever comes first.
Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) or otherwise specified values.
[a]National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Fatigue. Available at http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf.
[b]National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Palliative Care, version 2.2015. Fort Washington, NY. May 2015. Available at: http://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/generalcancer/pdf/facts.pdf. Attached as Appendix 11.
[c]National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Antiemesis, version 1.2015. Fort Washington, NY. April 2015. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Attached as Appendix 10.

For patients whose dose has been reduced due to neutropenia, anorexia or fatigue, dose re-escalation is permitted if the institution of supportive care measures has reduced these toxicities to Grade ≤ 1 or to baseline for at least 2 weeks. Dose re-escalation is only permitted for these adverse events when supportive measures have been successful.

6.3.3 Selinexor Dose Reduction in the Setting of Infection

Patients with active uncontrolled infections should have selinexor treatment withheld until the infection has resolved or the patient is clinically stable. After the infection has stabilized clinically or resolved, selinexor treatment may continue at the original dose. Missed doses will not be replaced. Patients may continue on antibiotics for prolonged periods while re-initiating their selinexor regimen at the discretion of the Investigator. Prophylactic antibiotics are permitted concurrently with selinexor treatment, but are not required. Opportunistic infections related to selinexor therapy have not been reported in 730 patients evaluable for safety as of 31 May 2015.

6.3.4 Dose Adjustments with Changes in BSA

Dose adjustments do not need to be made for weight gains/losses of ≤ 20%. For patients dosed on a mg/m^2 basis, patients with a Body Surface Area (BSA) of greater than 2.5 m² will receive a doses of selinexor based on a BSA of 2.5 m². For patients receiving selinexor doses of 60 mg or 80 mg, BSA will be calculated to ensure that the 60 mg or 80 mg dose does not result in a dose > 70 mg/m.^{2} If a patient's dose will exceed this limit, the Investigator should contact the Medical Monitor prior to administration to discuss appropriate dosing.

6.3.5 Missed or Vomited Doses

For once weekly dosing, a maximum of one dose may be given per week; for twice weekly dosing, a maximum of two doses may be given per week. Doses should not be administered less than 5 days apart for once weekly dosing and less than 36 hours apart for once weekly dosing. Every effort should be made to avoid missed doses.

Missed doses

Doses held due to AE(s) will not be considered missed.

Vomited doses

If a dose is vomited within one hour of ingestion, it will be replaced. If vomiting occurs more than 1 hour after dosing, it will still be considered a complete dose.

6.3.6 Dose Adjustments with impressive tumor response

If the shrinkage of the tumor is ≥ 50% compared to the baseline tumor assessment, the dose of selinexor may be reduced to once-weekly dosing.

6.4 Concomitant Medication and Treatment

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. Patients may continue their baseline medication(s). All concomitant medication(s) must be reported in the case report form (CRF). Any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s) and any clinical findings.

6.4.1 Permitted Concomitant Medication

Patients will receive concomitant medications to treat symptoms, adverse events and intercurrent illnesses that are medically necessary as standard care. Medications to treat concomitant diseases like diabetes, hypertension, etc. are allowed.

6.4.1.1 Prevention of Pregnancy

Patients should not become pregnant or father a child while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important that patients understand the need to use birth control while on this study. A woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant. This includes women on oral, injectable or mechanical contraception; women who are single and women whose male sexual partners have been vasectomized or whose male sexual partners have received or are utilizing mechanical contraceptive devices. Female patients of childbearing potential must have a negative serum pregnancy test at screening and agree to use reliable methods of contraception for three months after their last dose of medication. Such methods include intrauterine devices, hormonal contraceptives [contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release], abstinence or sterilization of the partner. Male patients must use a reliable method of contraception (abstinence or contraception with one of the above-described methods for your partner) if sexually active with a female of childbearing potential. Total (true) abstinence (when this is in line with the preferred and usual lifestyle of the patient), is an acceptable method of contraception. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post- ovulation methods) and withdrawal are not acceptable methods of contraception. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.

6.4.1.2 Use of Blood Products

During the administration of selinexor, patients may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines. Patients who require repeated transfusion support should be discussed with the Investigator, Sponsor and Medical Monitor.

Appropriate anti-coagulation is allowed during the study (e.g., LMW heparin, direct factor Xa inhibitors). Warfarin is allowed during the study provided that patients are monitored for INR twice a week during the first two cycles of therapy, then weekly to biweekly thereafter.

Patients may receive supportive care with erythropoietin, darbepoetin, G-CSF or GM-CSF, pegylated growth factors, and platelet stimulatory factors, in accordance with clinical practice or institutional guidelines prior to entry and throughout the study.

6.4.1.3 Glucocorticoid therapy

Ongoing glucocorticoids (e.g., ≤ 10 mg oral prednisone [or equivalent]) per day are permitted at baseline and during the study for non-malignant conditions (i.e., asthma) as needed.

As part of supportive care (e.g., for nausea or anorexia), oral dexamethasone, up to 40 mg/week, may be given to patients, in consultation with the Medical Monitor. Dexamethasone (4-12 mg) or prednisone (10-20 mg) on days of (± 1 day after) selinexor dosing (± 1 day after) may improve appetite, reduce nausea or vomiting, and minimize fatigue.

6.4.2 Restricted and Prohibited Medications

6.4.2.1 Concurrent Therapies

Concurrent therapy with any other approved or investigative anticancer therapeutic is not allowed. Other investigational agents should not be used during the study. Use of any immunosuppressive agents during the study must be confirmed by the Medical Monitor. Note that the use of denosumab is not allowed.

6.4.2.2 Alcohol (ethanol)

Ethanol should be avoided on selinexor dosing days as it may compete for glutathione (GSH)-mediated metabolism.

6.4.2.3 Acetaminophen (paracetamol) containing medications

There are no longer any restrictions on the use of acetaminophen (paracetamol) or acetaminophen (paracetamol) -containing products in combination with selinexor, EXCEPT on days of selinexor dosing, when acetaminophen (paracetamol) must not exceed a total daily dose of 1 gram. Although acetaminophen (paracetamol) use in combination with selinexor was restricted in previous selinexor studies based on theoretical interactions with GSH, ongoing clinical safety evaluations on the use of these drugs together have not shown any significant clinical or laboratory abnormalities with doses of acetaminophen (paracetamol) of up to 1 gram and selinexor up to 55 mg/m^2 (approximately 80-100 mg).

6.4.2.4 Miscellaneous

Patients should not take glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products during their participation in this study, as these products may enhance the metabolism of selinexor. See Appendix 15 for a list of representative products. Patients must report all prescription and non-prescription medicines to their physicians during this study.

6.5 Supportive Care Guidelines

6.5.1 Required Supportive Care Medication

5-HT3 Antagonists
In order to minimize nausea, unless contraindicated, all patients must receive 5-HT3 antagonists (ondansetron 8 mg or equivalent) starting before the first dose of selinexor and continued 2-3 times a day, as needed. Alternative anti-emetic therapy may be used for patients who cannot tolerate 5-HT3 antagonists.

6.5.2 Supportive Care Recommendations for Selinexor-Related Adverse Events

Supportive measures for optimal medical care should be provided during participation in this clinical trial. Based on clinical observations in over 560 adult patients treated with selinexor with evaluable safety data as of 01 February 2015, the main side effects are primarily related to anorexia with poor caloric and fluid intake, fatigue, and nausea. Thrombocytopenia also occurs, although it is rarely associated with bleeding.
Besides the required 5-HT3 (Section 6.5.1), supportive care including anti-nausea / anti-emetic therapy, acid suppression (proton pump inhibitors and/or H2-blockers) and other treatments may be administered as described below:

1. Glucocorticoids: dexamethasone (4-12 mg) or equivalent glucocorticoid (e.g., prednisone 10-20 mg) on days of, and 1 day after, selinexor dosing may improve appetite, reduce nausea or vomiting, and minimize fatigue. A maximum of 40 mg dexamethasone or equivalent may be given per week.
2. Appetite stimulants: megesterol acetate at a dose of 80-400 mg daily.
3. Centrally acting agents: per National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines® for antiemesis[98] and anorexia/cachexia (palliative care)[99] see Appendix 10 (antiemesis) and Appendix 11 (anorexia), respectively.
4. NK1R antagonist: aprepitant or equivalent should be considered and will be covered for selected patients who have severe nausea and vomiting.

6.5.3 Liver Enzyme Increase

Liver toxicities in rodents and monkeys were not observed in the GLP toxicology studies. To date, significant liver toxicity has not been reported in patients treated with selinexor. Patients should minimize their use of alcohol as this drug may deplete hepatic glutathione which could alter selinexor metabolism. Glutathione- (GSH-) replacing agents such as N-acetylcysteine or S-adenosylmethionine may be considered if selinexor induced liver dysfunction is suspected.

7 ADVERSE EVENT ASSESSMENT

The *Selinexor IB* is a reference source for selinexor and will be provided to the Investigators in the Investigator's File.

7.1 Adverse Events and Laboratory Abnormalities Reporting

7.1.1 Adverse Event

An adverse event (AE) is defined in the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment" (ICH E6: 1.2).

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is considered related to the medicinal product.

Pregnancy *per se* is not considered an AE. A medical occurrence observed in the mother or fetus/newborn would be an AE.

All AEs will be collected from the start of treatment, i.e., Cycle 1 Day 1, until 30 days (± 7 days) after the last dose of study medication.

Table 5: Classification of Adverse Events by Causality

Class	Description
Not related	The lack of a temporal relationship of the event to study treatment makes a causal relationship not reasonably possible, or by any other drugs, therapeutic interventions or underlying conditions that provide a sufficient explanation.
Possibly related	The temporal relationship of the event to study treatment makes a causal relationship reasonably possible, and the event is more likely explained by exposure to the study treatment than by any other drugs, therapeutic interventions or underlying conditions.
Related	The temporal relationship of the event to study treatment makes a definitive relationship, and the event is more likely explained by exposure to the study treatment than by any other drugs, therapeutic interventions or underlying conditions.

For the purpose of safety analyses, all AEs that are classified as related or possibly related will be considered treatment-related events.

The Investigator is responsible for ensuring that all adverse events observed by the Investigator or reported by patients are properly recorded in the patients' medical records and the electronic case report form.

The Investigator must assign the following attributes:

- Severity grade according to the NCI CTCAE criteria Version 4.03
- Start date and stop date (or date of last assessment)
- Outcome
- Causality to study drug and chemotherapy (to be assessed as either related or not related)
- Any action taken with the study drug

Pre-existing diseases, when worsening during study therapy, have to be considered as adverse events. They can lead to serious adverse events, if they meet the criteria described in Section 7.1.4.

7.1.2 Adverse Drug Reaction

Adverse drug reactions (ADRs) include all untoward and unintended responses to a medicinal product related to any dose administered.

The phrase “responses to a medicinal product” means that a causal relationship between the medicinal product and the AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

A serious ADR (SADR) is an ADR that meets the definition of serious (provided below).

7.1.3 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results pages of the eCRF. In the event of unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

Laboratory test value abnormalities as such should not be reported on the AE page of the eCRF as adverse events unless they are treatment-emergent and they satisfy one or more of the following conditions for clinical significance:

1. Accompanied by clinical symptoms
2. Leading to a change in study medication (e.g., dose modification, interruption or permanent discontinuation)
3. Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

Please note: Any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an adverse event in the eCRF.

7.1.4 Serious Adverse Event

SAEs will be collected from the time of Informed Consent through 30 days (± 7 days) after the last dose of study medication.

A serious adverse event (SAE) is defined as an adverse event that meets one or more of the following:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- other important medical events

A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a healthcare facility. Any adverse event that does not meet one of the definitions of serious (e.g. visit to A&E, outpatient surgery, or requires urgent investigation) may be considered by the Investigator to meet the “other significant medical hazard” criterion for classification as a serious adverse event. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical judgment should be exercised in deciding whether such an AE should be considered serious.

In addition, all cases of cerebellar toxicities of Grade 3 or higher must be captured as an SAE and reported to the regulatory authorities, IRBs, ECs, and Investigators in an expedited Safety Report within 7 days of awareness of the event.

7.1.5 Events NOT to be reported as SAEs

For this study, the following are **not** classified as SAEs:

- Progression or deterioration of the malignancy under study (including new metastatic lesions) or death due to progression.
- Hospitalization for the performance of protocol-required procedures or administration of study treatment. However, hospitalization or a prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Hospitalization or procedures planned prior to study start. A pre-planned procedure must be documented in the source documents. However, hospitalization or prolonged hospitalization for a complication remains to be reported as an SAE.
- An elective hospitalization for a pre-existing condition not related to the studied indication.
- Hospital admission that is not associated with an adverse event (e.g., social hospitalization for purpose of respite care).

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusions remains to be reported as an SAE.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

7.1.6 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Per the definitions provided above, SUSARs are adverse events that have been determined by the investigator to be serious, suspected of being caused by selinexor (related or possibly related) and are unexpected according to the most current version of the investigator's brochure for selinexor.

7.2 Reporting of SAEs

7.2.1 Primary Treatment Phase

Any clinical adverse event or abnormal laboratory test value that is serious occurring during the course of the study from the date of signing the informed consent, irrespective of the treatment received by the patient, must be reported to GSO within 24 hours following knowledge of the SAE.

The following detailed information must be recorded for each serious adverse event in the SAE report form:

- The severity grade as assessed by the investigator according to the definitions in NCI-CTCAE Version 4.03
- The date of becoming serious and the date of becoming known (if different)
- The reason for seriousness
- The outcome of the SAE at the time of the report
- Information on administration of the study drug and chemotherapy and any action taken
- Information on any procedures necessary to treat the SAE, concomitant medications, relevant lab tests and relevant medical history

The completed SAE form must be sent to:

GSO
Fax: 0049-40-44 19 54 78
EMail: signsae@gso-hamburg.com

Karyopharm Therapeutics will ensure the notification of the appropriate ethics committees, competent authorities and participating investigators of all SUSAR events occurring at the sites in accordance with local legal requirements, statutes and the European Clinical Trial Directive.

7.2.2 Maintenance Phase

See Section 18 (Appendix 16) for reporting of SAEs during the Maintenance Phase of the study (Version ≥3.2).

7.3 AE and SAE Follow-up

All AEs will be followed in accordance with good medical practice until they are resolved, stabilized or judged no longer clinically significant or, if a chronic condition, until fully characterized. Any AEs that are considered drug-related (possibly related or related) must be followed until resolution or until stabilization.

7.4 Pregnancy

Female patients must be instructed to immediately inform the Investigator if they become pregnant during the study. The study treatment must immediately be stopped and the patient must be withdrawn from the study. Pregnancies occurring up to 3 months after the completion of the last treatment cycle must also be reported to the Investigator. The Investigator must report all pregnancies within 24 hours of knowledge to GSO. GSO will forward all pregnancy reports to the sponsor within 24 hours. The Investigator should counsel the patient; discuss the risks of continuing the pregnancy and the possible effects on the fetus. The patient should be monitored until the conclusion of the pregnancy.

Pregnancy occurring in the partner of a patient participating in the study should also be reported to the Investigator, the sponsor and the CRO. The partner should be counseled and followed as described above.

8 STATISTICAL METHODS

8.1 Trial Design and Hypotheses

This trial has been designed as a multi-center, open-label, two-stage phase II study in 3 separate gynaecological cancer cohorts, with an additional set of patients in the ovarian cohort randomized into two different treatment regimens.

Study data may be analyzed and reported to competent regulatory authorities when ≥ 75% of patients have completed at least ≥ 2 cycles of treatment or discontinued from the study.

The primary objective is to determine the efficacy of selinexor in patients with advanced or metastatic gynaecological cancers as assessed by disease control rate (DCR). Disease control rate (DCR) is defined as complete response (CR) or partial response (PR) or stable disease (SD) for at least 12 weeks, assessed according to RECIST 1.1. The Simon's[97] two-stage optimal design will be used to address the primary trial objective, with the following hypothesis to be tested for DCR for each cohort:

H_0: true disease control rate ≤ 0.25 versus H_1: true disease control rate ≥ 0.50.

Secondary objectives are:

- Determine the efficacy of selinexor in patients with advanced or metastatic gynaecological cancers using:
  - Objective response rate (ORR)
  - Progression-free survival (PFS)
  - Overall Survival (OS) including OS rates at 12 and 24 months
- Evaluate safety and tolerability of selinexor in patients with advanced or metastatic gynaecological cancers.
- Evaluate QoL for patients with advanced or metastatic gynaecological cancers treated with selinexor.

Patients enrolled into the second part of the study in the ovarian cohort will be randomized using a centralized randomization via IWRS. Randomization will be performed within the ovarian cohort and will not be specific to the study site.

Complete details of data analysis and presentation will be included in a statistical analysis plan (SAP) which will be finalized prior to database lock.

