SENTINEL

An Investigator Initiated Phase 1 Trial To Evaluate mFOLFOX6 With Selinexor (KPT-330), An Oral Selective Inhibitor Of Nuclear Export (SINE), In Patients With Metastatic Colorectal Cancer

Study Code: Sentinel

Sponsor: GSO Global Clinical Research B.V.

Coordinating investigator Prof. Dr. Carsten Bokemeyer, Hamburg

Coordinating CRO: GSO mbH

EudraCT Number: 2014-003526-40

Confidentiality

Original protocol: Version 1.0, 2014.11.11 Current version: Version 1.1, 2015.01.22

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22.1.2015
Date (DD Month YYYY)

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Date (DD Month YYYY)

Investigator's Agreement

I have read the attached protocol entitled

"An Investigator Initiated Phase 1 Trial To Evaluate mFOLFOX6 With Selinexor (KPT-330), An Oral Selective Inhibitor Of Nuclear Export (SINE), In Patients With Metastatic Colorectal Cancer", dated 22.01.2015,

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 Month YYYY)

Investigator

Investigator's Institution

Synopsis

Protocol no.	SENTINEL
Protocol version (Date)	Version 1.1, 2015.01.22
Abbreviated Title	
Detailed title	An Investigator Initiated Phase 1 Trial To Evaluate Combination Treatment mFOLFOX6 With Selinexor (KPT-330) In Patients With Metastatic Colorectal Cancer
EudraCT no.	2014-003526-40
Coordinating investigator	Professor Dr. Carsten Bokemeyer, Hamburg
Sponsor	GSO Global Clinical Research B.V. Keizersgracht 62-64 1015 CS Amsterdam, The Netherlands
Study design	· Multi center, open-label, non-randomized phase I trial · Patients with metastatic colorectal cancer will receive FOLFOX6: Oxaliplatin 85mg/m² day 1, 5-FU 400 mg/m^2 iv bolus day 1, leucovorin 400 mg/m^2 day 1 and 5-FU 2400 mg/m² days 1-3 every 2 weeks; combined with Selinexor 40, 60 or 80 mg on day 1, 3 and 8 of each two-week cycle. Treatment will be continued until disease progression or significant toxicities occur or patient withdraws consent.
Anticipated start date	January 2015
Duration of study	With an estimated accrual rate of 2-3 patients per month, and a total number of 27 patients planned, the anticipated enrollment period will last about 12 months.
Total number of sites	4-8
Study population	Patients with metastatic colorectal cancer according to the inclusion and exclusion criteria below will be enrolled in this study trial.
Objectives	
Primary objective	Primary objective is the determination of the maximum tolerated dose (MTD) of selinexor in combination with mFOLFOX6 in patients with metastatic colorectal cancer.
Secondary objectives	Secondary objectives are efficacy parameters and tolerability.
Exploratory objectives	NA
Planned sample size	A sample size of 27 patients is planned and all patients receive mFOLFOX6 and Selinexor.
Inclusion criteria	1. Patients with histologically confirmed diagnosis of colorectal cancer presenting with unresectable stage IV (UICC) disease (primary tumor may be present) 2. Patients who are feasible for treatment with FOLFOX (prior adjuvant or palliative treatment is allowed) 3. ECOG Performance status ≤ 1 4. Life expectancy > 3 months 5. Age ≥18 years

	6. Haematologic function as follows (5% deviation allowed): · ANC ^{3} 1.5 x 109/L · platelets ^{3} 125 x10^{9}/L · hemoglobin ^{3} 9 g/dl or 5.59 mmol/l 7. Adequate liver function as follows (10% deviation allowed) · serum alanine transaminase (ALT) ≤ 2.5 x ULN (in case of liver metastases < 5 x ULN) · total bilirubin ≤ 1.5 x ULN (patients with Gilbert's syndrome total bilirubin ≤2.5 x ULN) 8. Adequate renal function as follows (10% deviation allowed) · creatinine ≤ 1.5 x ULN 9. Signed written informed consent 10. Women of child-bearing potential must have a negative pregnancy test
Exclusion criteria	Patients with any of the following will not be eligible for participation: 1. Patients with significant medical illness that in the investigator's opinion cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy; 2. Treatment with any systemic anticancer therapy ≤ 3 weeks prior to cycle 1 day 1 3. Uncontrolled active infection (Hepatitis B and C infection are NOT exclusion criteria) and/or known HIV infection; 4. Renal failure requiring haemodialysis or peritoneal dialysis; 5. Patients who are pregnant or breast-feeding; 6. Patients with significantly diseased or obstructed gastrointestinal tract, malabsorption, uncontrolled vomiting or diarrhea resulting in inability to swallow oral medications; 7. Presence of symptomatic CNS metastasis 8. Unresolved toxicity from previous anti-cancer therapy or incomplete recovery from surgery, in particular oxaliplatin-induced peripheral neuropathy > grade 1. 9. Any of the following within the 12 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis, or other thromboembolic event.
Treatment scheme	All enrolled patients will be treated with mFOLFOX6 every two weeks and escalating doses of Selinexor (according to the mentioned dose levels) mFOLFOX 6 Oxaliplatin at a dose of 85 mg/m^2 iv over two hours (day 1) 5-FU 400 mg/m^2 iv bolus (day 1) LV at a dose of 400 mg/m^2 iv over two hours (day 1)

	5-FU at a dose of 2400 mg/m^2 iv over 46 hours (day 1-3) Selinexor will be given orally on days 1, 3 and 8 of each two-week cycle. Dose-level 1 Selinexor will be administered at a dose of 40 mg. Dose-level 2 Selinexor will be administered at a dose of 60 mg. Dose-level 3 Selinexor will be administered at a dose of 80 mg. Dose-level -1 Selinexor will be administered at a dose of 20 mg Treatment will be continued until disease progression or significant toxicities occur.
Primary parameter	· Determination of the maximum tolerated dose (MTD)
Secondary parameters	· Overall response rate (RR) (acc. to RECIST v1.1) · Progression free survival (PFS) (acc. to RECIST v1.1) · Overall survival (OS) · Toxicity (acc. to NCI CTC AE v4.03)
Dose-limiting toxicities (DLT)	Toxicity and tolerance of the dose escalation of Selinexor with mFOLFOX6 will be evaluated. Six patients will be initially treated in a cohort. Safety data will be monitored in real time. As soon as last patient of the cohort (either 6th or 9th) reaches day 28, safety data of all patients within that cohort will be reviewed for decision about opening up a new cohort by moving to the next dose level or expand the cohort or discontinue dose escalation. **Dose escalation:** If 0-1/6 patients experience a DLT, dose will be moved to the next level. If 2-3/6 patients experience a DLT, 3 more patients will be treated on that dose level. If 4-6/6 patients experience a DLT, dose will be regarded as toxic and dose escalation will be stopped. In case the dose escalation will be stopped at dose level 1, dose level -1 will be included in the study and evaluated by the same design. Dose limiting toxicity should be at least possibly related to study drug Selinexor combinational therapy. Dose-Limiting Toxicity (DLT) is defined as any of the following occurring in the first 28 days (cycle 1 +Cycle2) of study participation that are considered at least possibly related to selinexor administration. · 2 missed doses (out of 3 doses) of selinexor per

cycle due to study drug related toxicity
- Delay of more than 14 days in initiating cycle 2 or 3 on the scheduled date due to study drug related toxicity
- Discontinuation of a patient due to study drug related toxicity before completing cycle 2

Haematological toxicities

1. febrile neutropenia
2. leukopenia or neutropenia Grade 4 > 7 days
3. thrombopenia Grade 4 or Grade 3 with clinically significant bleeding, petechiae or purpura thrombopenia

Non-haematological toxicities

4. Grade 3 nausea/vomiting, diarrhea for >3 days while taking optimal supportive medications
5. Grade 3 fatigue lasting for ≥5 days while taking optimal supportive care and with correction of dehydration, anorexia, anemia, endocrine, or electrolyte abnormalities.
6. Grade 3 dehydration lasting for ≥5 days while taking optimal supportive care
7. Grade 4 vomiting, dehydration and diarrhea
8. Any other Grade ≥3 non-hematological toxicity except Electrolyte abnormalities that are reversible and asymptomatic, hair loss, ALT, AST or alkaline phosphatase in the setting of baseline grade 2 elevations from disease
9. Any other grade 4 non-hematologic toxicity
10. For the purposes of DLT assessment, asymptomatic hyponatremia will be “graded” not by CTCAEv4 but rather by clinically meaningful criterion of <125mmol/L. Sodium <125mmol/L will be graded as DLT with the exception of asymptomatic translational hyponatremia due to hyperglycemia (see footnote below for calculation).
11. *In marked hyperglycemia, ECF osmolality rises and exceeds that of ICF, since glucose penetrates cell membranes slowly in the absence of insulin, resulting in movement of water out of cells into the ECF. Serum Na concentration falls in proportion to the dilution of the ECF, declining 1.6 mEq/ L for every 100 mg/dL (5.55 mmol/L) increment in the plasma glucose level above normal. This condition has been called translational hyponatremia because no net change in total body water (TBW) has occurred. No specific therapy is indicated, because Na concentration will return to normal once the plasma glucose concentration is lowered. Corrected Sodium (Hillier, 1999) = Measured sodium + 0.024 * (Serum glucose - 100)[32].
12. Mucositis Grade 4 persistent for >7 days
13. Heart-insufficiency Grade ≥3
14. Interstitial lung disease Grade ≥3

	15. Skin toxicity Grade 4 16. Hepatic toxicity Grade 3 (in case of hepatic metastasis Grade 4) 17. Any toxicity causing a delay of therapy continuation of more than 2 weeks more than one case of or 9 patients have been treated with no more than 3 cases of DLT.
IMP Definition	Selinexor will be supplied by Karyopharm Therapeutics and defined as IMP.
Assessments	**Screening** · Review of inclusion and exclusion criteria · Medical and medication history, physical examination including height, weight, vital signs (blood pressure, heart rate, respiratory rate, body temperature), ECOG-performance status · Laboratory Tests: o Hematology panel: hemoglobin, hematocrit, red blood cell (RBC) count, platelets, white blood cell (WBC) count and WBC differential (neutrophils, lymphocytes). o Chemistry panel: sodium, potassium, calcium, creatinine, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, LDH, amylase, lipase o Coagulation: INR, aPTT, PT o CEA, (CA 19-9 if appropriate) o Pregnancy test for women of childbearing potential within 7 days prior to start of the treatment o ECG o Radiological imaging of the chest, abdomen and all other sites of disease (CT/MRI-scan of the thoracic and abdominal region) (within 4 weeks before start of treatment). o Ophthalmological examination: required at screening and if clinically indicated. Prior to dilation: best corrected visual acuity, and slit lamp examination including tonometry; following dilation, fundoscopy and slit lamp exam to document lens clarity - if a cataract is seen during the exam, the cataract will be graded according to the Lens Opacities Classification System (LOCS III) (Appendix 7). **Treatment phase** **Day 1 of every 2 week cycle (+/-2 days allowed)** · Vital signs including weight, ECOG-performance status, assessment of toxicity, concomitant medication, physical

Examination (as clinically indicated)

- Laboratory Tests:
  - Hematology panel: hemoglobin, platelets, white blood cell, neutrophils, lymphocytes,
  - Chemistry panel: sodium, potassium, calcium, creatinine, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, LDH, amylase, lipase
  - Coagulation: INR, aPTT, PT

Day 8 during first two cycles

- Vital signs including weight, ECOG-performance status, assessment of toxicity, concomitant medication, physical Examination (as clinically indicated)
- Laboratory Tests:
  - Hematology panel: hemoglobin, platelets, white blood cell, neutrophils, lymphocytes,

Additional assessments every 8 weeks (+/- 7 days allowed)

- Radiological imaging of the chest, abdomen and all other sites of disease (CT or MRI scan of the thoracic and abdominal region)
- CEA, (CA 19-9)

End of treatment (30 days after last dose +/-7 days)

When any subject discontinues dosing of all study treatment, the following assessments should be made.

- Physical examination, vital signs including weight, ECOG-performance status, assessment of toxicity, concomitant medication
- Laboratory Tests: hemoglobin, platelets, white blood cell, neutrophils, lymphocytes, sodium, potassium, calcium, creatinine, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, amylase, lipase
- ECG
- Tumor response assessment (in case discontinuation is not due to progressive disease)

Follow-up

All subjects will be contacted every 3 months ± 28 days after EOT (for overall 2 years from study inclusion).

Tumor Response Assessment

During study treatment tumor response will be assessed by the

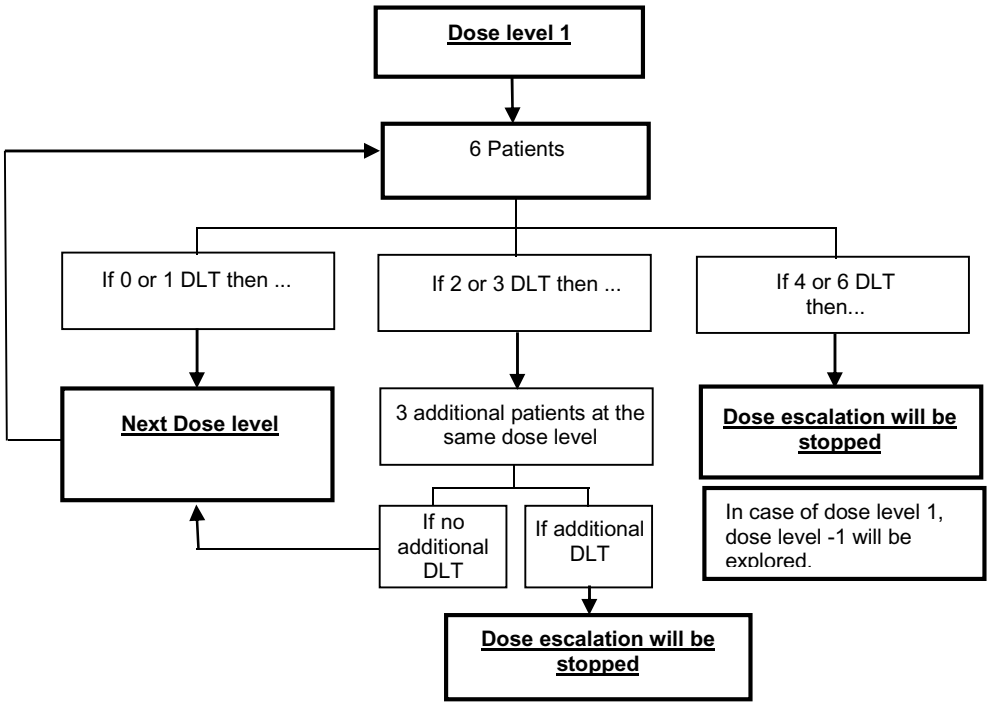
	investigator according to RECIST v1.1 (CT and/or MRI) at baseline (within 4 weeks before first study treatment) and every 8 weeks thereafter (during study treatment). CT and/or MRI scans will be retrospectively reviewed.
Safety assessment	All adverse events occurring during the course of the trial and for up to 30 days after the last dose of study medication will be captured, documented and reported. Safety blood samples include complete blood count, clinical chemistry, including liver function test, coagulation, and 12-lead electrocardiogram.
Timelines	Recruitment period: 12 months Follow up for survival 24 months.