8.2 Sample Size Calculation

CCI

8.3 Evaluation Categories for Patients

8.3.1 Modified Intent-to-Treat Population

The treated population (mITT) will consist of all patients who receive at least one dose of study medication and have at least one post-baseline efficacy follow-up assessment, unless the patient discontinued treatment prior to the first assessment due to death, toxicity, or PD. This population will be used for primary analyses of efficacy.

8.3.2 Per Protocol Population

The per-protocol population will consist of all patients who are compliant with study assessments and who have no protocol violations that would compromise the assessment of efficacy. Protocol violations will be determined independently of knowledge of response to therapy. This population will be used for supportive inferences concerning efficacy. If there are major differences between the results in this population and those obtained in the mITT population, this will be taken into consideration in the decision to continue to later phase studies, or in the design of further studies.

8.3.3 Safety Population

The safety population will consist of all patients who have received any amount of study medication.

8.4 Methods of Statistical Analysis

8.4.1 General Statistical Considerations

Tabulations will be produced for appropriate demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented, as well as two-sided 95% confidence intervals, unless otherwise stated. For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology using 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 95% confidence intervals, as well as percentage of censored observations.

No imputation of missing efficacy data is planned. For time to event analyses, patients who have no efficacy evaluations for disease recurrence will be considered censored at time 0.

For AEs, missing dates will not be imputed, however, if partial dates are available, they will be used to assess if the AE occurred during the treatment period. Missing severities of AEs will not be imputed and will be considered missing in any tabulations of AE severity. If an AE is missing a response to the question regarding relationship to treatment, the event will be considered to be related.

8.4.2 Demographics and Baseline Characteristics

The demographic characteristics to be summarized will include gender, race, ethnicity (Hispanic origin), and age at time of consent. For gender, race, and Hispanic origin, the summary statistics will be the number and percentage of patients within each group or the total sample. The categories for race will be those recorded in the database. For age at time of consent, the mean, median, minimum, maximum, and standard deviation will be provided for each group and the total sample.

Baseline characteristics include: ECOG performance status; duration from initial diagnosis; response to previous therapy (Y/N).

8.4.3 Efficacy Evaluation

Primary analysis disease control rate.

The analysis of disease control rate will be performed for each study cohort by calculating the point estimate of the percentage of patients in that cohort who have CR, PR, or SD for at least 12 weeks, assessed according to RECIST 1.1.

Duration of SD will be calculated as follows:

- For patients with documented disease progression, duration will be calculated from the date of start of study therapy until the date of disease progression.
- For patients without documented disease progression, duration will be calculated from the date of start of study therapy until the date of last disease assessment.

- For patients without at least one post baseline disease assessment, duration will be censored at time 0.

To be consistent with a Simon's two-stage optimal design, a lower one-sided 90% CI will be presented for the DCR in each study cohort; additionally, for descriptive purposes a two-sided 95% CI will also be calculated for each cohort, using exact methods. The DCR for each cohort will be presented for the first stage of the study and for both stages combined, consistent with the Simon's two-stage optimal design.

The analysis of differences in DCR for the randomized part of the study (Part 2) will be performed using Fisher's Exact test, accompanied by confidence intervals.

The analysis of duration of disease control will be based on the Kaplan-Meier method for estimation of summary statistics, and will include the 25th, 50th (median), and 75th percentiles and associated 95% CIs.

Secondary Analyses:

1. *Response to therapy per RECIST 1.1:* response for patients in each cohort will be determined by ORR, defined as either CR or PR using RECIST 1.1, calculated as a proportion and including a two-sided 95% CI for that cohort. Duration of response (DOR) will also be calculated; from the date of first documented occurrence of response (CR or PR) until the date of documented progression, or last disease assessment, should progression not have occurred. The analysis of DOR will be based on the Kaplan-Meier method for estimation of summary statistics, and include the 25th, 50th (median), and 75th percentiles and associated 95% CIs.
2. *Response to therapy per GCIG response criteria (RECIST 1.1 and CA-125):* response for patients in the ovarian cohort will also be assessed for DCR and ORR, as described above, using the GCIG response criteria. Only patients with sufficient data to be assessed based on this criteria (i.e., has a baseline CA-125 assessment) will be included. Number and frequency of patients in the ovarian cancer cohort who can be assessed using the GCIG response criteria will be presented.
3. *Median Progression-free Survival:* PFS for patients in each cohort will be calculated from the date of start of study therapy to the date of progression based on RECIST 1.1 , or date of death should progression not have occurred. Patients who drop out prior to study end or do not have documented PD will be censored at the day of last documented disease assessment. The analysis of PFS for patients in each cohort will be based on the Kaplan-Meier method for estimation of summary statistics, and include the 25^{th}, 50^{th} (median), and 75^{th} percentiles and associated 95% CIs. PFS will also be presented with progression defined per GCIG response criteria (RECIST 1.1 and CA-125) for patients in the ovarian cohort with sufficient data to be assessed based on this criteria (i.e., has a baseline CA-125 assessment).
4. *Overall Survival:* OS for patients in each cohort will be calculated from the date of start of study therapy to the date of death due to any cause. OS rate at 12 and 24 months will also be calculated. Patients who drop out prior to study end will be censored at the day they were last known to be alive. The analysis of OS for patients in each cohort will be based on the Kaplan-Meier method for estimation of

summary statistics, and include the 25th, 50th (median), and 75th percentiles and associated 95% CIs.

5. *Quality of Life (QoL)*: will be evaluated for patients in each cohort, and for all study patients combined by EORTC QLQ-C30 after 6 and 12 weeks of treatment and approximately every 8 weeks thereafter.

8.4.4 Safety Evaluation

Safety and tolerability of selinexor will be evaluated descriptively for all study patients combined, according to NCI CTCAE, v. 4.03. Safety endpoints include AEs, clinical laboratory data, vital signs, ECGs, and physical examinations, further described below.

8.4.4.1 Adverse Events

Adverse Events (AEs) will be coded using the MedDRA dictionary and displayed for all study patients combined, in tables and listings using System Organ Class (SOC) and Preferred Term.

Analyses of AEs will be performed for those events that are considered treatment emergent, where treatment-emergent is defined as any AE with onset or worsening of a pre-existing condition on or after the first administration of study medication through 30 days following last dose or any event considered drug-related by the Investigator through the end of the study. AEs with partial dates will be assessed using the available date information to determine if treatment-emergent; AEs with completely missing dates will be assumed to be treatment-emergent.

AEs will be summarized by patient incidence rates, therefore, in any tabulation, a patient contributes only once to the count for a given AE preferred term.

The number and percentage of patients with any treatment-emergent AE will be summarized for each dosing regimen and for all study patients combined. The number and percentage of patients with treatment-emergent AEs assessed by the Investigator as at least possibly related to treatment will also be tabulated. The number and percentage of patients with any grade ≥ 3 treatment-emergent AE will be tabulated in the same manner. In the event a patient experiences repeated episodes of the same AE, then the event with the highest severity and/or strongest causal relationship to study treatment will be used for purposes of tabulations.

Serious AEs will also be tabulated.

No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs (treatment emergent and post-treatment) will be listed in patient data listings.

By-patient listings will be provided for the following: patient deaths; serious AEs; and AEs leading to withdrawal.

8.4.4.2 Laboratory Data

The actual value and change from baseline for each on study evaluation will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry, for all study patients combined. In the event of repeat values, the last non-

missing value per study day/time will be used.

Severity of select clinical lab measures will be determined using CTCAE criteria (e.g., those measures that have a corresponding CTCAE grade classification). Labs with CTCAE grades ≥ 3 will be presented in a data listing. Shift tables that present changes from baseline to worst on-study values relative to CTCAE classification ranges will be produced.

8.4.4.3 Vital Signs and Physical Examinations

The actual value and change from baseline to each on study evaluation will be summarized for vital signs for all study patients combined. By-patient listings of vital sign measurements will be presented in data listings.

Physical examination results at screening will be summarized; all other abnormal physical examination data were to be recorded on the AE eCRF. All examination findings will be presented in a data listing.

8.4.4.4 Concomitant Medications

The use of concomitant medications will be included in by-patient data listings.

8.5 Interim and Final Analysis

In accordance with the Simon's two-stage optimal design of Part 1, there will be a preliminary assessment of efficacy for each cohort after the first 8 patients enrolled in that cohort have 6-month data available to assess DCR, as defined in Section 8.4.3. Note that this initial analysis for a cohort may take place sooner than when the 8th patient has available data, should there be 3 or more disease control achievers after fewer than 8 patients are enrolled. Should the trial be terminated at the first stage, all efficacy and safety analyses as noted above will be performed. Patient enrollment into the trial will continue while the first stage analysis is being conducted.

The final analysis of the primary endpoint DCR for each cohort will take place after the target number of patients evaluable for DCR has been reached. Additional data summarization may take place after all available survival data are collected, or after Sponsor decision, as appropriate.

9 DATA QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data are described in the Standard Operational Procedures of GSO. Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the Investigator's records by the study monitor (source document verification), and the maintenance of a drug–dispensing log by the Investigator. Data for this study will be recorded via eCRF. Data from the Maintenance Phase will be collected in a separate database to allow locking of the Primary Treatment Phase database after initiation of the Maintenance Phase. It will be transcribed by the site from the source documents onto the eCRF. Data are reviewed and checked for omissions, apparent errors, and values requiring further clarifications using computerized and manual procedures. Data queries requiring clarification are communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database and an audit trail will document all corrections.

10 ETHICAL ASPECTS

10.1 Good Clinical Practice

This clinical study was designed, implemented and shall be reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), Division 5 of the Health Canada Food and Drug Regulations - Drugs For Clinical Trials Involving Human Subjects, and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Patient Information and Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from each patient participating in this study, after an adequate explanation of the aims, importance, anticipated benefits, potential hazards and consequences of the study according to applicable local laws. Written informed consent must be obtained before any study-specific procedures are performed. It must be also explained to the patient that they are completely free to refuse to enter the study or to withdraw from it at any time, for any reason, without incurring any penalty or withholding of treatment on the part of the Investigator.

With the declaration of consent, the patient agrees to data about his/ her disease being recorded within the context of the clinical study and that it may be transferred to the Sponsor in pseudonymized form.

The patient also agrees to allow the monitor/auditor/health authorities to verify the patient data collected against the patient's original medical records for the purpose of source data verification.

The informed consent form (ICF) personally signed and dated by the patient must be kept on file by the Investigator and documented in the CRF and the patient's medical records. The Investigator must confirm with the sponsor that he/ she has obtained written informed consent.

If new safety information results in significant changes to the risk/ benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information and must give their written informed consent to continue in the study.

If family physicians are to be informed of their patients' participation in the clinical study, this should be mentioned in the consent form.

10.3 Independent Ethics Committees and Regulatory Authorities

10.3.1 Approval of the Study by the Regulatory Authority and Independent Ethics Committees

It is the responsibility of the Sponsor to obtain and maintain independent approval from the applicable regulatory authority and a positive opinion from the competent ethics committees to conduct the study in accordance with local legal requirements and statutes.

Indemnity insurance will be arranged for the trial patients in accordance with the applicable local laws.

10.3.2 Notification of the Study

The Sponsor is responsible for notifying the competent regional authority about the study and all Investigators at the participating investigational sites, if applicable by local law.

10.3.3 Obligation to Report and Document

The Sponsor and the Investigator are responsible for complying with the requirements for reporting and documentation in accordance with local legal requirements and statutes.

11 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to on-going studies must be made via amendment. The Sponsor is responsible for obtaining independent approval for substantial amendments from applicable regulatory authorities and a positive opinion from the competent ethics committees in accordance with local legal requirements, statutes, and the European Clinical Trial Directive. Approval must be obtained before any changes can be implemented, except for changes necessary in order to eliminate an immediate hazard to trial patients or when the changes are non-substantial and involve only logistical or administrative aspects of the trial (e.g., change of telephone numbers).

12 STUDY DOCUMENTATION, CRFS AND RECORD-KEEPING

12.1 Investigator's Files / Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories: Investigator's study file and subject/ patient data.

The Investigator's study file will contain all essential documents such as the protocol/ amendments, case report and query forms, patient information and informed consent form, ethics committee and regulatory authority approval, notification of the federal regulatory authority and competent regional authorities (if applicable), drug records, staff curriculum vitae and authorization forms, and other appropriate documents/correspondence, etc.

Patient data includes patient hospital/ clinic records (e.g., medical reports, surgery reports appointment book, medical records, pathology, laboratory reports, and ECG), signed ICFs and patient screening and eligibility screening forms.

The Investigator must keep these two categories of documents on file for as long as legally required by local and national regulations, or local IRB/ethics board policies whichever is longer, after completion or discontinuation of the study. The documents must be archived in a secure place and treated as confidential material.

Should the Investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the Investigator in the event of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made for storing outside of the site.

All documents must be archived in a secure place and treated as confidential material.

12.2 Source Documents and Background Data

The Investigator shall supply the Sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when case report forms are illegible or when errors in data transcription are suspected. In the event of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected. According to the standards of the data protection law, all data obtained in the course of a clinical study must be treated with discretion in order to guarantee the rights of the patient's privacy.

12.3 Audits and Inspections

This study may be audited by the Sponsor, any person authorized by the sponsor, or the competent health authority in order to determine the authenticity of the recorded data and compliance with the study protocol.

The Investigator must be aware that source documents for this trial should be made available to appropriately qualified personnel working on behalf of the sponsor/monitor/auditor/health authority inspectors after appropriate notification for the purposes of source data verification and proper review of the study progress. The verification of the eCRF data must be done via direct inspection of the source documents. The Investigator agrees to comply with the Sponsor and regulatory authority requirements regarding the auditing of the study.

All materials used in clinical studies are subjected to quality control.

12.4 Case Report Forms

For each patient enrolled, an electronic case report form (eCRF) must be completed and signed by the Investigator or an authorized delegate from the study team. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted in the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to document the outcome clearly.

13 MONITORING THE STUDY

The clinical monitor or clinical research associate is responsible for familiarizing the Investigator(s) and the entire center staff involved in the study with all study procedures, including the administration of the study drug.

The monitor will visit the clinical study center before the first patient has been enrolled (initiation visit). During the study, the monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs (source data verification), the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

Key study personnel must be available to assist the monitor during these visits. 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.

14 SAFETY MONITORING COMMITTEE

A Safety Monitoring Committee (SMC) will provide additional oversight on the safety of the investigational product, selinexor (KPT-330), as used in this study. The SMC is responsible for reviewing accumulated safety data from the study.

The SMC will have access to all data necessary to formulate their opinion on the safety of the study. This includes efficacy data at the scheduled meetings as this is relevant to assessing the acceptability of the AE profile observed.

15 CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The Investigator and the Sponsor (or designated person) will ensure that all data obtained in the course of this study is treated with discretion in order to guarantee the rights of the patients' privacy, according to the standards of the data protection law. CRFs or other documents should be submitted to the sponsor in pseudonymized form. The Investigator should keep a patient identification log showing codes and names. The Investigator should maintain documents not intended for submission to the sponsor, e.g. patients' written consent forms, in the strictest confidence.

16 STUDY REPORT AND PUBLICATION POLICY

Study data may be analyzed and reported to competent regulatory authorities when ≥ 75% of patients have completed at least ≥ 2 cycles of treatment or discontinued from the study. Therefore, multiple interim reports may be produced for regulatory submission. Any additional data for patients continuing to receive study treatment past the data cutoff, as allowed by the protocol, will be reported in a final Clinical Study Report once all evaluable patients have completed the long-term follow up period, died, withdrawn consent, discontinued due to toxicity, or been lost to follow up.

Karyopharm assures that the key design elements of this protocol will be posted in a publicly accessible database such as www.clinicaltrials.gov. In addition, upon study completion and analysis of the resulting clinical data, the study results will be:

- Reported to appropriate, competent regulatory authorities in full compliance with International Conference on Harmonization (ICH) E3: Structure and Content of Clinical Study Reports. An interim, primary clinical study report (CSR) may be written based on all available patient efficacy and safety data for the primary analysis; a final CSR may be submitted when all evaluable patients have completed the study, as described above.
- Submitted for publication and/or posted in a publicly accessible database of clinical study results. In this multi-center study, the main publication will be a full publication of all clinical data from all sites. Any publication of the results, either in part or in whole (abstracts in journals, oral presentations, etc.) by Investigators or their representatives will require a pre-submission review by the Sponsor and the coordinating Investigator. The coordinating Investigator will be the first author. The senior author of the study will be the last author. The remaining positions will be based on recruitment, good data quality and scientific input to the study. The final author list will be a joint agreement between the coordinating Investigator and the Sponsor. For all other publications, the order of the authors will be determined according to recruitment, data quality and significant scientific input to the study, after consulting the coordinating Investigator.
- CCI [redacted]

17 REFERENCES

1. Jemal A, Bray F, Center MM et al. Global Cancer Statistics. *CA Cancer J Clin* 2011;**6:**69-90.
2. Colombo N, Peiretti M, Parma G et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21:23-30.
3. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival Effect of Maximal Cytoreductive Surgery for Advanced Ovarian Carcinoma During the Platinum Era: A Meta-Analysis. *J Clin Oncol* 2002;20:1248-1259.
4. Vergote I. Role of surgery in ovarian cancer: an update. *Acta Chir Belg* 2004;104(3):246-56.
5. Markman M, Rothman R, Hakes T, et al. Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. J Clin Oncol 1991 Mar; 9 (3): 389-93
6. Chi DS, McCaughty K, Diaz JP, et al. Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma. Cancer 2006 May 1; 106 (9): 1933-9
7. Mirza MR, Lund B, Lindegaard JC, Keldsen N, Mellemgaard A, Christensen RD, Bertelsen K, et al. A phase II study of combination chemotherapy in early relapsed epithelial ovarian cancer using gemcitabine and pegylated liposomal doxorubicin. Gynecol Oncol. 2010 Oct; 119(1):26-31
8. Markman M, Blessing J,Rubin SC, et al. Phase II trial of weekly paclitaxel (80 mg/m²) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. Gynecol Oncol 2006 Jun; 101 (3): 436-40
9. Miller DS, Blessing JA, Krasner CN, et al. Phase II evaluation of pemetrexed in the treatment of recurrent or persistent platinum-resistant ovarian or primary peritoneal carcinoma: a study of the Gynecologic Oncology Group. J Clin Oncol 2009 Jun 1; 27 (16): 2686-91
10. Coleman RL, Brady WE, McMeekin DS, et al. A phase II evaluation of nanoparticle, albumin-bound (nab) paclitaxel in the treatment of recurrent or persistent platinum resistant ovarian, fallopian tube, or primary peritoneal cancer: A Gynecologic Oncology Group Study. Gynecol Oncol 2011 Jul; 122 (1): 111-5
11. Schilder RJ, Sill MW, Chen X, et al. Phase II study of gefitinib in patients with relapsed or persistent ovarian or primary peritoneal carcinoma and evaluation of epidermal growth factor receptor mutations and immunohistochemical expression: a Gynecologic Oncology Group study. Clin Cancer Res 2005 Aug 1; 11 (15): 5539-48
12. Schilder RJ, Sill MW, Lee RB, et al. Phase II evaluation of imatinib mesylate in the treatment of recurrent or persistent epithelial ovarian or primary peritoneal carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2008 Jul 10; 26 (20): 3418-25
13. Matei D, Sill M, DeGeest K, et al. Phase II trial of sorafenib in persistent or recurrent epithelial ovarian cancer (EOC) or primary peritoneal cancer (PPC): a Gynecologic Oncology Group (GOG) study [abstract no. 5537]. J Clin Oncol 2008; 26 (15 Suppl.)
14. Modesitt SC, Sill M, Hoffman JS, et al. A phase II study of vorinostat in the treatment of persistent or recurrent epithelial ovarian or primary peritoneal carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2008 May; 109 (2): 182-6
15. Behbakht K, Sill M, Darcy KM, et al. Phase II trial of the mTOR inhibitor temsirolimus and evaluation of circulating tumor cells in persistent or recurrent epithelial ovarian and primary peritoneal malignancies: a Gynecologic Oncology Group study [abstract no. 7]. Gynecol Oncol 2010; 116 (3)

16. Usha L, Sill M, Darcy KM, et al. A Gynecologic Oncology Group phase II trial of the protein kinase C-beta inhibitor enzastaurin and evaluation of markers with potential predictive and prognostic value in persistent or recurrent epithelial ovarian and primary peritoneal malignancies [abstract 37]. Gynecol Oncol 2010; 116 Suppl. 1
17. Rocereto TF, Brady WE, Shahin MS, et al. A phase II evaluation of mifepristone in the treatment of recurrent or persistent epithelial ovarian, fallopian or primary peritoneal cancer: a Gynecologic Oncology Group study. Gynecol Oncol 2010 Mar; 116 (3): 332-4
18. Sabbatini P, Sill MW, O'Malley D, et al. A phase II trial of paclitaxel poliglumex in recurrent or persistent ovarian or primary peritoneal cancer (EOC): a Gynecologic Oncology Group Study. Gynecol Oncol 2008 Dec; 111 (3): 455-60
19. Kavanagh JJ, Sill MW, Ramirez PT, et al. Phase II multicenter open-label study of karenitecin in previously treated epithelial ovarian and primary peritoneal cancer: a Gynecologic Oncology Group Study. Int J Gynecol Cancer 2008 May-Jun; 18 (3): 460-4
20. Monk BJ, Sill MW, Hanjani P, et al. Activity of docetaxel plus trabectedin in recurrent or persistent ovarian and primary peritoneal cancer: a phase II study of the Gynecologic Oncology Group [abstract no. 5046]. J Clin Oncol 2010; 28 (15 Suppl.)
21. Mutch DG, Orlando M, Goss T, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. J Clin Oncol 2007 Jul 1; 25 (19): 2811-8
22. Ferrandina G, Ludovisi M, Lorusso D, et al. Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. J Clin Oncol 2008 Feb 20; 26 (6): 890-6
23. Vergote I, Finkler N, del Campo J, et al. Phase 3 randomised study of canfosfamide (Telcyta, TLK286) versus pegylated liposomal doxorubicin or topotecan as third-line therapy in patients with platinum-refractory or -resistant ovarian cancer. Eur J Cancer 2009 Sep; 45 (13): 2324-32
24. Monk BJ, Herzog TJ, Kaye SB, et al. Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. J Clin Oncol 2010 Jul 1; 28 (19): 3107-14
25. Naumann RW, Symanowski JT, Ghamande SA, et al. PRECEDENT: a randomized phase II trial comparing EC145 and pegylated liposomal doxorubicin (PLD) in combination, versus PLD alone, in patients with platinum resistant ovarian cancer [abstract no. LBA5012b]. J Clin Oncol 2010; 28 (18 Suppl.)
26. Colombo N, Schwartz PE, Bamias A, et al. Results of a randomized, open-label, phase III trial of patupilone (P) versus pegylated liposomal doxorubicin (PLD) in taxane/ platinum refractory/resistant patients with recurrent ovarian, fallopian or peritoneal cancer. Ann Oncol 2010; 21 Suppl. 8
27. Nishimura S, Tsuda H, Hashiguchi Y, et al. Phase II study of irinotecan plus doxorubicin for early recurrent or platinum- refractory ovarian cancer: interim analysis. Int J Gynecol Cancer 2007 Jan-Feb; 17 (1): 159-63
28. Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer [published erratum appears in J Clin Oncol 2008 Apr 1; 26 (10): 1773]. J Clin Oncol 2007 Nov 20; 25 (33): 5180-6
29. Ray-Coquard I, Weber B, Cretin J, et al. Gemcitabine oxaliplatin combination for ovarian cancer resistant to taxane-platinum treatment: a phase II study from the GINECO group. Br J Cancer 2009 Feb 24; 100 (4): 601-7

30. Gupta D, Owers RL, Kim M, et al. A phase II study of weekly topotecan and docetaxel in heavily treated patients with recurrent uterine and ovarian cancers. Gynecol Oncol 2009 Jun; 113 (3): 327-30
31. Itani Y, Hosokawa K, Ito K, et al. A phase I/II study of docetaxel and gemcitabine combination for chemotherapy resistant ovarian cancer. Anticancer Res 2009 May; 29 (5): 1521-6
32. Vergote IB, Micha JP, Pippitt CH, et al. Phase II study of NKTR-102 in women with platinum-resistant/ refractory ovarian cancer [abstract]. J Clin Oncol 2010; 28 (15 Suppl.): 5012
33. Pujade-Laureine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, Sorio R, Vergote IB, Vitteveen P, Bamias A, Pereira D, Wimberger P, Oaknin A, Mirza MR, Follana P, Bollag DT, Ray-Coquard I, et al. AURELIA: A randomized phase III trial evaluating bevacizumab (BEV) plus Chemotherapy (CT) for platinum (PT)-resistant recurrent ovarian cancer (OC). J Clin Oncol, 2012 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 30, No 18_suppl (Jun 20 Supplement), 2012: LBA5002
34. Monk BJ, Herzog TJ. The evolution of cost-effective screening and prevention of cervical carcinoma: implications of the 2006 consensus guidelines and human papillomavirus vaccination. American Journal of Obstetrics and Gynecology 2007;197:337–9.
35. Mark AK. Preventing cancer with vaccines: progress in the global control of cancer. *Cancer Prev Res* 2012;**5:**24-29.
36. Colombo N, Carinelli S, Colombo A et al. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012;23:27-32.
37. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol* 2008;26:5802-5812.
38. Dueñas-Gonzalez A, Zarbá JJ, Patel F et al. A phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. *J Clin Oncol* 2011;29:1678-1685.
39. Waggoner SE. Cervical cancer. Lancet 2003;361:2217–25.
40. Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Journal of Clinical Oncology 2004;22: 3113–9.
41. McQuellon RP, Thaler HT, Cella D, Moore DH. Quality of life (QOL) outcomes from a randomized trial of cisplatin versus cisplatin plus paclitaxel in advanced cervical cancer: a Gynecologic Oncology Group study. Gynecologic Oncology 2006;101:296–304.
42. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. Journal of Clinical Oncology 2009;27:4649–55.
43. Lorusso D, Pietragalla A, Mainenti S, Masciullo V, Di Vagno G, Scambia G. Review role of topotecan in gynaecological cancers: current indications and perspectives. Critical Reviews in Oncology/ Hematology 2010;74:163–74.
44. Pectasides D, Kamposioras K, Papaxoinis G et al. Chemotherapy for recurrent cervical cancer. *Cancer Treat Rev* 2008;34:603-613.
45. Fracasso PM, Blessing JA, Wolf J, Rocetero TF, Berek JS, Waggoner S, et al. Phase II evaluation of oxaliplatin in previously treated squamous cell carcinoma of the cervix: a gynecologic oncology group study. Gynecol Oncol. 2003 Jul; 90(1):177-80.

46. Goncalves A, Fabbro M, Lhommé C, Gladieff L, Extra JM, Floquet A, Chaigneau L, Carrasco AT, Viens P et al. A phase II trial to evaluate gefitinib as second- or third-line treatment in patients with recurring locoregionally advanced or metastatic cervical cancer. Gynecol Oncol. 2008 Jan; 108(1): 42-6.
47. Long HF 3rd, Bundy BN, Grendys EC Jr, Benda JA, McMeekin DS, Sorosky J, Miller DS, Eaton LA, Fiorica JV; Gynecologic Oncology Group Study, et al. Randomized phase III trial of cisplatin with or without topotecan on carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. J Clin Oncol. 2005 Jul 20;23(21):4626-33.
48. Rose PG, Blessing JA, Lele S, Abulafia O, et al. Evaluation of pegylated liposomal doxorubicin (Doxil) as second-line chemotherapy of squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol. 2006 Aug;102(2):2010-3.
49. Tinker AV, Ellard S, Welch S, Moens F, Allo G, Tsao MS, Squire J, Tu D, Eisenhauer EA, Mackay H, et al. Phase II study of temsirolimus (CCI-779) in women with recurrent, unresectable, locally advanced or metastatic carcinoma of the cervix. A trial of the NCIC Clinical Trials Group (NCIC CTG IND 199). Gynecol Oncol. 2013 Aug;130(2):269-74.
50. Wright JD, Viviano D, Powell MA, Gibb RK, Mutch DG, Grigsby PW, Rader JS, et al. Bevacizumab combination therapy in heavily pretreated, recurrent cervical cancer. Gynecol Oncol. 2006 Nov;103(2):489-93.
51. Zighelboim I, Wright JD, Gao F, Case AS, Massad LS, Mutch DG, Powell MA, Thaker PH, Eisenhauser EL, Cohn DE, Valea FA, Alvarez Secord A, Lippmann LT, Dehdashti F, Rader JS, et al. Multicenter phase II trial of topotecan, cisplatin and bevacizumab for recurrent or persistent cervical cancer. Gynecol Oncol. 2013 Jul;130(1):64-8.
52. Siegel R, Naishadham D, Jemal A. Cancer statistics 2013. CA Cancer J Clin 2013;63(1):11-30.
53. Colombo N, Preti E, Landoni F et al. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2011;22:35-39.
54. Maggi R, Lissoni A, Spina A et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomized trial. Br J Cancer 2006;95:266-271.
55. Hogberg T, Signorelli M, de Oliveira CF et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer – results from two randomized studies. Eur J Cancer 2010;16(13):2422-2431.
56. Lewin SN, Herzog TJ, Barrena Medel NI, et al. Comparative performance of the 2009 international Federation of gynecology and obstetrics' staging system for uterine corpus cancer. Obstet Gynecol. 2010;116:1141–1149.
57. Amant F, Mansoor RM, Creutzberg CL. Carcinoma of the corpus uteri. *Int J Gynaecol Obstet*. 2012;119(suppl 2):S110–S117.
58. Randall ME, Filliaci VL, Muss H, et al. Randomized phase III trial of whole abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2006;24:36–44.
59. Keys HM, Roberts JA, Bruneto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2004;92:744–751.
60. Creutzberg CL, van Putten WL, Koper PC, et al. PORTEC Study Group. Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol. 2003;89:201–209.

61. Ueda SM, Kapp DS, Cheung MK, et al. Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths. Am J Obstet Gynecol. 2008;198:218e1–218e6.
62. Boruta DM II, Gehrig PA, Fader AN, et al. Management of women with uterine papillary serous cancer: a Society of Gynecologic Oncology (SGO) review. Gynecol Oncol. 2009;115:142–153.
63. Olawaiye AB, Boruta DM II. Management of women with clear cell endometrial cancer: a Society of Gynecologic Oncology (SGO) review. Gynecol Oncol. 2009;113:277–283.
64. Hamilton CA, Cheung MK, Osann K, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer. 2006;94:642–646.
65. Carcangiu ML, Chambers JT. Early pathologic stage clear cell carcinoma and uterine papillary serous carcinoma of the endometrium: comparison of clinicopathologic features and survival. Int J Gynecol Pathol. 1995;14:30–38.
66. Hendrickson M, Ross J, Eifel P, et al. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. Am J Surg Pathol. 1982;6:93–108.
67. Del Carmen MG, Boruta DM II, Schorge JO. Recurrent endometrial cancer. Clin Obstet Gynecol. 2011;54:266–277.
68. Alvarez EA, Brady WE, Walker JL, Rotmensch J, Zhou XC, Kendrick JE, Yamada SD, Schilder JM, Cohn DE, Harrison CR, Moore KN, Aghajanian C, et al. Phase II trial of combination bevacizumab and temsirolimus in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2013 Apr;129(1):22-7.
69. Aghajanian C, Sill MW, Darcy KM, Greer B, McMeekin DS, Rose PG, Rotmensch J, Barnes MN, Hanjani P, Leslie KK, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol. 2011 Jun 1;29(16):2259-65.
70. Coleman RL, Sill MW, Lankes HA, Fader AN, Finkler NJ, Hoffmann JS, Rose PG, Sutton GP, Drescher CW, McMeekin DS, Hu W, Deavers M, Godwin AK, Alpaugh RK, Sood AK, et al. A phase II evaluation of aflibercept in the treatment of recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. Gynecol Oncol. 2012 Dec;127(3):538-43.
71. Colombo N, McMeekin DS, Schwartz PE, Sessa C, Gehrig PA, Holloway R, Braly P, Matei D, Morosky A, Dodion PF, Einstein MH, Haluska F, et al. Ridaforolimus as a single agent in advanced endometrial cancer: results of a single-arm, phase 2 trial. Br J Cancer. 2013 Mar;108(5):1021-6.
72. Dizon DS, Blessing JA, McMeeking DS, Sharma SK, Disilvestro P, Alvarez RD, et al. Phase II trial of ixabepilone as second-line treatment in advanced endometrial cancer: gynecologic oncology group trial 129-P. J Clin Oncol. 2009 Jul 1;27(19):3104-8.
73. Garcia AA, Blessing JA, Nolte S, Mannel RS; Gynecologic Oncology Group, et al. A phase II evaluation of weekly docetaxel in the treatment of recurrent or persistent endometrial carcinoma: a study by the Gynecologic Oncology Group. Gynecol Oncol. 2008 Oct;111(1):22-6.
74. McMeekin DS, Sill MW, Benbrook D, Darcy KM, Stearns-Kurosawa DJ, Eaton L, Yamada SD; Oncology Group study, et al. A phase II trial of thalidomide in patients with refractory endometrial cancer and correlation with angiogenesis biomarkers: a Gynecologic Oncology Group study. Gynecol Oncol. 2007 May;105(2)508-16.
75. Oza AM, Elit L, Tsao MS, Kamel-Reid S, Biagi J, Provencher DM, Gotlieb WH, Hoskins PJ, Ghatage P, Tonkin KS, Mackay HJ, Mazurka J, Sederias J, Ivy O, Dancey JE, Eisenhauser

EA, et al. Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trial Group. J Clin Oncol. 2011 Aug 20;29(24):3278-85.