Information to be provided regarding SAEs/Pregnancy

In the case of a serious adverse event (SAE) or pregnancy, the following person must be contacted by fax within 24 hours of knowledge:

Clinical Trial Manager	**Dr. Anne L. Kranich**
Address:	**GSO mbH** Harvestehuder Weg 21 20148 Hamburg Germany
Phone:	**0049-40-44 19 54 60**
Fax:	**0049-40-44 19 54 78**

Dose escalation scheme



Dose levels:

Dose level 1: Oxaliplatin at a dose of 85 mg/m^2 IV over two hours (Day 1)
5-FU 400 mg/m^2 IV bolus (Day 1)
Leucovorin 400 mg/m^2 IV over two hours (Day 1)
5-FU 2400 mg/m^2 IV over 46 hours (Day 1-3)
Selinexor 40 mg, PO (Day 1, 3 and 8)

Dose level 2: Oxaliplatin at a dose of 85 mg/m^2 IV over two hours (Day 1)
5-FU 400 mg/m^2 IV bolus (Day 1)
Leucovorin 400 mg/m^2 IV over two hours (Day 1)
5-FU 2400 mg/m2 iv over 46 hours (Day 1-3)
Selinexor 60 mg, PO (Day 1, 3 and 8)

Dose level 3: Oxaliplatin at a dose of 85 mg/m2 iv over two hours (Day 1)
5-FU 400 mg/m2 iv bolus (Day 1)
Leucovorin 400 mg/m2 iv over two hours (Day 1)
5-FU 2400 mg/m2 iv over 46 hours (Day 1-3)
Selinexor 80 mg, PO (Day 1, 3 and 8)

Dose level -1: Oxaliplatin at a dose of 85 mg/m^2 IV over two hours (Day 1)
5-FU 400 mg/m^2 IV bolus (Day 1)
Leucovorin 400 mg/m^2 IV over two hours (Day 1)
5-FU 2400 mg/m^2 IV over 46 hours (Day 1-3)
Selinexor 20 mg, PO (Day 1, 3 and 8)

Initially, 6 patients will be enrolled into each cohort. After enrollment of the sixth patient of a cohort, further recruitment will be temporarily stopped and dose-limiting toxicities will be

assessed. When the last patient of a given cohort has completed the first 4 weeks of treatment, all adverse events and other relevant safety data available up to that date will be reviewed by the coordinating investigator and the principal investigators and a decision will be made regarding dose escalation, expansion of cohort or end of escalation. To ensure that the assessment of a DLT is consistent between the sites, the Investigators from the sites will have a TC to discuss the DLT information at each dose escalation meeting. Before the TC all documentation of AEs and SAEs will be provided in writing. A new cohort may only be opened after a favourable decision has been made. The decision will be documented in writing and sent out to all sites on the same day.

If MTD was exceeded, another three patients will be treated at the previous dose level if there were only six patients treated at that level.

The MTD is defined as the highest dose level at which six patients have been treated with no more than one case of DLT or 9 patients have been treated with no more than 3 cases of DLT.

Flow Chart: Schedule of Assessments during the study

	Screening/ Baseline	**Treatment phase**			**End of treatment**	**Follow-up**
	Within 14 days prior to registration	**Day 1 of each cycle (-2 days)**	**Day 8 of cycle 1 and 2 (+/-1 day)s**	**Additionally every 8 weeks (+/-7 days)**	**30-days after last dose (+/- 7 days)**	**Every 3 months ± 28 days**
Informed consent [1]	X					
Inclusion and exclusion criteria	X					
Demographics	X					
Medical history [2]	X					
Pregnancy test (if applicable) [3]	X					
Physical examination and ECOG[4]	X	X	X		X	
Body height and weight [5]	X	X	X		X	
BSA	X					
Vital signs [6]	X	X	X		X	
Standard clinical neurologic examination	X				X	
Ophthalmological exam[7]	X					
12-lead ECG	X				X	
Hematology [8]	X	X	X		X	X
Calculation [9] (or measurement) of GFR	X				X	
Clinical Chemistry[10]	X	X			X	
Urine dipstick	X	X			X	
CEA (CA19-9)	X			X		
Coagulation test [11]	X	X			X	
Assessment of signs and symptoms, AE	X	X			X	
Concomitant medication	X	X			X	

	Screening/ Baseline	Treatment phase			End of treatment	Follow-up
	Within 14 days prior to registration	**Day 1 of each cycle (-2 days)**	**Day 8 of cycle 1 and 2 (+/-1 day)s**	**Additionally every 8 weeks (+/-7 days)**	**30-days after last dose (+/- 7 days)**	**Every 3 months ± 28 days**
CT/ MRI chest and abdomen[12]	X			X	X	X[13]
Survival						X

Notes

1 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 Applicable for women of childbearing potential. Serum 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
4 Full physical examination for baseline and end of study visit. Physical examinations during the study should be symptom directed.
5 Body height will be measured at screening only.
6 Vital signs: blood pressure, heart rate, respiratory rate and temperature
7 Ophthalmologic exam: required at screening and if clinically indicated. Prior to dilation: best corrected visual acuity, and slit lamp examination including tonometry; following dilation, fundoscopy and slit lamp exam to document lens clarity - if a cataract is seen during the exam, the cataract will be graded according to the Lens Opacities Classification System (LOCS III) Appendix 7.
8 Hematology: hemoglobin, red blood cell (RBC) count, hematocrit, platelets, white blood cell (WBC) count and WBC differential (neutrophils, lymphocytes),.
9 Calculated GFR according to the formula of Cockroft and Gault .
10 Clinical chemistry: Sodium, Potassium, Calcium, Creatinine, Total Bilirubin, Alkaline Phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Total Protein, Albumin, LDH
11 Coagulation test include prothrombin time (PT), activated partial thromboplastin time (aPTT) and INR
12 CT/MRI abdomen must include pelvis. PET/CT is allowed, but ultrasound of the abdomen and x-ray of thorax is not allowed. Within 4 weeks of treatment start and every 8 weeks thereafter during treatment phase.
13 Patients who discontinued for reasons other than progression of disease should be encouraged to continue visit the clinic for evaluation of their disease as per local hospital policy until progression of disease is determined..