76. Ray-Coquard I, Favier L, Weber B, Roemer-Becuwe C, Boufnoux P, Fabbro M, Floquet A, Joly F, Plantade A, Paraiso D, Pujade-Lauraine E, et al. Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO. Br J Cancer. 2013 May 14;108(9):1771-7.
77. Slomovitz BM, Lu KH, Johnston T, Coleman RL, Munsell M, Broaddus RR, Walker C, Ramondetta LM, Burke TW, Gershenson DM, Wolf J, et al. A phase 2 study of the oral mammalian target of rapamycin inhibitor, everolimus, in patients with recurrent endometrial carcinoma. Cancer. 2010 Dec 1;116(23):5415-9.
78. Homesley HD, Blessing JA, Sorosky J, et al. Phase II trial of liposomal doxorubicin at 40 mg/m^2 every 4 weeks in endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2005;98:294-298.
79. Lincoln S, Blessing JA, Lee RB, et al. Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2003;88:277-281.
80. Moore DH, Blessing JA, Dunton C, et al. Evaluation of dactinomycin in the treatment of recurrent or persistent endometrial carcinoma: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol 1999;75:473-475.
81. Muggia FM, Blessing JA, Sorosky J, et al. Phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2002;20:2360-2364.
82. Miller DS, Blessing JA, Lentz SS, et al. Evaluation of topotecan in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2002;87:247-251.
83. Fracasso PM, Blessing JA, Molpus KL, et al. Phase II study of oxaliplatin as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2006;103:523-526.
84. Stauber RH, Mann W, Knauer SK. Nuclear and Cytoplasmic Survivin: Molecular Mechanism, Prognostic, and Therapeutic Potential. Cancer Res. 2007 July;67(13):5999-6002.
85. Gartel AL, Tyner AL. The role of the cyclin-dependent kinase inhibitor p21 in apoptosis. Mol Cancer Ther. 2002 Jun;1(8):639-49.
86. Kashyap, T, Crochiere, M, Friedlander, S, et al. Selective Inhibitors of Nuclear Export (SINE) Block the Expression of DNA Damage Repair Proteins and Sensitize Cancer Cells to DNA Damage Inducing Therapeutic Agents. 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, 2014.
87. Ferreiro-Neira I, Torres NE, Liesenfeld LF, et al. XPO1 Inhibition Enhances Radiation Response in Preclinical Models of Rectal Cancer. Clin Cancer Res 2016 Apr;22(7):1663-73.
88. Lassen U, Mau-Sorensen M, Kung AL, et al. A Phase 2 Study on Efficacy, Safety and Intratumoral Pharmacokinetics of Oral Selinexor (KPT-330) in Patients with Recurrent Glioblastoma (GBM). Presentation given at the annual meeting of the American Society for Clinical Oncology, May 29-June 2, 2015.
89. Noske A, Niesporek S, et al. Expression of the nuclear export protein chromosomal region maintenance/exportin 1/Xpo1 is a prognostic factor in human ovarian cancer. Cancer 2008;112(8):1733-43.

90. Wang Y, Wang Y, Xiang J et al. Knockdown of CRM1 inhibits the nuclear export of $p27^{Kip1}$ phosphorylated at serine 10 and plays a role in the pathogenesis of epithelial ovarian cancer. Cancer Letters. 2014;343(1):6-13.
91. Jönsson JM, Johansson I, Dominguez-Valentin M, Kimbung S, Jönsson M, Bonde JH, Kannisto P, Måsbäck A, Malander S, Nilbert M, Hedenfalk I. Molecular subtyping of serous ovarian tumors reveals multiple connections to intrinsic breast cancer subtypes. PLoS One. 2014 Sep 16;9(9):e107643.
92. Burgess M and Puhalla S. BRCA ½-mutation related and sporadic breast and ovarian cancers: more alike than different. Front Oncol. 2014; 27;4:19
93. Audeh MW, Carmichael J, Penson RT, Friedlander M, Powell B, Bell-McGuinn KM, Scott C, Weitzel JN, Oaknin A, Loman N, Lu K, Schmutzler RK, Matulonis U, Wickens M, Tutt A. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet. 2010 Jul 24;376(9737):245-51.
94. Van der Watt P, Maske CP, Hendricks DT et al. The Karyopherin protein, Crm1 and Karyopherin β1, are overexpressed in cervical cancer and are critical for cancer cell survival and proliferation. Int.J.Cancer. 2009;124:1829-1840.
95. Ranganathan P, Yu X, Na C, et al. Preclinical activity of a novel CRM1 inhibitor in acute myeloid leukemia. Blood. 2012;120(9):1765–73.
96. Etchin J, Sanda T, Mansour MR, Kentis A, Montero J, Le BT, Christie AL, McCauley D, Rodig SJ, Kauffman M, Shacham S, Stone R, Letai A, Kung AL, Look TA. KPT-330 inhibitor of CRM1 (XPO1)-mediated nuclear export has selective anti-leukaemic activity in preclinical models of T-cell acute lymphoblastic leukaemia and acute myeloid leukaemia. Br JHaematol. 2013b Apr;161(1):117-27.
97. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10:1–10.
98. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Antiemesis, version 1.2015. Fort Washington, NY. April 2015. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdfhttp://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf.
99. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Palliative Care, version 2.2015. Fort Washington, NY. May 2015. Available at: http://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/generalcancer/pdf/facts.pdfhttp://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/generalcancer/pdf/facts.pdf.
100. Rustin GJS, Vergote I, Eisenhauer E, et al. Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIC). Int J Gynecol Cancer 2011;21: 419-423.
101. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (Version 1.1). European Journal of Cancer 2009;45:228–247.
102. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Fatigue. version 2.2015. Fort Washington, NY. January 2015. Available at http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf.

Appendix 1: Summary of Efficacy Data from Recent Trials for Ovarian Cancer

Table 6: Summary of Efficacy Data from Recent Trials for Ovarian Cancer

Source	Prior treatment	Number of patients enrolled (evaluable)	Drug	Dose	ORR (CR / PR)	SD	PFS (months)	OS (months)
Mirza et al. (2010) [7]	average ≥ 2	79 (-)	PLD (with Gemcitabine)	average 5 cycles PLD 25mg/m² Gemcitabine: 800mg/m²	5% CR 28% PR	56%	6,4	12,5
Markman et al. (2006) [8]	average 1	48 (-)	Paclitaxel (weekly)	(80 mg/m²/week)	21% (-)	(-)	4,9	13,1
Miller et al. (2009) [9]	average 1	51 (-)	Pemetrexed	900 mg/m² every 21 days (median, 4 cycles)	21% (1 CR, 9 PR)	35%	2,9	11,4
Coleman et al. (2011) [10]	average 1	51 (47)	Nab-paclitaxel	100 mg/m² days 1,8,15 on a 28-day schedule, median 4 cycles	23% (1 CR, 10 PR)	36%	4,5	17,4
Schilder et al. (2005) [11]	average 1-2	30 (27)	Gefitinib	500 mg daily, 1 cycle =28 days;median 2 cycles	4% (-)	(-)	2,2	12,2
Schilder et al. (2008) [12]	average 1-2	56 (56)	Imatinib	400 mg twice daily	2% (1 CR, 0 PR)	13%	2,0	16,0
Matei et al. (2011) [13]	average 1-2	73 (71)	Sorafenib	400 mg orally twice per day, 1 cycle = 4 weeks, median 2	3% (0 CR, 2 PR)	34%	2,1	16,3
Modesitt et al. (2008) [14]	average 1-2	27 (-)	Vorinostat	400 mg daily	4% (0 CR, 1 PR)	(-)	3,4	(-)
Behbakht et al. (2011) [15]	average 1-2	60 (54)	Temsirolimus	25 mg weekly iv, 1 cycle =4 weeks, median 2,5	9% (0 CR, 5 PR)	41%	3,2	11,6
Usha et al (2011) [16]	average 1-2	27 (-)	Enzastaurin	loading dose of 375 mg TID on day 1 followed by continuous treatment with 500 mg daily, 1 cycle =28 days, median 2 cycles	7% (-)	22%	1,9	15,1
Rocereto et al. (2010) [17]	average 1-2	24 (22)	Mifepristone	200 mg daily, 1 cycle =28 days	5% (0 CR, 1 PR)	(-)	(-)	(-)
Sabbatini et al. (2008) [18]	average 1-2	78 (-)	Paclitaxel poliglumex	175 mg/m² every 21 days	16% (0 CR, 8 PR)	41%	2,8	15,4
Kavanagh et al. (2008) [19]	average 1-2	27 (26)	Karenitecin (Cositecan)	1.0 mg/m² daily for 5 days every 21 days	12% (1 CR, 2 PR)	(-)	4,5	15,0

Source	Prior treatment	Number of patients enrolled (evaluable)	Drug	Dose	ORR (CR / PR)	SD	PFS (months)	OS (months)
Monk et al. (2011) [20]	average ≤ 3	71 (71)	Docetaxel + trabectedin	average 6 cycles Docetaxel 60mg/m² Trabectedin 1,1 mg/m²	30% (-)	(-)	4,5	16,9
Mutch et al. (2007) [21]	1st line with platinum-based CT	99 (-)	PLD	50 mg/m²	8% (2 CR, 6 PR)	39%	3,1	13,5
		96 (-)	Gemcitabine	1000 mg/m²	6% (1 CR, 5 PR)	55%	3,6	12,7
Ferrandina et al. (2008) [22]	average 1 (platinum, paclitaxel)	76 (-)	PLD	40 mg/m²	16% (3 CR, 8 PR)	43%	16 wk	56 wk
		77 (-)	Gemcitabine	1000 mg/m²	29% (3 CR, 15 PR)	43%	20 wk	51 wk
Vergote et al. (2009) [23]	average 2	229 (-)	PLD or Topotecan	PLD 50mg/m² Topo 1,5 mg/m²	11% (-)	(-)	19 wk	59 wk
		232 (-)	Canfosfamide	1000 mg/m²	4% (-)	(-)	10 wk	37 wk
Monk et al. (2010) [24]	average 1	335 (-)	PLD	50 mg/m²	19% (4 CR, 59 PR)	(-)	5,8	(-)
		337 (-)	PLD + Trabectedin	PLD 30mg/m² Trabectedin 1,1 mg/m²	28% (2 CR, 91 PR)	(-)	7,3	(-)
Naumann et al. (2010) [25]	average ≤ 2	31 (-)	PLD	50 mg/m²	15%	(-)	12 wk	(-)
		60 (-)	PLD + EC145	EC145: 2,5 mg PLD 50 mg/m²	17% (-)	(-)	24 wk	(-)
Colombo et al. (2012) [26]	average ≤ 3	417 (-)	PLD	50 mg /m²	8% (0 CR, 33 PR)	48%	3,7	12,7
		412 (-)	Patupilone	10 mg/m²	16% (0 CR, 64 PR)	44%	3,7	13,2
Nishimura et al. (2007) [27]	(-)	19 (13)	Irinotecan + Doxorubicin	every 4 weeks Irinotecan: 50mg/m² Doxorubicin: 40mg/m²	31% (-)	(-)	(-)	(-)
Cannistra et al. (2007) [28]	average 3	44 (-)	Bevacizumab	15 mg/kg intravenously every 3 weeks	16% (0 CR, 16 PR)	(-)	4,4	10,7
Ray-Coquard et al. (2009) [29]	average 1-2	50	Gemcitabine + Oxaliplatin	median 6 cycles Oxa: 100 mg/m² Ge 1000 mg/m²	31% (-)	31%	4,6	11,4
Gupta et al. (2009) [30]	average 2	27 (24)	Topotecan + Docetaxel	6 cycles Topotecan: 3,5 mg/m² Docetaxel: 30 mg/m²	25% (8% CR, 17% PR)	13%	8,5	18,5
Itani et al. (2009) [31]	average > 2	34 (32)	Gemcitabine + Docetaxel	average ≥ 4 cycles DL1 DOC 70 mg/m² GEM 800 mg/m²	22% (1 CR, 6 PR)	19%	4,8	13,0

Source	Prior treatment	Number of patients enrolled (evaluable)	Drug	Dose	ORR (CR / PR)	SD	PFS (months)	OS (months)
				DL2 DOC 70 mg/m² GEM 1000 mg/m²				
Vergote et al. (2010) [32]	average 3	71 (-)	Irinotecan (NKTR-102)	NKTR-102: 145 mg/m²	27% (-)	(-)	(-)	(-)
Pujade-Lauraine et al (2012) AURELIA [33]	average 2	361 (-)	Chemotherapy + Bevacizumab	every 2 weeks until PD 10 mg/kg	31% (-)	(-)	6,7	not stated

(-)=not assessed

Appendix 2: Summary of Efficacy Data from Recent Trials for Cervical Cancer

Table 7: Summary of Efficacy Data from Recent Trials for Cervical Cancer

Source	Prior treatment	Number of patients enrolled (evaluable)	Drug	Dose	ORR (CR / PR)	SD	PFS (months)	OS (months)
Fracasso et al (2003) [45]	average 1	28 (22)	Oxaliplatin	Cisplatin 130 mg/m²	8% (1 CR, 1 PR)	38%	(-)	(-)
Goncalves et al (2008) [46]	average 1	30 (28)	Gefitinib	Gefitinib 500 mg daily	0% (0 CR, 0 PR)	20%	37 days	3,5
Long et al (2005) [47]	average 1	146	Cisplatin (CPT)	average 3 cycles cisplatin 50 mg/m²	13% (4 CR, 14 PR)	50%	2,9	6,5
		147	Topotecan + Cisplatin (CT)	average 4 cycles Topotecan 0,75 mg/m² + Cisplatin 50 mg/m²	27% (14 CR, 22 PR)	45%	4,6	9,4
Rose et al (2006) [48]	average 1	27 (26)	PLD	average 2 cycle PLD 40 mg/m²	11% (0 CR, 3 PR)	(-)	(-)	(-)
Tinker et al (2013) [49]	average 1	38 (33)	Temsirolimus	Temsirolimus 25mg	3% (0 CR, 1 PR)	58%	3,5	(-)
Wright et al (2006) [50]	(-)	6 (-)	Bevacizumab	(-)	34% (1 CR, 1 PR)	33%	4,3	(-)
Zighelboim et al (2013) [51]	average 1	27 (26)	Cisplatin + Topotecan + Bevacizumab	average 3 cycles cisplatin 50 mg/m², topotecan 0,75 mg/m² and bevacizumab 15 mg/kg	35% (1 CR, 8 PR)	39%	7,1	13,2

(-)=not assessed

Appendix 3: Summary of Efficacy Data from Recent Trials for Endometrial Cancer

Table 8: Summary of Efficacy Data from Recent Trials for Endometrial Cancer

Source	Prior treatment	Number of patients enrolled (evaluable)	Drug	Dose	ORR (CR / PR)	SD	PFS (months)	OS (months)
Alvarez et al (2013) [68]	average 1 or 2	53 (49)	Bevacizumab + Temsirolimus	Bevacizumab 10 mg/kg + Temsirolimus 25 mg weekly	25% (1 CR, 11 PR)	(-)	5,6	16,9
Aghajanian et al (2011) [69]	average 1 or 2	56 (52)	Bevacizumab	average 5 cycles Bevacizumab 15 mg/kg every 3 weeks	14% (1 CR, 6 PR)	50%	4,2	10,5
Coleman et al (2012) [70]	average 2	49 (45)	Aflibercept	Aflibercept 4 mg/kg	7% (0 CR, 3 PR)	(-)	2,9	14,6
Colombo et al (2013) [71]	average of more than 2	45	Ridaforolimus	Ridaforolimus 12mg	11 % (0 CR, 5 PR)	18%	(-)	(-)
Dizon et al (2009) [72]	average 1	52 (50)	Ixabepilone	average 4 cycles Ixabepilone 40mg/m²	12% (1 CR, 5 PR)	60%	2,9	8,7
Garcia et al (2008) [73]	average 1	27 (26)	Docetaxel	Docetaxel 36 mg/m²	8% (0 CR, 2 PR)	31%	(-)	(-)
McMeekin et al (2007) [74]	average 1	27 (24)	Thalidomide	Thalidomide 200 mg daily	13% (0 CR, 3 PR)	8%	1,7	6,3
Oza et al (2011) [75]	average 1	27 (25)	Temsirolimus	average 3 cycles Temsirolimus 25 mg	4% (0 CR, 1 PR)	48%	3,3	(-)
Ray-Coquard (2013) [76]	average 1	44	Everolimus	Everolimus 10 mg	5% (O CR, 2 PR)	29%	2,8	8,1
Slomovitz et al (2010) [77]	average 1 or 2	35 (28)	Everolimus	Everolimus 10 mg	0% (0 CR, 0 PR)	43%	4,5	(-)
Homesley et al (2005) [78]	(-)	56 (52)	Liposomal doxorubicin	at least one to max of 20 cycles Liposomal doxorubicin 40mg/m²	12% (2 CR, 4 PR)	60%	(-)	(-)
Lincoln et al (2003) [79]	average 1 or 2	48 (44)	Paclitaxel	average of 2 cycles Paclitaxel 200mg/m² or 175 mg/m² for patients with prior pelvic	27% (3 CR, 9 PR)	(-)	4,2	10,3

Source	Prior treatment	Number of patients enrolled (evaluable)	Drug	Dose	ORR (CR / PR)	SD	PFS (months)	OS (months)
				radiation therapy				
Moore et al (1999) [80]	average of 1	27 (25)	Dactinomycin	Dactinomycin 2 mg/m²	12% (1 CR, 2 PR)	(-)	(-)	(-)
Muggia et al (2002) [81]	average of 1	46 (42)	Liposomal doxorubicin	average of 2,5 courses PLD 50 mg/m² every 4 weeks	10% (0 CR, 4 PR)	(-)	(-)	8,2
Miller et al (2002)[82]	average of 1	29 (22)	Topotecan	2 to 11 courses Topotecan 0,5 to 1,5 mg/m² every 3 weeks	9% (1 CR, 1 PR)	55%	(-)	(-)
Fracasso et al (2006)[83]	average of 1	54 (50)	Oxaliplatin	Oxaliplatin 130 mg/m² every 21 days	14% (3 CR, 4 PR)	29%	(-)	(-)

(-)=not assessed

Appendix 4: Adverse Event Categories for Determining Relationship to Test Drug

(a) Related (must satisfy one of the following)

This category applies to those adverse events that are considered to be related to the test drug. An adverse event may be considered related if:

1. It follows a reasonable temporal sequence from administration of the drug
2. It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject
3. It disappears or decreases on cessation or reduction in dose. (There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists: e.g. (1) bone marrow depression, (2) tardive dyskinesias.)
4. It follows a known pattern of response to the suspected drug
5. It reappears upon rechallenge

(b) Not related

This category is applicable to those adverse events which are judged to be clearly and incontrovertibly due only to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under related.

Appendix 5: Definitions According to ICH Topic E2A Clinical Safety Data Management, Definitions and Standards for Expedited Reporting

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject who has been administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment.

Adverse reactions are defined as all untoward and unintended responses to an investigational medicinal product related to any dose administered. The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

A serious adverse event or serious adverse reaction is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any adverse event that at any dose fulfills at least one of the following criteria:

- is fatal (results in death) *(NOTE: Death is an outcome, not an event)*
- is life-threatening *(NOTE: The term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe)*
- required in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically significant or requires intervention to prevent one or other of the outcomes listed above

Medical and scientific judgement should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in A&E or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

An unexpected adverse event, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product)

Causality is initially assessed by the Investigator. With respect to the obligation to report and document (regulatory authorities, ethics committees and other Investigators) serious adverse events, causality can be one of two possibilities:

- No (not related; equals not drug-related)
- Yes (remotely, possibly or probably drug-related)

All adverse events not assessed as definitively “not drug-related” by the Investigator will be considered as adverse drug reactions.

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction whose nature or severity is not consistent with the applicable product information.

It is important that the severity of an adverse event is not confused with the seriousness of the event. For example, vomiting which persists for many hours may be severe, but is not necessarily a serious adverse event. On the other hand, stroke which results in only a limited degree of disability may be considered a mild stroke, but would be a serious adverse event.

A serious adverse event occurring during the study or which comes to the attention of the Investigator within three weeks of stopping the treatment or during the protocol-defined follow-up period, if this is longer, must be reported, whether considered treatment-related or not. In addition, serious adverse events occurring after this time should be reported if considered related to test “drug”.

Such preliminary reports will be followed by detailed descriptions later that will include copies of hospital case reports, autopsy reports and other documents.

For serious adverse events, the following must be assessed and recorded on the adverse events page of the case report form: intensity, relationship to test substance, action taken, and outcome to date.

The obligation to document and report must be adhered to according to the national and international laws and regulations.

For contact details and fax no. for SAE and pregnancy reporting, please refer to page 14.

Appendix 6: ECOG Performance Status Scale

GRADE	SCALE
0	Fully active, able to carry out 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 housework, office work
2	Ambulatory and capable of all self-care, but unable to carry out 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 out any self-care. Totally confined to bed or chair.
5	Dead

Appendix 7: Cockroft-Gault Formula

Calculated CL_{CR} (ml/min) = $\frac{[(140 - \text{subject's age in years}) \times \text{subject's actual body weight in kilograms}]}{72 \times \text{subject's serum creatinine (in mg/dL)}}$ *

*: x 0.85 for females

Calculated CL_{CR} (ml/min) = $\frac{[(140 - \text{subject's age in years}) \times \text{subject's actual body weight in kilograms}] \times K^*}{\text{subject's serum creatinine (in µmol/L)}}$

K*: 1.05 for females

Appendix 8: NCI-CTCAE Version 4.03

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Appendix 9: Ophthalmic Exam

An ophthalmic examination by an optometrist or ophthalmologist is required at screening and if clinically indicated during the study (e.g., monitoring of pre-existing cataracts, visual disturbances).
The examination is to include the following:

Prior to dilation:

- best corrected visual acuity
- slit lamp examination
- tonometry

Following dilation:

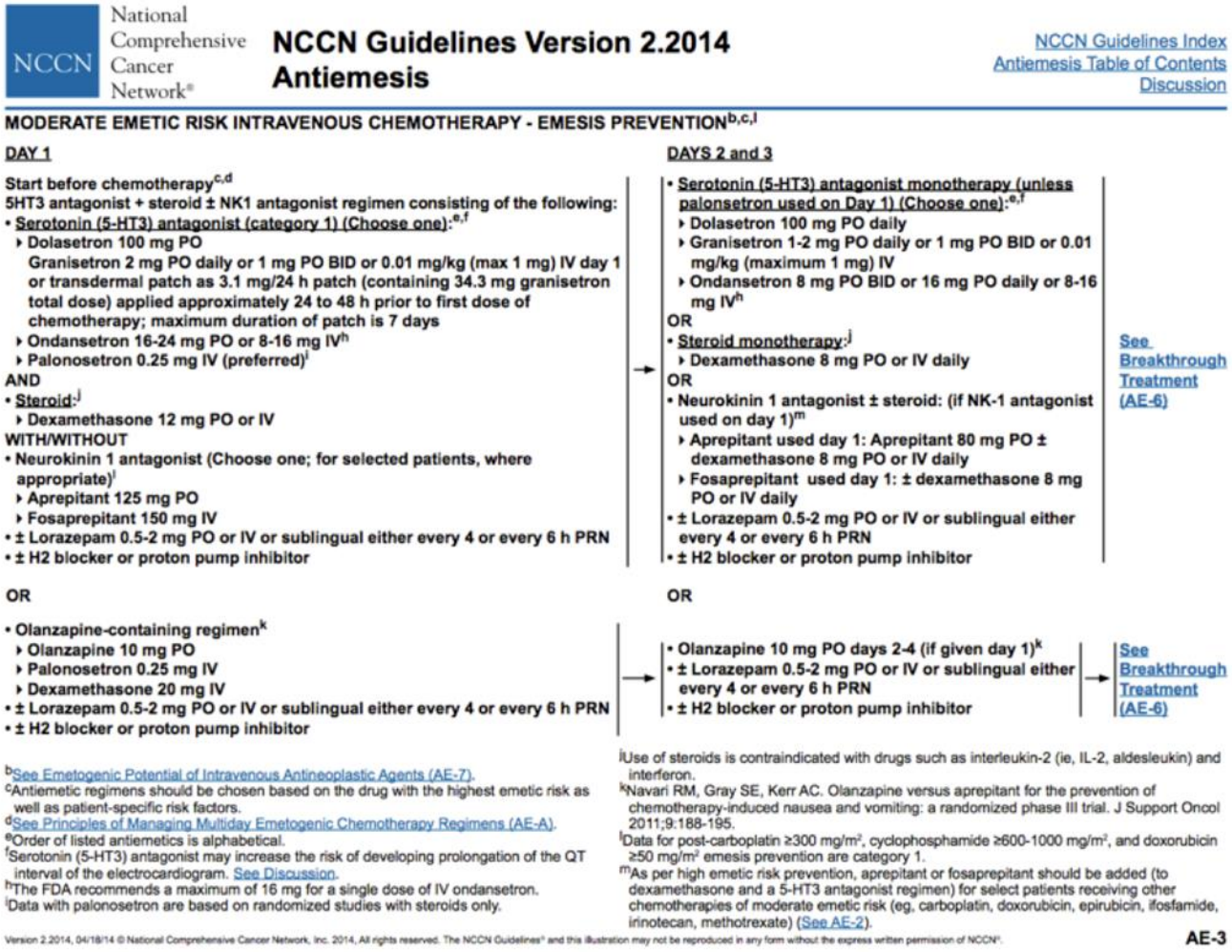
- fundoscopy
- slit lamp examination to document lens clarity

If a cataract/lens opacity is seen during the examination, the cataract/lens opacity will be graded according to a Grade 1-4 system (modified from Optometric Clinical Practice Guideline: Care of the Adult Patient with Cataracts: available on the American Optometric Association website: www.aoa.org).

Please note: patients enrolled under a prior version of the protocol who had detectable cataracts graded according to the LOCS III will continue to have their cataracts graded according to LOCS III and will not switch to the new Grade 1-4 cataract scale. For new patients or patient for whom no cataracts have been detected to date, if cataracts are detected they will be graded according to the Grade 1-4 scale.

Grading of Cataracts*				
Cataract Type	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Nuclear Yellowing and sclerosis of the lens nucleus	Mild	Moderate	Pronounced	Severe
Cortical Measured as aggregate percentage of the intrapupillary space occupied by the opacity	Obscures 10% of intrapupillary space	Obscures 10% -50% of intra-pupillary space	Obscures 50% -90% of intra-pupillary space	Obscures >90% of intrapupillary space
Posterior subcapsular Measured as the aggregate percentage of the posterior capsular area occupied by the opacity	Obscures 10% of the area of the posterior capsule	Obscures 30% of the area of the posterior capsule	Obscures 50% of the area of the posterior capsule	Obscures >50% of the area of the posterior capsule
*Designation of cataract severity that falls between grade levels can be made by addition of a + sign (e.g., 1+, 2+). Grading of cataracts is usually done when pupil is dilated.				

Appendix 10: NCCN Clinical Practice Guidelines in Oncology: Antiemesis



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NCCN Guidelines Version 2.2014
Antiemesis

NCCN Guidelines Index
Antiemesis Table of Contents
Discussion

MODERATE EMETIC RISK INTRAVENOUS CHEMOTHERAPY - EMESIS PREVENTION[b,c,l]

DAY 1

Start before chemotherapy[c,d]
5HT3 antagonist + steroid ± NK1 antagonist regimen consisting of the following:
- **Serotonin (5-HT3) antagonist (category 1) (Choose one):[e,f]**
  - **Dolasetron 100 mg PO**
    Granisetron 2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (max 1 mg) IV day 1 or transdermal patch as 3.1 mg/24 h patch (containing 34.3 mg granisetron total dose) applied approximately 24 to 48 h prior to first dose of chemotherapy; maximum duration of patch is 7 days
  - **Ondansetron 16-24 mg PO or 8-16 mg IV[h]**
  - **Palonosetron 0.25 mg IV (preferred)[i]**

AND
- **Steroid:[j]**
  - **Dexamethasone 12 mg PO or IV**

WITH/WITHOUT
- **Neurokinin 1 antagonist (Choose one; for selected patients, where appropriate)[i]**
  - **Aprepitant 125 mg PO**
  - **Fosaprepitant 150 mg IV**
- **± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN**
- **± H2 blocker or proton pump inhibitor**

→

DAYS 2 and 3

- **Serotonin (5-HT3) antagonist monotherapy (unless palonsetron used on Day 1) (Choose one):[e,f]**
  - **Dolasetron 100 mg PO daily**
  - **Granisetron 1-2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (maximum 1 mg) IV**
  - **Ondansetron 8 mg PO BID or 16 mg PO daily or 8-16 mg IV[h]**

OR
- **Steroid monotherapy:[j]**
  - **Dexamethasone 8 mg PO or IV daily**

OR
- **Neurokinin 1 antagonist ± steroid: (if NK-1 antagonist used on day 1)[m]**
  - **Aprepitant used day 1: Aprepitant 80 mg PO ± dexamethasone 8 mg PO or IV daily**
  - **Fosaprepitant used day 1: ± dexamethasone 8 mg PO or IV daily**
- **± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN**
- **± H2 blocker or proton pump inhibitor**

→ See Breakthrough Treatment (AE-6)

OR

- **Olanzapine-containing regimen[k]**
  - **Olanzapine 10 mg PO**
  - **Palonosetron 0.25 mg IV**
  - **Dexamethasone 20 mg IV**
- **± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN**
- **± H2 blocker or proton pump inhibitor**

→

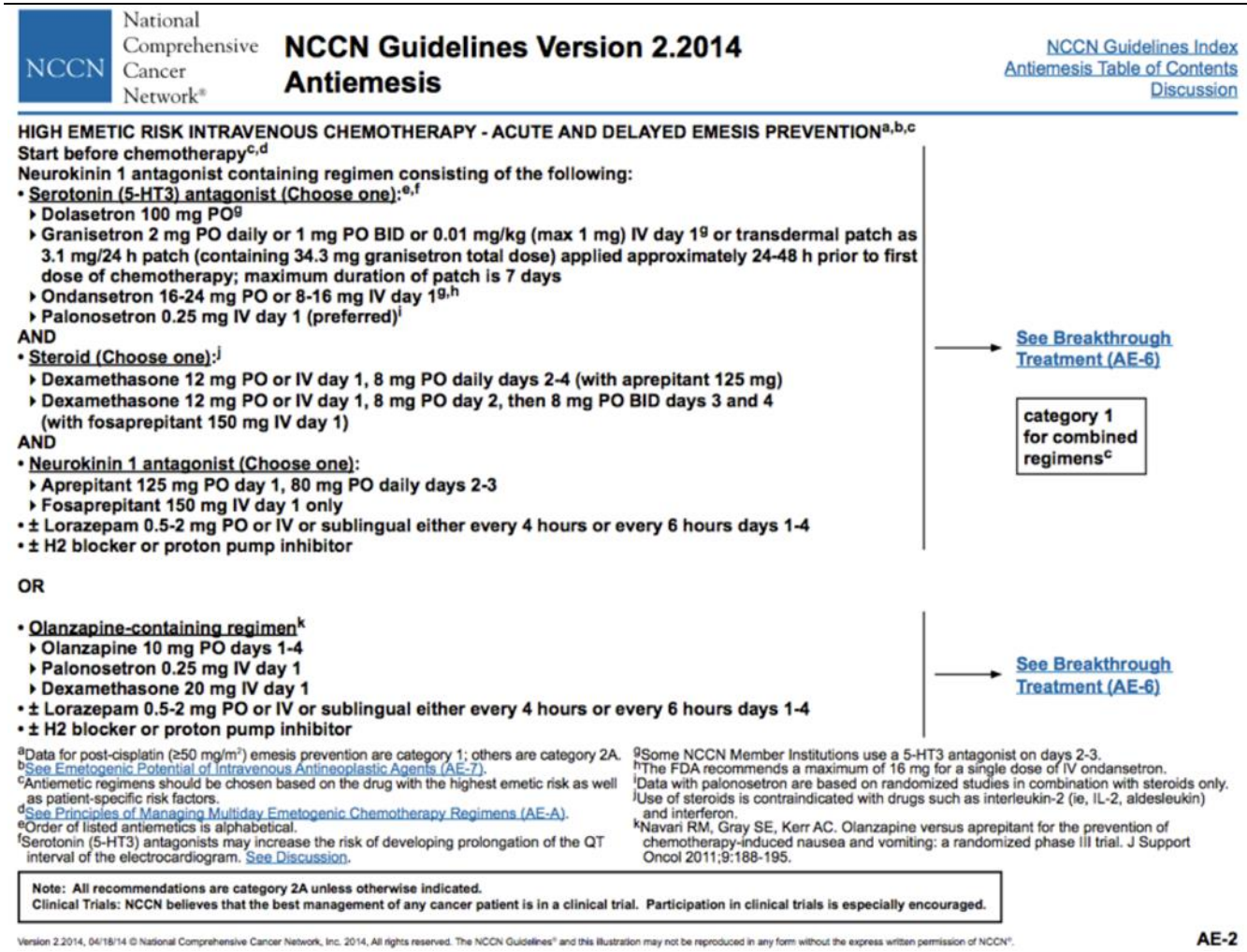
OR

- **Olanzapine 10 mg PO days 2-4 (if given day 1)[k]**
- **± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN**
- **± H2 blocker or proton pump inhibitor**

→ See Breakthrough Treatment (AE-6)

[b] See Emetogenic Potential of Intravenous Antineoplastic Agents (AE-7).
[c] Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.
[d] See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).
[e] Order of listed antiemetics is alphabetical.
[f] Serotonin (5-HT3) antagonist may increase the risk of developing prolongation of the QT interval of the electrocardiogram. See Discussion.
[h] The FDA recommends a maximum of 16 mg for a single dose of IV ondansetron.
[i] Data with palonosetron are based on randomized studies with steroids only.
[j] Use of steroids is contraindicated with drugs such as interleukin-2 (ie, IL-2, aldesleukin) and interferon.
[k] Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. J Support Oncol 2011;9:188-195.
[l] Data for post-carboplatin ≥300 mg/m², cyclophosphamide ≥600-1000 mg/m², and doxorubicin ≥50 mg/m² emesis prevention are category 1.
[m] As per high emetic risk prevention, aprepitant or fosaprepitant should be added (to dexamethasone and a 5-HT3 antagonist regimen) for select patients receiving other chemotherapies of moderate emetic risk (eg, carboplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, methotrexate) (See AE-2).