Glossary of Abbreviations

β-HCG	Beta human chorionic gonadotropin
5-FU	5-Fluoruracil
ADR	Adverse drug reaction
AE	Adverse event
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute Neutrophile Count
aPTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate aminotransferase
BID	Twice a day
BSA	Body surface area
CA 19-9	Carbohydrate-Antigen 19-9
CEA	Carcinoembryonales Antigen
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CRM1	Chromosome region maintenance protein 1
CRO	Contract research organisation
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
DLT	Dose-limiting toxicity
DNA	Desoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
ESMO	European Society for Medical Oncology
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP	Good Laboratory Practice
GRP	Growth regulatory protein
h	Hour
HIV	Human immunodeficiency virus
HR	Hazard ratio
HUS	Hemolytic-uremic syndrome
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
LDH	Lactate dehydrogenase
LOCS	Lens Opacities Classification System
LV	Leucovorin
m^2	Square metre (body surface area)
mg	Milligram
min	Minute
mL	Millilitre
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network

NCI	National Cancer Institute
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PO	Per os
PPS	Per protocol set
PR	Partial response
PRN	As needed (Pro re nata)
PT	Prothrombin time
RECIST	Response Evaluation Criteria In Solid Tumors
RR	Response rate
RBC	Red blood cell
SAE	Serious adverse event
SD	Stable disease
SINE	Selective inhibitor of nuclear export
SmPC	Summary of product characteristics
SADR	Serious adverse drug reaction
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
TID	Three times a day
TSP	Tumor suppressor protein
UICC	Union for International Cancer Control
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization
XPO1	Exportin 1

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1 BACKGROUND AND RATIONALE

1.1 BACKGROUND

1.1.1 COLORECTAL CANCER

Colorectal cancer (CRC) represents the third most commonly diagnosed cancer worldwide[1]. Despite a decrease in incidence and mortality colorectal cancer (CRC) with nearly 1.25 million patients diagnosed per year still represents the second leading cause of cancer death. Consequently, CRC is considered a prominent global health problem.

Approximately 25 percent of patients with CRC will have metastatic disease at the time of diagnosis and further 25% will develop metastatic disease after curative resection of localised CRC. Over the last two decades, the development of treatment options has significantly improved the prognosis for metastatic CRC patients.

Traditionally, systemic chemotherapy in this setting has been based on fluoropyrimidines regimens. By the introduction of cytotoxic agents, such as irinotecan and oxaliplatin the response rate (RR), time to progression, and OS has improved from 15-20%, 5-6 and 10-12 months to 30-40%, 8 and 20-24 months, respectively [2] [3])

Multiagent regimens, including a combination of 5-fluorouracil (5-FU) plus leucovorin (LV) with oxaliplatin or irinotecan, are superior to 5-FU plus LV alone[29,30] and achieve a median survival of around 20 months[4,5,6]. Both, oxaliplatin combined with bolus and continuous infusion 5-FU plus LV (FOLFOX) and irinotecan combined with bolus and continuous infusion 5-FU plus LV (FOLFIRI) are recognized as standard first-line therapies for mCRC.

More recent studies have shown that survival outcomes can further be improved by adding biologic agents to combination chemotherapy regimens in first and second line therapy or use these agents as monotherapy in more advanced treatment situations. In particular angiogenesis inhibitors (bevacizumab, aflibercept), the epidermal growth factor receptor (EGFR) antibodies (cetuximab, panitumumab) and the multitarget tyrosine kinase inhibitor regorafenib have shown to improve the efficacy and extend overall survival[7] for a summary of efficacy in recent trials see appendix 1). Despite the inclusion of molecular agents, the median survival of mCRC does not exceed 30 months and therefore new treatment options are urgently needed.

1.1.2 SELINEXOR

More than 10 major tumor suppressor pathways have evolved in order to prevent the development and progression of neoplasia. Because the vast majority of tumor suppressor (TSP) and growth regulatory (GRP) proteins require nuclear localization in order to carry out their antineoplastic activities, enhancing their nuclear export leads to their functional inactivation.

The major TSP/GRP are exported exclusively by the protein CRM1 (also called XPO1), and tumors showing elevated CRM1 levels with cytoplasmic mislocalization of TSP/GRP.

Further detailed information is provided in the Investigator's Brochure.

Selinexor is an orally available, slowly reversible, potent and Selective Inhibitor of Nuclear Export (SINE) that specifically blocks XPO1. It is selectively cytotoxic for cells with genomic damage, i.e., for tumor cells, both in vitro and in vivo. Normal cells, with minimal or no DNA damage, remain in transient, reversible cell cycle arrest until the export block is relieved. Selinexor and other SINE compounds are not intrinsically cytotoxic; rather, they can restore the highly effective tumor suppressing pathways that lead to selective elimination of genomically damaged (i.e., neoplastic) cells. Tumors of hematopoietic lineage are particularly susceptible to induction of apoptosis by XPO1 inhibition; normal hematopoietic cells and their functions are largely spared.

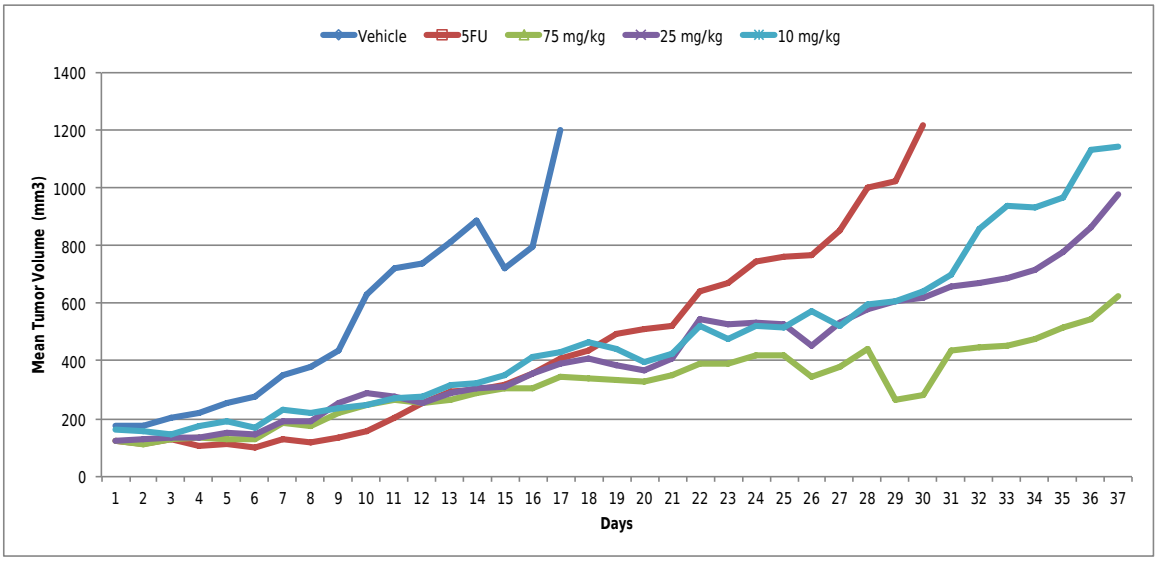
1.1.2.1 Preclinical Efficacy and Safety

Preclinical Efficacy

In a xenograft efficacy model of colorectal cancer (HCT-116 cell line with genetic mutation status of: $p53^{wt}$, K-ras G13D, MLH^{-}, $PIK3CA^{mut}$, $p14ink4a^{del}$, $CTNNB1^{mut}$, APC^{wt}) SINE was administered at 10-75mg/kg QDx5 each week, and the positive control 5-fluorouracil (5-FU) was injected intraperitoneally at 50 mg/kg on Days 1 and 3; as shown in Figure 1.