AE-3



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NCCN Guidelines Version 2.2014
Antiemesis

NCCN Guidelines Index
Antiemesis Table of Contents
Discussion

HIGH EMETIC RISK INTRAVENOUS CHEMOTHERAPY - ACUTE AND DELAYED EMESIS PREVENTION[a,b,c]

Start before chemotherapy[c,d]

Neurokinin 1 antagonist containing regimen consisting of the following:

- **Serotonin (5-HT3) antagonist (Choose one):[e,f]**
  - **Dolasetron 100 mg PO[g]**
  - **Granisetron 2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (max 1 mg) IV day 1[g] or transdermal patch as 3.1 mg/24 h patch (containing 34.3 mg granisetron total dose) applied approximately 24-48 h prior to first dose of chemotherapy; maximum duration of patch is 7 days**
  - **Ondansetron 16-24 mg PO or 8-16 mg IV day 1[g,h]**
  - **Palonosetron 0.25 mg IV day 1 (preferred)[i]**

AND

- **Steroid (Choose one):[j]**
  - **Dexamethasone 12 mg PO or IV day 1, 8 mg PO daily days 2-4 (with aprepitant 125 mg)**
  - **Dexamethasone 12 mg PO or IV day 1, 8 mg PO day 2, then 8 mg PO BID days 3 and 4 (with fosaprepitant 150 mg IV day 1)**

AND

- **Neurokinin 1 antagonist (Choose one):**
  - **Aprepitant 125 mg PO day 1, 80 mg PO daily days 2-3**
  - **Fosaprepitant 150 mg IV day 1 only**
- **± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 hours or every 6 hours days 1-4**
- **± H2 blocker or proton pump inhibitor**

→ See Breakthrough Treatment (AE-6)

category 1 for combined regimens[c]

OR

- **Olanzapine-containing regimen[k]**
  - **Olanzapine 10 mg PO days 1-4**
  - **Palonosetron 0.25 mg IV day 1**
  - **Dexamethasone 20 mg IV day 1**
- **± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 hours or every 6 hours days 1-4**
- **± H2 blocker or proton pump inhibitor**

→ See Breakthrough Treatment (AE-6)

[a]Data for post-cisplatin (≥50 mg/m²) emesis prevention are category 1; others are category 2A.
[b]See Emetogenic Potential of Intravenous Antineoplastic Agents (AE-7).
[c]Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.
[d]See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).
[e]Order of listed antiemetics is alphabetical.
[f]Serotonin (5-HT3) antagonists may increase the risk of developing prolongation of the QT interval of the electrocardiogram. See Discussion.
[g]Some NCCN Member Institutions use a 5-HT3 antagonist on days 2-3.
[h]The FDA recommends a maximum of 16 mg for a single dose of IV ondansetron.
[i]Data with palonosetron are based on randomized studies in combination with steroids only.
[j]Use of steroids is contraindicated with drugs such as interleukin-2 (ie, IL-2, aldesleukin) and interferon.
[k]Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. J Support Oncol 2011;9:188-195.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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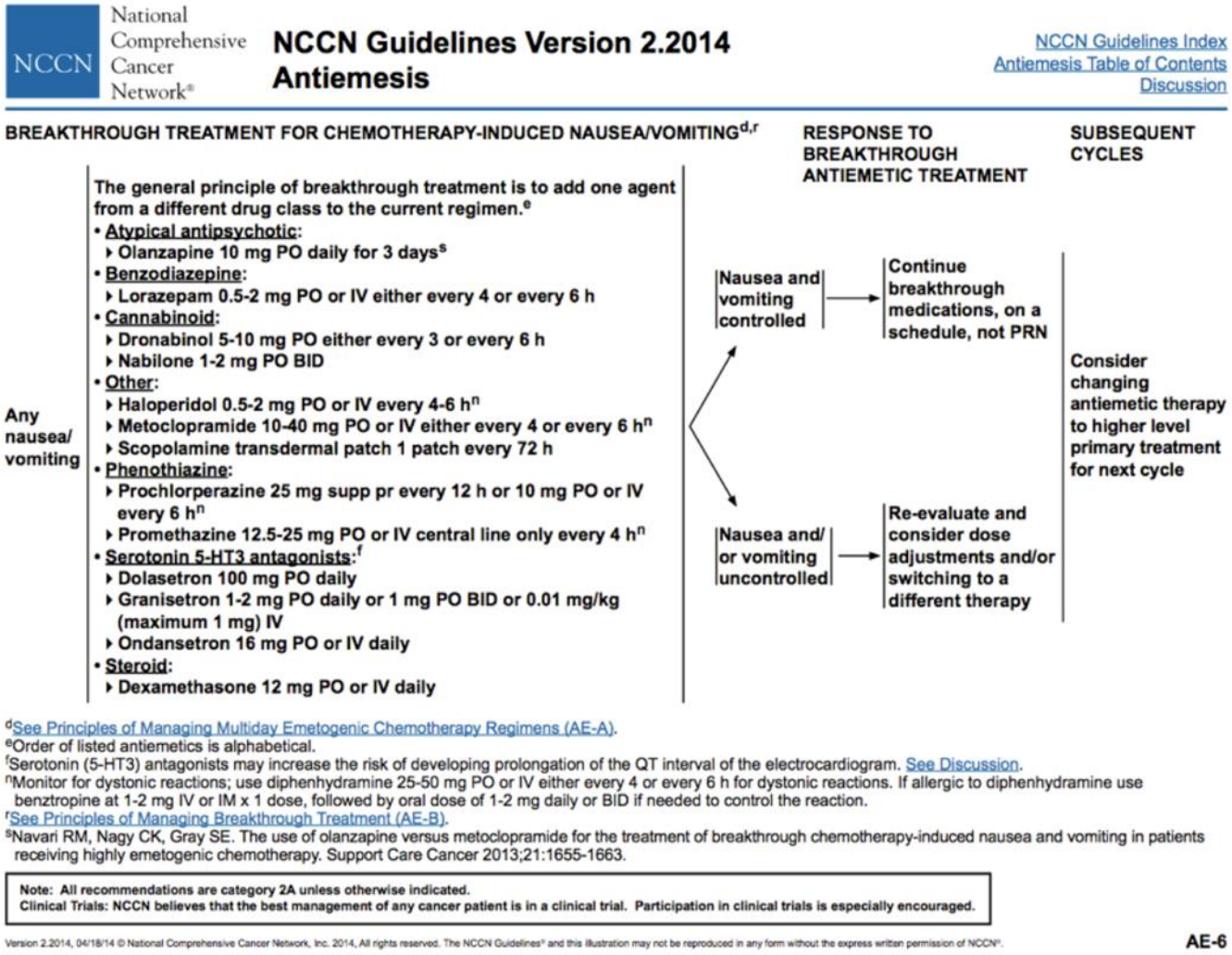
AE-2



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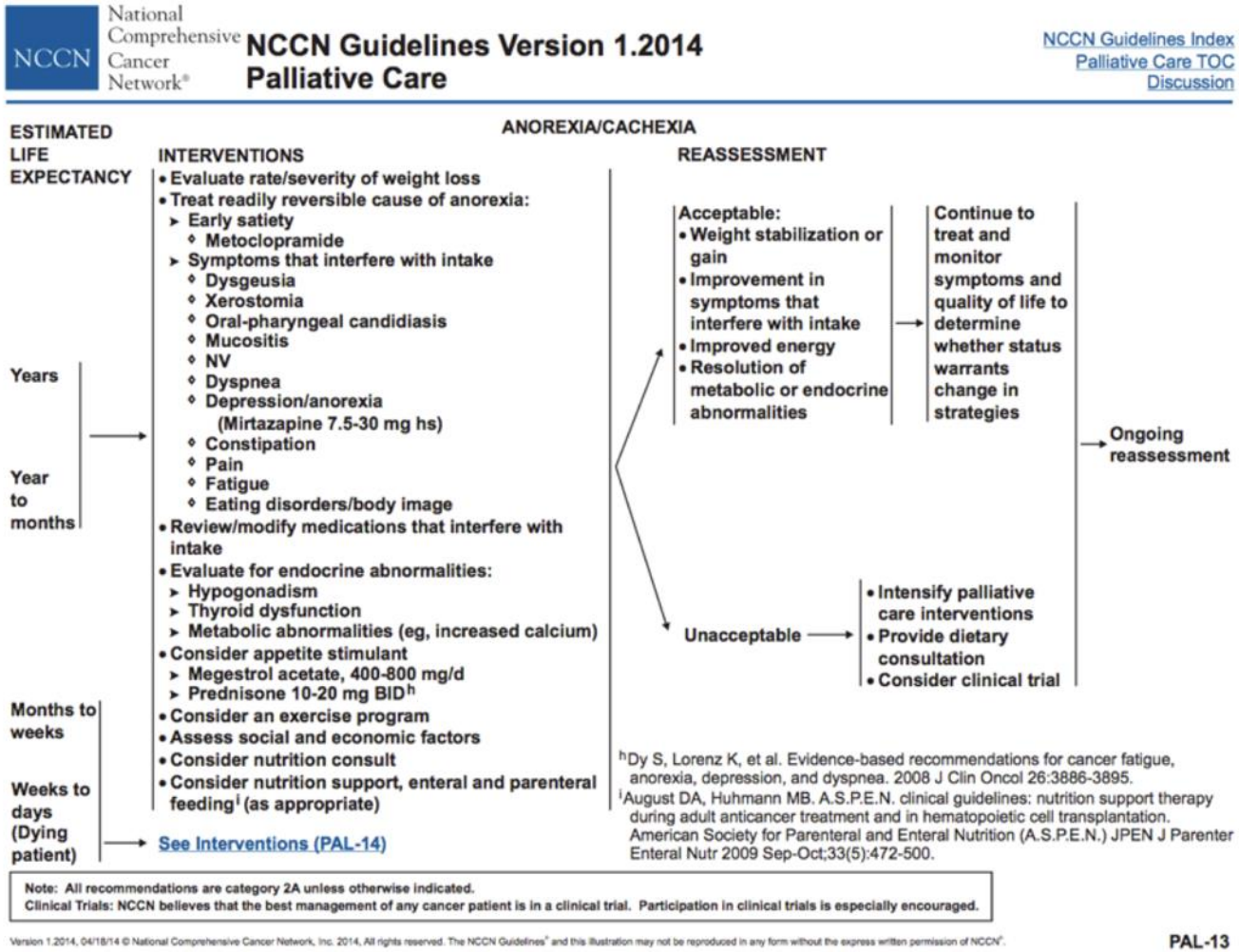
Appendix 11: NCCN Clinical Practice Guidelines in Oncology: Anorexia/Cachexia



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Appendix 12: Evaluation of Response According to CA-125

(Modified from *Rustin, Vergote, Eisenhauer et al*)

A CA-125 response is defined as at least a 50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.

To calculate CA-125 responses accurately, the following rules apply:

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within the reference range of CA-125 levels will not interfere with the response definition.
- For each patient, the same assay method must be used, and the assay must be tested in a quality control scheme.
- Patients are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human anti-mouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days (e.g., paracentesis). If assessing therapy that includes 2 treatment modalities for relapse (e.g., surgery and chemotherapy), any CA-125 response results from both treatment modalities. CA-125 cannot distinguish between the effects of the 2 treatments

The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response. To calculate response, an intent-to-treat analysis should be used that includes all patients with an initial CA-125 level of at least twice the upper limit of the reference range as eligible and evaluable. In addition, as a separate analysis, those patients who have a CA-125 response and whose CA-125 level falls to within the reference range can be classified as CA-125 complete responders.

In Table 9 (Appendix 13) and Table 10 (Appendix 14) where CA-125 is stated as normalized or normal, means within the reference range. Patients who have a fall of CA-125 to within the reference range but whose initial CA-125 was less than twice the upper limit of the reference range have not had a CA-125 response and cannot therefore be classified as a CA-125 complete responder.

Appendix 13: Evaluation of Best Overall Response in Patients Without Initial Measurable Disease and Who Are Evaluable by CA-125

Table 9: Evaluation of Best Overall Response in Patients Without Initial Measurable Disease and Who Are Evaluable by CA-125

CA-125	Nontarget Lesions[a]	New Lesions	Overall Serological Response	Best Response for this Category also Requires
Response and Normalized	CR	No	CR	Confirmed and maintained for at least 28 days
Response	Non-PD	No	PR	
Normalized but no response	Non-CR/Non-PD	No	SD	
Non-PR/non-PD	Non-PD	No	SD	
PD	Any	Yes or No	PD	
Any	PD[b]	Yes or No	PD	
Any	Any	Yes	PD	

[a] Nontarget lesions include ascites and peritoneal thickening, which are not measureable according to RECIST.
[b] Unequivocal progression in nontarget lesions maybe accepted as disease progression.
CR-complete response; PD-progressive disease; PR-partial response; SD-stable disease

Appendix 14: Best Overall Response in Patients with Measureable Disease and Who Are Also Evaluable by CA-125

Table 10: Best Overall Response in Patients with Measureable Disease and Who Are Also Evaluable by CA-125

Target Lesion[a]	Nontarget[b]	New Lesion	CA-125	Overall Best Response	Comments
CR	CR	No	Normal	CR	Best RECIST 1.1 response for CR and PR also requires it to be confirmed and maintained for at least 28 days if response is primary endpoint
CR	Non-CR Non-PD	No	Not PD	PR	
CR	CR	No	PR but not normal	PR	
CR	NE	No	PR	PR	
PR	Non-PD or NAE	No	Not PD	PR	
NAE	Non-PD	No	PR	PR	
PD or New	>28 days from CA-125 PR[d]	--	PR	PR	
SD[c]	Non-PD	No	PR	PR	
SD[c]	Non-PD or NAE	No	Not PR and not PD	SD	
PD or New	≤28 days from CA-125 PR[d]	--	PR	PD	
PD	Any	Yes or No	Any	PD	
Any	PD	Yes or No	Any	PD	
Any	Any	Yes	Any	PD	
Any	Any	Yes or No	PD	PD	

[a] Target lesions include up to 5 measurable lesions (2 per organ) as defined by RECIST 1.1.
[b] Nontarget lesions include ascites and peritoneal thickening which are not measureable according to RECIST 1.1.
[c] The protocol should specify the minimum time interval between 2 measurements for classification as stable disease.
[d] Patients who have CA-125 response that occurs more than 28 days from PD according to RECIST 1.1 are considered a PR, according to best response, but PD if the RECIST 1.1 PD is within 28 days of CA-125 response.
CR-complete response; PD-progressive disease; PR-partial response; SD-stable disease; NE-not evaluable; NAE-not all evaluated

Appendix 15: Glutathione (GSH), N-Acetylcysteine (NAC), or S-Adenosylmethionine (SAM)-Containing Products (Representative List)**Glutathione (GSH)**		**N-acetylcysteine (NAC)**		**S-adenosylmethionine (SAM)**	
Product Name	**Ingredient**	**Product Name**	**Ingredient**	**Product Name**	**Ingredient**
Glutathione	glutathione	Antidote for acetaminophen overdose	acetylecysteine	SAM-e Complete	S-adenosyl-methionine
L-Glutathione	L-glutathione	Cerefolin NAC: medical food for age-related memory loss	L-methylfolate vitamin B12 N-acetyl cysteine	SAMe	S-adenosyl-L-methionine
Glutathione reduced	glutathione	NAC	N-acetyl cysteine	Double Strength SAMe 400	S-adenosyl-methionine
Reduced glutathione with alpha lipoic acid	Setria L-glutathione	N-A-C Sustain	N-acetyl L-cysteine		
Glutathione, Cysteine & C	glutathione L-cysteine vitamin C	Best NAC Detox Regulators	N-acetyl cysteine		
(Mega-) Liposomal Glutathione	glutathione				
Lypospheric GSH	glutathione				
Ivory Caps Skin Enhancement Formula	glutathione				

18 PROTOCOL VERSION ≥3.2: MAINTENANCE PHASE

Appendix 16 Maintenance Phase

1. INVESTIGATIONAL PLAN FOR THE MAINTENANCE PHASE

1.1. Maintenance Phase Design

As of Version 3.2 of the protocol, Karyopharm will terminate the Primary Treatment Phase of the study and the remaining patients on study will transfer to the Maintenance Phase of the study to continue treatment with selinexor and/or survival follow-up. These patients will be followed primarily for safety. The patients will be allowed to receive treatment until disease progression, Investigator or patient decision to discontinue study treatment, pregnancy, unacceptable AEs or toxicity that cannot be managed by supportive care, withdrawal of consent, death, or termination of the study. Data from the Maintenance Phase will be collected in a separate database to allow locking of the Primary Treatment Phase database after initiation of the Maintenance Phase.

1.1.1. Transition from Primary Treatment Phase to Maintenance Phase

Patients will complete their current cycle in the Primary Treatment Phase and then transition to the Maintenance Phase of the study (Maintenance Phase Cycle 1 Day 1).

1.1.2. Study Treatment

The treatment under investigation in the Maintenance Phase of the study (i.e., the "investigational medicinal product" [IMP]) is selinexor 20 mg tablets for oral administration. Patients will continue on the same dose of selinexor (as they were receiving prior to this amendment) and dosing may be modified as needed according to the guidelines in this protocol. For more details on selinexor dosing see Section 1.1.2.2.

1.1.2.1. Selinexor Tablets

Selinexor 20 mg tablets will be provided as coated, immediate-release tablets for oral administration in blister packs. Patients will be given a supply of tablets for non-clinic dosing days. Additional information about selinexor is available in the *Selinexor IB*.

1.1.2.1.1. Labeling

All labels will include conditions for storage, lot number, and other pertinent information such as Sponsor and caution statement. Selinexor should not be used after the expiration date.

1.1.2.1.2. Dispensing Directions

Dispensing instructions for selinexor will be provided in the *Pharmacy Manual*.

1.1.2.1.3. Storage

Selinexor tablets should be stored at or below 86°F (30°C) in a secured area with access restricted to the site staff pharmacist or designee(s) at room or refrigerated temperature.

Room temperature storage is preferred. The tablets must not be stored at freezer temperatures or frozen. Refer to the *Pharmacy Manual* for detailed information on selinexor storage, stability, and administration.

1.1.2.1.4. Accountability

The Investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Study treatment accountability will be noted by the clinical research associate during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the time of study treatment discontinuation or at the end of the study (See Section 1.1.5 for definition of end of study).

1.1.2.2. Selinexor Dosing

Patients will receive the same selinexor dose and schedule during the Maintenance Phase as they received during the Primary Treatment Phase. Selinexor doses will be administered in 20 mg dose increments (e.g., 20 mg, 40 mg, 60 mg, etc.), consistent with the dose that the patient received in the Primary Treatment Phase of the study. However, if the patient was previously receiving a dose that was in between these 20 mg doses (e.g., 30 mg), the Investigator should consult with the Medical Monitor to determine the appropriate dose for that patient in the extension study. In no instance will the dose of selinexor exceed 70 mg/m^2.

1.1.2.3. Concurrent Treatments

Concurrent treatments, if any, that the patient received in the Primary Treatment Phase of the study, may be continued, at the discretion of the Investigator, but they will not be provided by Karyopharm. No new, additional treatments for the patient's malignancy (except for supportive care) may be added without the consent of the Medical Monitor.
The patient should receive concomitant treatment, as needed per standard of care and institutional standards. In addition, the patient will receive concomitant medications to treat symptoms, AEs, and intercurrent illnesses that are medically necessary as part of standard care. See Section 6.4.2 for prohibited medications.

1.1.3. Study Visits

During the Maintenance Phase of the study, assessments will take place at once-monthly visits for Cycles 1-7, then, provided that the patient is clinically stable, at every-other month visits thereafter for Cycles > 7. Each cycle will last 28 days.

1.1.4. Study Assessments

Safety will be assessed by adverse events (AEs) graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v. 4.03 (as was done in antecedent studies). Disease assessment (response to treatment), where appropriate, to monitor disease status and response to therapy are not required per protocol, but it is requested that if possible the Investigator provide any disease status and response to treatment information obtained from disease assessments performed as part of institutional standard of care. Treatment will continue until disease progression,

Investigator or patient decision to discontinue study treatment, pregnancy, or unacceptable AEs or toxicity that cannot be managed by supportive care, withdrawal of consent, death, or termination of the study. See Table 11 for a full schedule of assessments.

1.1.5. End of Treatment (EOT) and End of Study

The EOT Visit will occur ≤ 14 days after the patient receives their last dose of study treatment. A Safety Follow-up Call/Visit will be performed 30 days (+7 days) after last dose of study treatment. Follow-up ends when the patient has either completed that 30-day follow-up, withdrawn consent, been withdrawn by the Investigator, died, or been lost to follow-up. The end of study (EOS) will occur upon completion of the 30-day follow-up period for the last patient treated, or when Karyopharm has decided to end the study.

Table 11: Schedule of Assessments

	Maintenance Phase				
Activity/Assessment[1]	**Cycle 1**	**Cycles 2-7 Visits**	**Cycles >7 (Every Other Cycle) Visits**	**End-of-Treatment (EoT) Visit**	**Safety Follow-up Call/Visit[5]**
	Day 1	**Day 1 (± 3 Days)**	**Day 1 (± 3 Days)**	**≤ 14 Days Post Last Dose**	**30 Days (+ 7 Days) Post Last Dose**
Clinical Assessments					
Weight and BSA	X	X	X	X	
Vital signs (BP, pulse, temperature)	X	X	X	X	
Complete physical exam	X				
Symptom-directed physical exam		X	X		
Ophthalmic examination	As clinically indicated				
Laboratory Assessments					
Urinalysis	X	X	X	X	
CBC with differential	X	X	X	X	
Complete serum chemistry	X	X	X	X	
Serum amylase and lipase levels[2]	X	X	X	X	

	Maintenance Phase				
Activity/Assessment[1]	**Cycle 1**	**Cycles 2-7 Visits**	**Cycles >7 (Every Other Cycle) Visits**	**End-of-Treatment (EoT) Visit**	**Safety Follow-up Call/Visit[5]**
	Day 1	**Day 1 (± 3 Days)**	**Day 1 (± 3 Days)**	**≤ 14 Days Post Last Dose**	**30 Days (+ 7 Days) Post Last Dose**
Coagulation tests	X	X		X	
Serum hCG pregnancy test[3]	As clinically indicated				
Administration of selinexor in clinic[4]	X	X	X		
AE/SAE reporting	THROUGHOUT				
Concomitant medication use	THROUGHOUT				
Telephone contact					X
Antineoplastic therapy after EoT				X	X
Abbreviations: AE: adverse event; BSA = body surface area; CBC = complete blood count; hCG = serum human chorionic gonadotropin; SAE = serious adverse event.					

[1] If study treatment is administered on a visit day, assessments for that visit should be performed before study treatment is administered. Disease assessments to monitor disease status and response to therapy are not required per protocol, but it is requested that if possible the Investigator provide any disease status and response to treatment information obtained from disease assessments performed as part of institutional standard of care.

[2] If not included in the complete serum chemistry panel, amylase and lipase levels must be performed at the same time points as the complete serum chemistry.

[3] Applicable for women of childbearing potential only.

[4] Dosing on days of clinic visits will occur in the clinic; dosing on subsequent days within a cycle will be done at home.

[5] At the 30-day safety follow-up the patient should be contacted (by phone or visit) to assess survival status, disease status, overall medical condition, and collect information on any antineoplastic therapies used after discontinuation of study treatment.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

To provide continued access to selinexor (KPT-330) for the patients remaining on treatment at the time of the termination of the Primary Treatment Phase.

2.1.2. Secondary Objectives

To collect additional long-term safety, tolerability, and disease response (as collected through standard of care) data for selinexor.

2.2. Endpoints

Safety and tolerability of study treatment will be evaluated by means of AE reports, physical examination results (including vital signs), clinical laboratory results, and ophthalmic examination results where appropriate.

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events [CTCAE], v. 4.03 will be used for grading the severity of AEs. For all AEs and SAEs, Investigators will provide their assessment of causality as either related or not related.

Efficacy data will be collected per standard of care.

3. SELINEXOR SUPPORTIVE CARE AND DOSE MODIFICATIONS

3.1. Supportive Care

Supportive measures for optimal medical care should be provided to patients as needed. Based on clinical observations in 730 adult patients analyzed for safety as of 31 May 2015, the most frequently reported side effects seen with selinexor are primarily related to anorexia with poor caloric and fluid intake leading to weight loss, fatigue, and nausea. Thrombocytopenia also occurs, although it is rarely associated with bleeding.

In order to minimize nausea, unless contraindicated, the patient will receive 5 HT3 antagonists (ondansetron 8 mg or equivalent) twice daily (bid) – three times a day(tid) as needed (prn).

Supportive care including additional anti-nausea/anti-emetic therapy, acid suppression (proton-pump inhibitors and/or H2-blockers) and other treatments should be administered per Investigator judgement and institutional guidelines.

3.1.1. Infection

Appropriate broad-spectrum intravenous antibiotics and antifungal agents should be started immediately in patients who develop fever or other signs of systemic infection. Selinexor should be suspended the patient develops Grade 4 infection or clinical sepsis

(in the absence of documented infection) until the condition is stabilized. Selinexor can then be re-started at the same dose.

3.2. Selinexor Dose Modifications for Toxicity

Based on observations from the ongoing Phase 1 studies in patients with advanced hematological and solid tumors (KCP-330-001 to -003), selinexor shows a reasonably wide therapeutic range with activities from ~15 mg to ≥100 mg (~10 mg/m^2 to ≥ 60 mg/m^2). Therefore, in order to optimize specific antitumor activity and tolerability by the patient, dose reductions and/or schedule modifications will be allowed after discussion with the Medical Monitor. Patients should also be treated aggressively with supportive care, as needed, to reduce toxicities.

In general, if a patient experiences an AE that the Investigator believes is associated with selinexor, appropriate supportive care should be implemented per institutional standards. If the AE does not resolve, the Investigator should discuss the possibility of holding, discontinuing, or lowering the dose of selinexor with the Medical Monitor. If selinexor dosing is held, it may be re-introduced upon recovery to Grade ≤ 1 or Baseline at one dose level lower, at the discretion of the Investigator, after consulting the Medical Monitor.

3.2.1. Reporting of SAEs

Any clinical AE or abnormal laboratory test value that is serious occurring during the course of the study from the date of signing the informed consent, irrespective of the treatment received by the patient, must be reported to the Sponsor within 24 hrs (expedited notification). For each patient, all SAEs must be reported up to 30 days after the last dose of investigational product. SAEs occurring more than 30 days after a patient is discontinued from the study treatment may be reported at the discretion of the Investigator.

The completed SAE form must be sent to:

Pharmacovigilance Department
Karyopharm Therapeutics Inc.
Email: pharmacovigilance@karyopharm.com
Fax: +1-617-334-7617 (US)
+49-89-9218-5650 (Germany)

The Sponsor will medically review all SAEs.

The following detailed information must be recorded for each SAE in the SAE report form:

- A description of the AE
- The severity grade as assessed by the Investigator according to the definitions in NCI-CTCAE Version 4.03 (Appendix 8)
- The date of becoming serious and the date of becoming known (if different)
- The reason for seriousness
- The outcome of the SAE at the time of the report
- Information on administration of the study drug and any action taken

- Information on any treatment procedures necessary for the SAE, concomitant medications, relevant lab tests and relevant medical history

If in any one patient the same SAE occurs on several occasions, then the SAE in question must be documented and assessed anew each time.

The Investigator is required to submit SAE Follow-up reports until the SAE has resolved or stabilized and all queries have been answered.

Appendix 17: Summary and Rationale for Changes to Protocol KCP 330-005

Summary and Rationale for Changes to Version 3.1 Protocol KCP-330-005

Karyopharm Therapeutics Inc.

A Phase II, Open-label Study of Efficacy and Safety of the Selective Inhibitor of Nuclear Export/SINE Compound KPT-330 (Selinexor) in Patients with Advanced Gynaecologic Malignancies

Clinical Trial Protocol No:	Sponsor Protocol No. **KCP-330-005**
Development Phase:	Phase II
Investigational Product:	Selinexor (KPT-330)
Indication:	Gynaecologic malignancies
Sponsor:	Karyopharm Therapeutics Inc.
Drug Discoverer:	Karyopharm Therapeutics Inc.
Sponsor Address:	85 Wells Avenue Newton, MA USA 02459

***From**: Version 3.1 dated January 08, 2016*
***To**: Version 3.2 dated August 04, 2016*

The clinical study protocol KCP-330-005, *A Phase II, Open-label Study of Efficacy and Safety of the Selective Inhibitor of Nuclear Export/SINE Compound KPT-330 (Selinexor) in Patients with Advanced Gynaecologic Malignancies* has been amended by the Sponsor to incorporate changes suggested internally, improve clarity by eliminating inconsistencies among sections, and correcting errors from previous versions.

The revised protocol Version 3.2 dated 04 August 2016 will be submitted by the Principal Investigator or designee to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

Descriptions of the key changes that have been made in protocol KCP-330-005 Version 3.2, from the previous Version 3.1, including the rationales for these changes, are provided below.

Administrative

- Updated the version number and date of protocol from Version 3.1 dated 08 January 2016 to Version 3.2 dated 04 August 2016 (**Modified sections**: Global)

Background

- Updated introduction text (**Modified sections**: Section 1.1)

References

- Updated to reflect the revised introduction text (**Modified sections**: Section 17)

Rationale, Objectives, Investigational Plan (including study treatment), Supportive Care and Dose Modifications

- Due to the termination of the Primary Treatment Phase of the study, a maintenance schedule has been added to allow the existing patients on the study to continue treatment with selinexor and/or survival follow-up. The revised Maintenance Phase includes study treatment, schedule of assessments, supportive care, dose modification and data collection for separate Maintenance Phase database. (**Modified sections [added sections]**: Synopsis, Table 1, Section 1.4, Section 2.1, Section 2.2, Section 3.1, Section 5.1, Section 5.2, Section 5.3, Section 5.7, Section 6.2.1, Section 6.2.2, Section 6.3, Section 7.2.1, Section 7.2.2, Section 9, Section 17, and Section 18 [Appendix 16])

Appendix 18: Summary and Rationale for Changes to Protocol KCP 330-005

Summary and Rationale for Changes to Version 3.0 Protocol KCP-330-005

Karyopharm Therapeutics Inc.

A Phase II, Open-label Study of Efficacy and Safety of the Selective Inhibitor of Nuclear Export/SINE™ Compound KPT-330 (Selinexor) in Patients with Advanced Gynaecologic Malignancies

Clinical Trial Protocol No:	Sponsor Protocol No. **KCP-330-005**
Development Phase:	Phase II
Investigational Product:	Selinexor (KPT-330)
Indication:	Gynaecologic malignancies
Sponsor:	Karyopharm Therapeutics Inc.
Drug Discoverer:	Karyopharm Therapeutics Inc.
Sponsor Address:	85 Wells Avenue Newton, MA USA 02459

***From**: Version 3.0 dated November 12, 2014*
***To**: Version 3.1 dated January 08, 2016*

The clinical study protocol KCP-330-005, *A Phase II, Open-label Study of Efficacy and Safety of the Selective Inhibitor of Nuclear Export/SINE™ Compound KPT-330 (Selinexor) in Patients with Advanced Gynaecologic Malignancies* has been amended by the Sponsor to incorporate changes suggested internally, improve clarity by eliminating inconsistencies among sections, and correcting errors from previous versions.

The revised protocol Version 3.1 dated 08 January 2016 will be submitted by GSO to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

Descriptions of the key changes that have been made in protocol KCP-330-005 Version 3.1, from the previous Version 3.0, including the rationales for these changes, are provided below.