SINE slowed down tumor growth at all doses in a statistically significant manner when compared to vehicle and 5-FU. In this model, all vehicle animals were euthanized due to tumor burden by Day 17. Animals treated with 5-FU survived up to Day 30 and tumor growth was statistically significantly reduced when compared to vehicle treated animals. SINE administered orally at 10, 25 and 75 mg/kg slowed down tumor growth when compared to vehicle and 5-FU. And there was a significant improvement on survival benefit associated with SINE treatment.

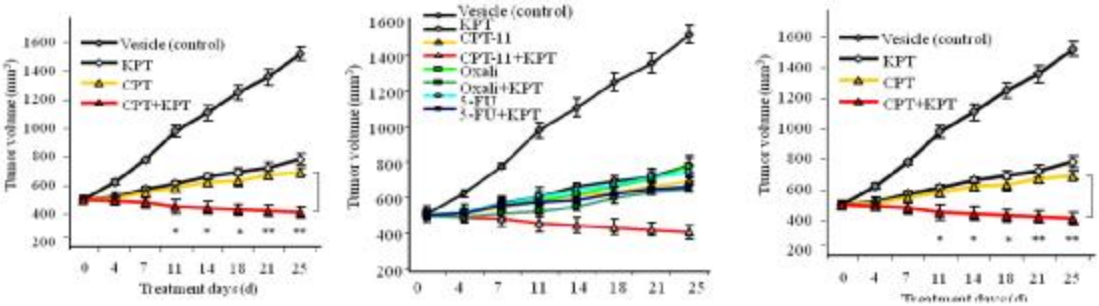
Figure 1



Data showing that when combined with CPT-11, oxaliplatin or 5FU, SINE displays a synergistic cytotoxic effect was previously generated *in vitro*. *In vivo* synergistic effects of SINE to three conventional colon cancer therapeutic regimens were assessed using a LoVo colon cancer xenograft model (Figure 2). Mice were treated with vehicle or 75 mg/kg of SINE twice a week via oral route with or without CPT-11 (33mg/kg, i.v., twice a week), or oxaliplatin (10 mg/kg, i.p., one time), or 5-FU (33 mg/kg, i.p., twice a week). All treatments were continued until 4 weeks. In oxaliplatin-treated or 5- FU-treated groups, tumor inhibition effects were slightly enhanced by addition of SINE p=0.09 (oxaliplatin) and p=0.07 (5-FU),

whereas inhibition effects were definitively enhanced by addition of SINE in CPT-11- treated group ($p < 0.001$).

Figure 2



In conclusion, XPO1 blockade by the orally bioavailable SINEs show significant single agent anti-tumor activity on colon cells *in vitro* and *in vivo*, and striking synergy in combination with the major clinically relevant colon cancer treatments irinotecan (CPT-11), oxaliplatin, and 5-FU. These results support the further development of SINEs for the single agent and combination treatment of colorectal cancer for advanced stage colorectal cancer.

Preclinical Safety

In the Selinexor non-clinical safety program in Sprague-Dawley rats and cynomolgus monkeys, the primary effects of oral Selinexor were dose-dependent reductions in food intake and body weight (or reductions in body weight gain), with minimal clinical symptoms (no or mild non-bloody diarrhea), associated primarily with gastrointestinal atrophy. Similar effects are observed in mice and dogs. At high repeated doses of Selinexor associated with marked weight loss, there were changes in cerebellar granular layer neurons in both rats (≥300 mg/m²) and monkeys (≥72 mg/m²), but only monkeys showed any CNS symptoms. No central nervous system (CNS)-related adverse side effects were observed in the GLP, rat and monkey 4-cycle toxicity studies. A GLP, rat neurofunctional study (Irwin test) has also been performed at dose levels of 12, 60, or 300 mg/m² (2, 10, and 50 mg/kg). No behavioral changes were observed at all doses tested.

In the pivotal, GLP, 4-week monkey study, there was no evidence of a direct or indirect effect of Selinexor on the morphology and intervals of the ECG at up to 36 mg/m² (3 mg/kg). Based on these results, QT prolongation or other cardiac effect does not appear to be a safety concern for Selinexor.

In summary, dose limiting toxicity (DLT)/mortality in both rats and monkeys is related primarily to marked weight loss with atrophy of the gastrointestinal (GI) tract and noncritical effects on other major organs.

Further detailed information is provided in the Investigator's Brochure

1.1.2.2 Clinical Efficacy and Safety

Clinical Evidence of Anti-Cancer Activity

Karyopharm Therapeutics is currently conducting three open label Phase 1 clinical trials to assess the safety, tolerability and anti-tumor activity of of selinexor given orally 2-3 times per week. The first study (KCP-330-001) is in patients with advanced hematological malignancies, the second (KCP-330-002) is in patients with advanced or metastatic solid tumor malignancies and the third (KCP-330-003), a food effect study, is in patients who have metastatic, locally advanced or locally recurrent soft tissue or bone sarcomas. All patients entering these single-agent phase 1 studies have relapsed after available therapies and have objectively progressing tumors at time of study drug initiation. To date, selinexor has been administered to over 400 patients.

Efficacy in KCP-330-002 (selinexor in patients with advanced solid tumors)

Data was generated across a variety of heavily pretreated, progressing solid tumors including melanoma, head & neck, ovarian, cervical, colorectal, and chemotherapy refractory prostate cancers. Enrolled patients had a mean of 3.7 prior therapies and were progressing at study entry. Patients received doses of selinexor ranging from 3 - 85 mg/m2. The disease control rate was 49% (stable disease or better). Partial responses were observed in 4 patients: colorectal cancer (KRAS mutant), melanoma (BRAFwt), ovarian adenocarcinoma, and cervical. Stable disease was noted in 47 patients, with 17 patients (16%) experiencing stable disease for six months or longer. Seven of eight evaluable patients with hormone and chemotherapy refractory prostate cancer achieved stable disease and remained on study for 70 to 317+ days. Among 14 evaluable patients with head and neck cancer, nine achieved stable disease with eight on study for 75 - 401+ days.

Table 1 Best Responses in Solid Tumor Patients as of 13-May-2014

Cancer Type	N	PRs and SD (%)	PR (%)	SD (%)	PD (%)
Colorectal	39	14 (36%)	1 (3%)	13 (33%)	25 (64%)
Head & Neck	14	9 (64%)	--	9 (64%)	5 (36%)
Prostate	8	7 (88%)	--	7 (88%)	1 (12%)
Cervical	5	4 (80%)	1 (20%)	3 (60%)	1 (20%)
Ovarian	5	3 (60%)	1 (20%)	2 (40%)	2 (40%)
GBM	5	--	--	--	5 (100%)
Melanoma	3	2 (67%)	1 (33%)	1 (33%)	1 (33%)
Sarcoma	8	7 (88%)	--	7 (88%)	1 (12%)
Other	19	6 (32%)	--	6 (32%)	13 (68%)
Total	**106**	**52 (49%)**	**4 (4%)**	**48 (45%)**	**54 (51%)**

PR=Partial Response, SD=Stable Disease, PD=Progressive Disease

Side effects were generally low grade and typically gastrointestinal in nature, or fatigue. These common side effects decreased over time, in part due to prophylactic use of standard supportive care. Major organ dysfunction or clinically significant cumulative toxicities have not been observed. The recommended single agent dose for Phases 2 and 3 is 65 mg/m^2 twice weekly.