Administrative

- Internal changes were made to improve clarity and to eliminate inconsistencies among sections, and to correct previously existing errors. (**Modified sections**: Global)
- Updated the version number and date of protocol from Version 3.0 dated 12 November 2014 to Version 3.1 dated 08 January 2016. (**Modified sections**: Global)
- Minor corrections were made to grammar and punctuation throughout. (**Modified sections**: Global)

Background

- Replaced Figure 1 with an updated (similar) figure of the mechanism of action of selinexor, which appears in the most recent *Selinexor Investigator's Brochure* (**Modified section:** 1.1.2)
- Deleted Figure 2: KPT-SINE Compounds (XPO1 Inhibitors) Induce Distinct Outcomes in Normal and Malignant Cells because it was unnecessary (**Modified section:** 1.1.2)
- In the Pre-clinical Safety sub-section, moved the brief description of histotoxicology studies performed in rats and monkeys from Section 1.1.4: Clinical Summary to Section 1.1.3 (Pre-clinical).
- Revised selinexor clinical summary and replaced outdated and unnecessary information with more recent information (**Modified section**: Section 1.1.5)
- Updated patient exposure to selinexor to 730 patients, which is consistent with Selinexor Investigator's Brochure, v.5, dated 12 August 2015. (**Modified section:** 1.1.4)
- Updated (favorable) results, seen in an interim analysis performed on 29 April 2015 (**Modified section:** 1.2)

Study Design

- Clarified the definitions of platinum refractory and platinum resistant in the inclusion criteria. (**Modified sections:** Synopsis – inclusion criteria; Section 4.2.1)
- Clarified that dose escalation can occur if there is tolerability and no sign of progression after 12 weeks of treatment for patients in Parts 1 and 2. (**Modified sections:** Synopsis – treatment scheme; Section 3.1, Section 6.3.1)
- Revised wording related to the number of subjects to specify that 21 and 32 evaluable patients are needed in Parts 1 and Part 2, respectively. (**Modified sections:** Synopsis [planned sample size, sample size calculation], Section 3.2, Section 8.2)

- Removed supportive care text for the following events as guidance for these events is now provided in the dose adjustment/supportive care table in Section 6.3.2: Anorexia, fatigue, emesis, acute emesis, diarrhea, and thrombocytopenia. (**Modified sections:** former sections – Section 6.5)
- Consolidated and reformatted guidance for restricted and prohibited medications into one section. (**Modified section**: Section 6.4.2)
- Clarified that the overall survival objective will include overall survival rates at 12 and 24 months. (**Modified sections**: Synopsis, Section 2.3, Section 8.4.3)
- Clarified reasons for which the study can be discontinued (**Modified section:** Section 5.5)
- Clarified primary and secondary parameters, including details of the efficacy evaluation). (**Modified sections:** Synopsis – primary and secondary parameters, Section 8.4.3)
- Added total abstinence as a method of prevention of pregnancy. (**Modified section:** Section 6.4.1.1)
- Modified the definitions of the ITT population. (**Modified section:** Section 8.3.1)
- Added a provision to perform a primary analysis for submission in a CSR when patients are still on treatment, and subsequently perform a final analysis (to be reported in a final CSR) after all patients have completed treatment. (**Modified section:** 16)
- A table of GSH-, NAC-, and SAM-containing products was added as an appendix based on FDA feedback on a different protocol. (**Modified sections**: Section 17, Appendix 14)

Study Assessments

- Clarified the timing of collection of AEs and SAEs. (**Modified sections:** Schedule of Assessments, Section 7.1.1, Section 7.1.3)
- Revised the window for assessments to be completed following 6 weeks of treatment for gynaecological cancers from ±5 days to ±7 days. (**Modified sections:** Schedule of assessments)
- Added a baseline assessment for CA-125 to comply with CGIG CA-125 response criteria requirements (**Modified sections:** Schedule of assessments, Section 5.2.1)

Selinexor Dosing

- The use of 20 mg tablets was added for increased tolerability based on the results of the ongoing Phase 1 studies. (**Modified section**: Section 6.2.1.)
- Clarified that doses of selinexor must be at least 36 hours apart for twice weekly dosing and at least 5 days apart for once weekly dosing. (**Modified sections**: Synopsis – treatment scheme, Section 3.1, Section 3.1.1, Section 6.2.1.2, Section 6.3.5)

Summary and Rationale for Changes to Version 2.0 Protocol KCP-330-005

Karyopharm Therapeutics Inc.

A Phase II, Open-label Study of Efficacy and Safety of the Selective Inhibitor of Nuclear Export/SINE™ Compound KPT-330 (Selinexor) in Patients with Advanced Gynaecologic Malignancies

Clinical Trial Protocol No:	Sponsor Protocol No. **KCP-330-005**
Development Phase:	Phase II
Investigational Product:	Selinexor (KPT-330)
Indication:	Gynaecologic malignancies
Sponsor:	Karyopharm Therapeutics Inc.
Drug Discoverer:	Karyopharm Therapeutics Inc.
Sponsor Address:	85 Wells Avenue Newton, MA USA 02459

***From**: Version 2.0 dated September 09, 2014*
***To**: Version 3.0 dated November 12, 2014*

The clinical study protocol KCP-330-005, *A Phase 2, Open-label Study of Efficacy and Safety of the Selective Inhibitor of Nuclear Export/SINE™ Compound KPT-330 (Selinexor) in Patients with Advanced Gynaecologic Malignancies* has been amended by the Sponsor to incorporate changes suggested internally and to provide clarity to eliminate inconsistencies between sections, and to correct prior errors.

The revised protocol Version 3.0 dated 12 November 2014 will be submitted by GSO to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

Description of the key changes that have been made to protocol KCP-330-005 Version 3.0 from the previous Version 2.0, including rationale for the changes, are listed below.

Administrative

- Internal changes suggested by the sponsor to provide clarity and to eliminate inconsistencies between sections, and to correct prior errors (**Modified sections**: Global)
- Updated the version number and date of protocol from Version 2.0 dated 09 September 2014 to Version 3.0 dated 12 November 2014 (**Modified sections**: Global)
- Minor corrections to grammar throughout (**Modified sections**: Global)

Inclusion/Exclusion Criteria

- Revised inclusion criterion # 5 to specify that patients with ovarian cancer must have disease that is measureable according to RECIST or assessable according to the GCIG CA-125 criteria. (**Modified sections:** Synopsis [inclusion criteria] and Section 4.2)
- Revised exclusion criterion # 11 to clarify that receipt of an investigational drug within 3 weeks prior to Cycle 1 Day 1 is prohibited; however, participation in an anti-cancer study within 3 weeks prior to receiving study drug is acceptable. (**Modified sections:** Synopsis [Exclusion criteria], Section 4.3)

Study Design

- Revised the dosing schedule for Part 2, Schedule 1 from 35 mg/m^2 twice weekly during Weeks 1-3 of a 4-week cycle for a total of 6 doses per cycle to 35 mg/m^2 twice weekly during Weeks 1-4 of a 4-week cycle for a total of 8 doses per cycle to enable comparison of 4-week dosing between Part 2 Schedules 1 and 2. In Part 1, the dose is 50 mg/m^2 twice weekly for a total weekly dose of 100 mg/m^2. Two additional doses are being evaluated in Part 2 of the study: in Schedule 1 the dose is 35 mg/m^2 twice weekly for a total weekly dose of 70 mg/m^2 and 280 mg/m^2 per cycle; in Schedule 2 the dose is 50 mg/m^2 once weekly for a total weekly dose of 50 mg/m^2 and 200 mg/m^2 per cycle. The dosing schedule for Part 2, Schedule 1 was revised from 35 mg/m2 twice weekly during Weeks 1-3 of a 4-week cycle to 35 mg/m^2 twice weekly during Weeks 1-4 of a 4-week cycle. This change was made so that all Part 2 patients would receive doses in each week of their 4-week cycle, enabling a more direct comparison of the Part 2 results obtained with 35 mg/m^2 twice weekly versus 50 mg/m^2 once weekly dosing. (**Modified sections:** Synopsis [Study design, treatment scheme], Section 3.1, Section 3.1.1, Section 6.2.1.2, Section 6.3.1, Section 8.2).
- Added CA-125 response definition (**Modified sections:** Synopsis [inclusion criteria], Section 4.2, Appendix 13)

Safety and Tolerability

- Removed the acetaminophen restriction as ongoing clinical safety evaluations on the use of selinexor in combination with acetaminophen have not shown any significant clinical or laboratory abnormalities with doses of acetaminophen up to 1 gram and selinexor up to 55 mg/m^2 (approximately 80-100 mg). (**Modified sections:** Section 6.4, Section 6.4.2, Section 6.5.8)
- Revised the prophylactic and supportive care: During Part 1 of the study, gynaecological patients primarily suffered from anorexia secondary to nausea and vomiting; treatment of these symptoms with neurokinin-1 receptor antagonist is highly effective. Mirtazapine and olanzapine will be retained only as a second line of treatment. Additionally, treatment with dexamethasone (or equivalent) was changed from required prophylactic treatment to recommended supportive care because some patients enrolled in the study may be intolerant of glucocorticoids. (**Modified sections:** Section 1.1.4, Section 5.2.1, Section 6.3.2 [Table 4], Section 6.5.1)
- Revised the dose modification table to include revised dose modification guidance for thrombocytopenia and nausea/emesis, and specified that guidance used for Grade 3 toxicities should also be used for toxicities that are Grade ≥ 3. The table was also revised to include specific guidance for Part 1 and Part 2 (Schedules 1 and 2). For thrombocytopenia, this change was made as in preclinical and ongoing Phase 1 studies thrombocytopenia has been observed to be time dependent rather than dose dependent. Therefore, reducing the frequency of dosing with KPT-330 instead of reducing the dose of KPT-330 can decrease the recovery time from thrombocytopenia. For nausea/emesis, these changes were made as during Part 1 of the study, gynaecological patients primarily suffered from anorexia secondary to nausea and vomiting; treatment of these symptoms with neurokinin-1 receptor antagonist is highly effective. Mirtazapine and olanzapine should be considered a second line of treatment (**Modified sections:** Section 6.3.2 [Table 4])
- Revised the pre-specified dose/schedule modifications for adverse events (AEs) related to study drug for Part 2, Schedules 1 and 2. For both schedules, it is specified that upon the discontinuation of dosing, patients will continue to be assessed. These changes were made to improve tolerance to treatment with selinexor in the context of various AEs. (**Modified sections:** Synopsis [Treatment scheme], Section 6.3 [Table 3], Section 6.3.2 [Table 4]). The following changes were made:
    - Schedule 1
        - Dose level -1 was changed from 25 mg/m^2 twice weekly to 50 mg/m^2 once weekly.
        - Dose level -2 was changed from discontinue dosing to 35 mg/m^2 once weekly.
        - Dose level -3 (discontinue dosing) was added.
    - Schedule 2
        - Dose level -1 was changed from 40 mg/m^2 once weekly to 35 mg/m^2 once weekly.
        - Dose level -2 (discontinue dosing) was added.

Study Assessments

- CCI [redacted]
- Reactivated the collection of blood for the assessment of CTCs as a direct correlation was made between the presence of CTC in the blood of patients on this trial to their response. Therefore, additional CTC samples will be collected to test the hypothesis that the presence of CTC in the blood of patients on the trial may predict their response to treatment with selinexor. (**Modified sections:** Synopsis [Companion translational study], Flow chart, Section 5.1.2, Section 5.2.2)
- CCI [redacted]

Summary and Rationale for Changes to Version 1.0 Protocol KCP-330-005

Karyopharm Therapeutics Inc.

A Phase II, Open-label Study of Efficacy and Safety of the Selective Inhibitor of Nuclear Export (SINE) KPT-330 (Selinexor) in Patients with Advanced Gynaecologic Malignancies

Clinical Trial Protocol No:	Sponsor Protocol No. **KCP-330-005**
Development Phase:	Phase II
Investigational Product:	Selinexor (KPT-330)
Indication:	Gynaecologic malignancies
Sponsor:	Karyopharm Therapeutics Inc.
Drug Discoverer:	Karyopharm Therapeutics Inc.
Sponsor Address:	85 Wells Avenue Newton, MA USA 02459

***From**: Version 1.0 dated November 11, 2013*
***To**: Version 2.0 dated September 09, 2014*

The clinical study protocol KCP-330-005, *A Phase 2, Open-label Study of Efficacy and Safety of the Selective Inhibitor of Nuclear Export (SINE) KPT-330 (Selinexor) in Patients with Advanced Gynaecologic Malignancies* has been amended by the Sponsor to incorporate changes suggested internally and to provide clarity to eliminate inconsistencies between sections, and to correct prior errors.

The revised protocol Version 2.0 dated 09 September 2014 will be submitted by GSO to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A description of the key changes that have been made to protocol KCP-330-005 Version 2.0 from the previous Version 1.0, including rationale for the changes, are listed below.

Administrative

- Internal changes suggested by the sponsor to provide clarity and to eliminate inconsistencies between sections, and to correct prior errors (**Modified sections**: Global)
- Updated the version number and date of protocol from Version 1.0 dated 11 Nov 2013 to Version 2.0 dated 09 September 2014 (**Modified sections**: Global)
- Minor corrections to grammar throughout (**Modified sections**: Global)
- Updated sponsor's name and address (**Modified sections**: Global)
- Adjustment of study duration due to expanded number of patients (**Modified sections**: Synopsis [Duration of study], Section 3.3).
- Updated background on clinical safety and anti-tumor activity (**Modified section**: Section 1.1.4)
- Updated the electronic mail address to which the patient registration form will be sent from CCI [redacted] to CCI [redacted] (**Modified section:** Section 3.2)
- Addition of a Safety Monitoring Committee to provide oversight on the safety of the investigational product for this study. The Safety Monitoring Committee will be responsible for reviewing accumulated safety data from the study. (**Modified section:** Section 14)

Inclusion/Exclusion Criteria

- Revised inclusion criterion # 3 to specify that Carcinosarcomas (Malignant Mixed Mullerian Tumor) are allowed based on input from study Investigators. (**Modified sections:** Synopsis [inclusion criteria], Section 4.1, Section 4.2)
- Revised inclusion criterion # 1 to specify that chemotherapy for relapsed or advanced (stage IIIc) disease is allowed for endometrium patients based on input from study Investigators. (**Modified sections:** Synopsis [inclusion criteria], Section 4.2)
- Revised inclusion criterion # 9 to define liver function (**Modified sections:** Synopsis [inclusion criteria], Section 4.2)

- Revised age at time of enrollment from >18 years to ≥18 years (Inclusion criterion #4). (**Modified sections:** Synopsis [inclusion criteria], Section 4.2)
- Revised inclusion criterion # 15 to specify that patients of childbearing potential must agree to use effective contraception during treatment and up to 3 months from last dose (**Modified sections:** Synopsis [inclusion criteria], Section 4.2)

Study Design

- Expanded the number of patients in the ovarian cohort, to an additional 32 patients. The ovarian cohort will now be randomly enrolled into Schedule 1 or 2 with 16 patients per schedule. A twice-weekly schedule will be used in one arm, at 35 mg/m^2, and dosing in this schedule will be only in Weeks 1-3 of each 4-week cycle. A once-weekly dosing schedule at 50 mg/m^2 will also be used. (**Modified sections:** Synopsis [Planned sample size, study design, duration of study treatment, treatment scheme, sample size calculation], Section 3.1, Section 3.1.1, Section 3.3, Section 8.2)
- Added overall survival to secondary objectives and removed it from exploratory objectives (**Modified section**: Synopsis [Objectives], Section 2.2)
- Removed male contraception text. (**Modified section**: Section 6.4.1.1).

CCI [redacted]

Study Assessments

- Additional collection of CA-125 blood test for clinical chemistry for ovarian patients only. (**Modified sections**: Schedule of Assessments, Section 5.2.3).

CCI [redacted]

- The ophthalmological examination assessment was revised to specify that if a cataract is seen during the examination, the cataract will be graded according to the Lens Opacities Classification System (LOCS III). This change was made to more accurately assess the status of any cataract. (**Modified sections:** Schedule of Assessments, Section 5.2.2, Appendix 10)
- Change in frequency of several assessments: They will now be done at baseline and if clinically indicated. (**Modified section**: Schedule of Assessments)
- Addition of optional PET scan at baseline. (**Modified section**: Schedule of Assessments, Section 5.2.2)

Safety and Tolerability

- Updated the electronic mail address to which the SAE forms will be sent from CCI [redacted] to CCI [redacted]. (**Modified section:** Section 7.2)
- Supportive care and prophylactic guidelines were updated based on recent Phase 1 clinical trial results and Investigator input. (**Modified section**: Section 5.2.1)
- Added Classification of Adverse Events by Causality, Table 5 to adverse event section for clarification of AEs related or not related to study drug. (**Modified section:** Section 7.1.1)
- The dose adjustment guidelines have been updated based on recent results of the Phase 1 clinical trials. (**Modified section:** Section 6.3.2)
- The dose adjustment guidelines have been updated based on new enrollment schedule added to this clinical trial. (**Modified section:** Section 6.3.2)
- Updated information related to the MTD to specify that escalating beyond 70 mg/m^2 twice weekly is prohibited in any study. Details of these updates to KPT-330 dosing information were documented in a May 20, 2014 addendum to the Investigators Brochure and provided to all Investigators. (**Modified section:** Section 1.1.4)
- Added intrapatient dose escalation. (**Modified section**: Section 6.3.1)