In the Phase I study, KCP-330-003, tumor shrinkage and disease stabilization were observed in patients with advanced sarcomas including Liposarcoma and Leiomyosarcoma. Among 19 patients evaluable for response, stable disease was observed in 52% of patients. Five patients remain on study (61-211$^+$ days).

Table 2.

Cancer Type	**N**	**SD (%)**	**PD (%)**	**NE (%)**
Sarcoma Type				
Leiomyosarcoma	6	3 (50%)	2 (33%)	1 (17%)
Liposarcoma	4	4 (100%)	--	--
Synovial Sarcoma	3	--	3 (100%)	--
Chondrosarcoma	2	1 (50%)	1 (50%)	--
Others	6	3 (50%)	2 (33%)	1 (17%)
Total	**21**	**11 (52%)**	**8 (38%)**	**2 (10%)**

SD=Stable Disease, PD=Progressive Disease, NE=Non-Evaluable

Clinical Safety

In patients with solid tumors, the most common AEs suspected to be related to selinexor are anorexia, fatigue, nausea, vomiting, diarrhea, and thrombocytopenia. Virtually all of these side effects can be managed effectively with dose modification and/or supportive care initiated prior to first dosing. Overall, the most frequently observed laboratory abnormalities include thrombocytopenia, hyponatremia, and a decrease in red blood cells. The majority of these have been mild to moderate. Please refer to the KPT-330 (selinexor) Investigator's Brochure for the most current information.

One patient, heavily pre-treated for recurrent pancreatic cancer, developed acute cerebellar syndrome following 4 doses of selinexor at 85 mg/m^2 BSA twice weekly. The patient experienced abnormal speech, loss of coordination, and was unable to walk. Since the time of the initial reported event, this patient is recovering both her speech and mobility. No other patients have reported such symptoms to date.

Reproductive Risks

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 for patients to understand the need to use birth control while on this study. Female patients of child bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening, and male patients must use an effective barrier method of contraception if sexually active with a female of child bearing potential. Acceptable methods of contraception are condoms with contraceptive foam; oral, implantable or injectable contraceptives; contraceptive patch; intrauterine device; diaphragm with spermicidal gel; or a sexual partner who is surgically sterilized or post-menopausal. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.

1.2 STUDY RATIONALE

Current guidelines recommend an intensive first line three-drug regimen (chemodoublet and biological agent) for patients with either potentially resectable or symptomatic disease (ESMO group 1 and 2[10]) However, the large majority of patients are either asymptomatic or definitely unresectable due to spread of disease or co-morbidity (ESMO group 3). For these patients a sequential approach with a two-drug combination (e.g. FOLFOX) is recommended. Moreover, a certain group of patients might not be amenable for VEGF or EGFR inhibition in combination with chemotherapy and might thus be treated with FOLFOX regimen in second line. To further enhance the efficacy of the mFOLFOX6 combination regimen while maintaining an acceptable tolerability is worth to be explored. Selective inhibition of nuclear export (SINE) is a novel therapeutic strategy that could potentially be applicable to many cancers. In the phase I solid tumor study 35 heavily pretreated patients with CRC have been included and showed promising results. Moreover, preclinical studies has shown a strong synergistic effect of Selinexor and 5FU and oxaliplatin.

2 OBJECTIVES OF THE STUDY

2.1 PRIMARY OBJECTIVE

The primary objective is to determine the maximum tolerated dose (MTD) of selinexor in combination with mFOLFOX6 in patients with metastatic colorectal cancer.

2.2 SECONDARY OBJECTIVES

Secondary objectives of the study are:

- To determine the efficacy and tolerability of selinexor in combination with mFOLFOX6 in patients with metastatic colorectal cancer by
  - Overall response rate (RR) (acc. to RECIST v1.1)
  - Progression free survival (PFS) (acc. to RECIST v1.1)
  - Time to progression (acc. To RECIST v1.1)
  - Overall survival (OS)
  - Toxicity (acc. to NCI CTC AE v4.03)

2.3 EXPLORATORY OBJECTIVES

Not applicable within the study.

3 STUDY DESIGN

3.1 OVERVIEW OF STUDY DESIGN AND DOSING REGIMEN

This is a multi center, open-label, non-randomized phase I trial study to determine the MTD of a combination of mFOLFOX6 and selinexor in patients with metastatic colorectal cancer.

After screening and registration in the study, all enrolled patients will be treated with oxaliplatin (85 mg/m² IV over 2 hours, Day 1), 5-FU (400 mg/m^2 IV bolus, Day 1), leukovorin (400 mg/m^2 IV over 2 hours, Day 1) and 5-FU (2,400 mg/m² continuous infusion, Days 1-3) every 2 weeks and escalating doses of selinexor as follows:

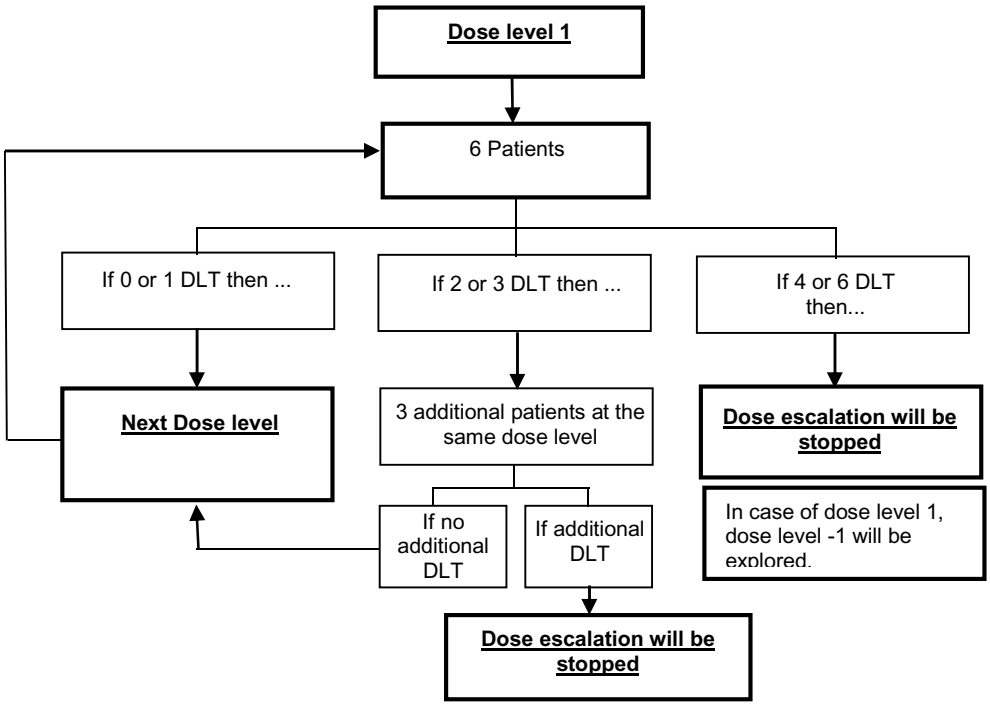
Patients in Dose Level 1 will receive oral selinexor 40 mg on day 1, 3, and 8.

Patients in Dose Level 2 will receive oral selinexor 60 mg on day 1, 3, and 8.

Patients in Dose Level 3 will receive oral selinexor 80 mg on day 1, 3, and 8.

Patients in Dose Level -1 will receive oral selinexor 20 mg on day 1, 3, and 8.

Figure 3: Dose escalation scheme



The MTD is defined as the highest dose level at which six patients have been treated with no Toxicity and tolerance of the dose escalation of Selinexor with mFOLFOX6 will be evaluated.

Six patients will be initially treated in a cohort. Safety data will be monitored in real time. As soon as last patient of the cohort (either 6th or 9th) reaches day 28, safety data of all patients within that cohort will be reviewed for decision about opening up a new cohort by moving to the next dose level or expand the cohort or discontinue dose escalation.

Dose escalation:

If 0-1/6 patients experience a DLT, dose will be moved to the next level.

If 2-3/6 patients experience a DLT, 3 more patients will be treated on that dose level.

If 4-6/6 patients experience a DLT, dose will be regarded as toxic and dose escalation will be stopped.

In case the dose escalation will be stopped at dose level 1, dose level -1 will be included in the study and evaluated by the same design.

3.1.1 DEFINITION OF DLT

Dose limiting toxicity should be at least possibly related to study drug Selinexor combinational therapy. Dose-Limiting Toxicity (DLT) is defined as any of the following occurring in the first 28 days (cycle 1 +Cycle2) of study participation that are considered at least possibly related to selinexor administration.

- ·2 missed doses (out of 3 doses) of selinexor per cycle due to study drug related toxicity
- ·Delay of more than 14 days in initiating cycle 2 or 3 on the scheduled date due to study drug related toxicity
- ·Discontinuation of a patient due to study drug related toxicity before completing cycle 2

Haematological toxicities

1. febrile neutropenia
2. leukopenia or neutropenia Grade 4 > 7 days
3. thrombopenia Grade 4 or Grade 3 with clinically significant bleeding, petechiae or purpura thrombopenia

Non-haematological toxicities

4. Grade 3 nausea/vomiting, diarrhea for >3 days while taking optimal supportive medications
5. Grade 3 fatigue lasting for ≥5 days while taking optimal supportive care and with correction of dehydration, anorexia, anemia, endocrine, or electrolyte abnormalities.
6. Grade 3 dehydration lasting for ≥5 days while taking optimal supportive care
7. Grade 4 vomiting, dehydration and diarrhea
8. Any other Grade ≥3 non-hematological toxicity except Electrolyte abnormalities that are reversible and asymptomatic, hair loss, ALT, AST or alkaline phosphatase in the setting of baseline grade 2 elevations from disease
9. Any other grade 4 non-hematologic toxicity
10. For the purposes of DLT assessment, asymptomatic hyponatremia will be “graded” not by CTCAEv4 but rather by clinically meaningful criterion of <125mmol/L. Sodium <125mmol/L will be graded as DLT with the exception of asymptomatic translational hyponatremia due to hyperglycemia (see footnote below for calculation).

11. *In marked hyperglycemia, ECF osmolality rises and exceeds that of ICF, since glucose penetrates cell membranes slowly in the absence of insulin, resulting in movement of water out of cells into the ECF. Serum Na concentration falls in proportion to the dilution of the ECF, declining 1.6 mEq/ L for every 100 mg/dL (5.55 mmol/L) increment in the plasma glucose level above normal. This condition has been called translational hyponatremia because no net change in total body water (TBW) has occurred. No specific therapy is indicated, because Na concentration will return to normal once the plasma glucose concentration is lowered. Corrected Sodium (Hillier, 1999) = Measured sodium + 0.024 * (Serum glucose - 100)[32].
12. Mucositis Grade 4 persistent for >7 days
13. Heart-insufficiency Grade ≥3
14. Interstitial lung disease Grade ≥3
15. Skin toxicity Grade 4
16. Hepatic toxicity Grade 3 (in case of hepatic metastasis Grade 4)
17. Any toxicity causing a delay of therapy continuation of more than 2 weeks more than one case of or 9 patients have been treated with no more than 3 cases of DLT.

3.1.2 DEFINITION OF TREATMENT CYCLE

A treatment cycle in this study consists of application of mFOLFOX6 chemotherapy regimen and Selinexor given twice weekly. Cycles will be repeated on Day 15.

3.1.3 TREATMENT DURATION

Patients will be treated until progression of disease, intolerable toxicity, or secondary resection. Treatment with oxaliplatin should not exceed 6 months and patients may continue with 5FU/LV and Selinexor afterwards.

3.1.4 END OF TREATMENT VISIT

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

3.1.5 FOLLOW-UP PHASE

Patients who discontinued for reasons other than withdrawal of consent for participation in the trial will be followed every 3 months ± 28 days for overall survival for 2 years from study inclusion. Patients who discontinued for reasons other than progression of disease should be encouraged to continue visit the clinic for evaluation of their disease as per local hospital policy until progression of disease is determined.

Of note, a patient may decide to discontinue study treatment. This is not the same as fully withdrawal of consent to participate in the trial and these patients should be encouraged to continue to be followed up as for other patients for event free and overall survival. If a patient chooses to have no further interaction regarding the study (fully withdrawal of consent), the investigator must provide written documentation of the patient's decision to fully withdraw from the study.

3.2 STUDY TIMELINES

Patients will be recruited within 12 months. Analysis of primary endpoint and preliminary analysis of secondary endpoints RR and toxicities will be done after 8 weeks of therapy of the last patient included. Additional analysis for PFS and OS as well as follow-up analysis of secondary endpoints RR and toxicities will be performed up to 2 years after registration of last patient.

4 SELECTION OF THE STUDY POPULATION

4.1 TARGET POPULATION

Patients with metastatic colorectal cancer according to the inclusion and exclusion criteria below will be enrolled in this study trial. Both male and female patients are enrolled.

The baseline assessment must have taken place within 2 weeks (4 weeks for radiographic evaluation) prior to start of treatment. Under no circumstances are patients, who were once enrolled in this study, permitted to be re-enrolled into the same study.

4.2 INCLUSION CRITERIA

To be eligible for this trial, patients must fulfil the following criteria:

1. Patients with histologically confirmed diagnosis of colorectal cancer presenting with unresectable stage IV (UICC) disease (primary tumor may be present)
2. Patients who are feasible for treatment with FOLFOX (prior adjuvant or palliative treatment is allowed)
3. ECOG Performance status ≤ 1
4. Life expectancy > 3 months
5. Age ≥18 years
6. Haematologic function as follows (5% deviation allowed):
    - ANC ≥ 1.5 x 10^9/L
    - platelets ≥ 100 x10^9/L

- hemoglobin ≥ 9 g/dl or 5.59 mmol/l

7. Adequate liver function as follows (10% deviation allowed)
   - serum alanine transaminase (ALT) ≤ 2.5 x ULN (in case of liver metastases < 5 x ULN)
   - total bilirubin ≤ 1.5 x ULN (patients with Gilbert's syndrome total bilirubin ≤2.5 x ULN)
8. Adequate renal function as follows (10% deviation allowed)
   - creatinine ≤ 1.5 x ULN
9. Signed written informed consent
10. Women of child-bearing potential must have a negative pregnancy test

4.3 EXCLUSION CRITERIA

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

1. Patients with significant medical illness that in the investigator's opinion cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy;
2. Treatment with any systemic anticancer therapy ≤ 3 weeks prior to cycle 1 day 1
3. Uncontrolled active infection (Hepatitis B and C infection are NOT exclusion criteria) and/or known HIV infection;
4. Renal failure requiring haemodialysis or peritoneal dialysis;
5. Patients who are pregnant or breast-feeding;
6. Patients with significantly diseased or obstructed gastrointestinal tract, malabsorption, uncontrolled vomiting or diarrhea resulting in inability to swallow oral medications;
7. Presence of symptomatic CNS metastasis
8. Unresolved toxicity from previous anti-cancer therapy or incomplete recovery from surgery, in particular oxaliplatin-induced peripheral neuropathy > grade 1.
9. Any of the following within the 12 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis, or other thromboembolic event.

4.4 REGISTRATION OF PATIENTS

Patients will be screened for eligibility and eligibility check form/Patient Registration Form will be sent to **GSO**.

Patient eligibility will be reviewed by **GSO** for all patients participating in the study prior to receiving study treatment.

PROTOCOL SPECIFIC QUESTIONS:

- all eligibility criteria will be checked one by one
- date of written informed consent (*day*/*month*/*year*)

Patient eligibility will be checked by **GSO** once all screening procedures are completed. There will be no exceptions. Any questions should be addressed **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 the patient will participate in.

GSO mbH
Fax: 0049-40-44 19 54 78

If slots within one cohort have been filled, i.e. after enrollment of 6th patient or 9th patient in case of expanded cohort further recruitment will be temporarily stopped and dose-limiting toxicities will be assessed. GSO will send a notification to investigational sites concerning hold of accrual. The decision of the cohort review, i.e. opening new cohort at next dose level, expansion of cohort or stop of dose escalation will be documented in writing and sent out to all sites.

5 SCHEDULE OF ASSESSMENT AND PROCEDURES

5.1 STUDY ASSESSMENTS

5.1.1 RESPONSE ASSESSMENTS

Objective response will be evaluated based on RECIST criteria Version 1.1 (see Appendix 7) using CT scan or MRI scan. For patients with multiple measurable lesions, up to 5 lesions in total and 2 lesions per organ should be identified.

The exact technique used for measurement of lesions (i.e., either CT or MRI scan) 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 individual. The CT/ MRI abdomen must include the pelvis. A PET/CT is allowed, but ultrasound and x-ray of thorax is not allowed.

All lesions identified at screening have to 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 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 > 15 mm are considered measurable and assessable a 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 > 10 mm but < 15 mm) should be considered non-target lesions. In cases where there is suspicion of progression before the next scheduled assessment, an unscheduled tumor assessment should be performed.

In case a detected increase in tumor size is below the resolution limit of the CT/ MRI scanner, it is accepted to continue with treatment until a second assessment at a later time point unequivocally confirms progressive disease.

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 computed tomography (CT) or magnetic resonance imaging (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.

Thereafter, tumor assessments by CT/MRI 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. 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 TRANSLATIONAL ANALYSES

Not applicable in this study.

5.1.3 SAFETY ASSESSMENTS

Throughout the treatment period until the EOT visit, patients will be assessed for all adverse events. Common terminology criteria for adverse events (CTCAE v4.03) will be used for grading. If necessary, the patient may be withdrawn from the study treatment.

- **Medical history** including concurrent illnesses and information on dates and description of initial diagnosis of colorectal cancer and prior cancer treatment history will be reviewed and recorded at the screening visit.

- **Concomitant medications** will be documented during screening and throughout the treatment phase until the EOT visit.
- **Adverse events** (see also section 7): All patients will be closely monitored for adverse events from the date of informed consent through the end of treatment visit. Adverse events should be followed up until they have returned to baseline status or stabilized.
- **Pregnancy test** a serum β-HCG test within 7 days before the first dose of study drug will be performed for women with childbearing potential. A urine test will be done if the date of the first result exceeds the 7 day window.

5.1.4 LABORATORY ASSESSMENTS

Blood samples will be taken for hematological and serum chemistry monitoring at screening, during the treatment phase before start of each treatment cycle and at the end of treatment visit. The local laboratory will perform the analyses and provide reference ranges.

5.2 STUDY PROCEDURES

5.2.1 SUPPORTIVE CARE

a. 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 twice daily (bid) – three times a day(tid) as needed (prn).

b. 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 400 adult patients treated with selinexor as of 01 October 2014, 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, 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 and anorexia/cachexia [palliative care]

see Appendix 5.

4. NK1R antagonist: aprepitant or equivalent should be considered and will be covered for selected patients who have severe nausea and vomiting.

Additional information on supportive care and dose modifications for specific adverse events can be found in Table 4.

5.2.2 SCREENING PROCEDURES

All patients will be screened and screening procedures performed within 14 days prior to the start of treatment unless specified otherwise below. These include the following:

Signed written informed consent	Obtained prior to any study specific assessments
Demographics and medical history	Age, gender, ethnic background Tumor diagnosis including dates and description of initial diagnosis of colorectal cancer Details on prior 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, heart rate, respiratory rate , temperature Physical examination
ECOG performance status	Please refer to Appendix 4
Standard clinical neurological examination	A neurological exam will be performed to assess motor, sensory and balance functions
Cardiac evaluation	12-lead ECG
Ophthalmological examination	Required at screening and if clinically indicated. Prior to dilation: best corrected visual acuity, and slit lamp examination including tonometry; following dilation, fundoscopy and slit lamp exam to document lens clarity - if a cataract is seen during the exam, the cataract will be graded according to the Lens Opacities Classification System (LOCS III). See Appendix 7.
Calculation (or measurement) of GFR	Please refer to Appendix 6
Urine dipstick	Urine bilirubin, glucose, hemoglobin, ketones, pH, protein
Hematology	Hemoglobin, red blood cell (RBC) count, platelets, white blood cell (WBC) count, WBC differential (neutrophils, lymphocytes)
Clinical chemistry	Sodium, Potassium, Calcium, Creatinine, Total

	Bilirubin, Alkaline Phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Total Protein, Albumin, LDH
Coagulation tests	prothrombin time (PT), activated partial thromboplastin time (aPTT) and INR
Tumor marker	CEA, CA19-9
Assessment of disease status (Day -28 to 0)	The disease status will be measured by CT/MRI and evaluated according to RECIST 1.1 criteria
Concomitant medication	Concomitant medication currently used

5.2.3 TREATMENT PHASE

During the treatment phase the following assessments are to be performed according to the study flow chart within the allowed visit windows (page14-15):

Physical examination and vital signs	Body weight BSA Blood pressure, heart rate, respiratory rate, temperature Physical examination (symptom directed)
ECOG performance status	Please refer to Appendix 4
Urine dipstick	Urine bilirubin, glucose, hemoglobin, ketones, pH, protein
Hematology	Hemoglobin, white blood cell (WBC) count, neutrophils, lymphocytes, platelets,
Clinical chemistry	Sodium, Potassium, Calcium, Creatinine, Total Bilirubin, Alkaline Phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Total Protein, Albumin, LDH
Tumor marker (every 8 weeks)	CEA, CA19-9
Assessment of disease status (every 8 weeks)	The disease status will be measured by CT/MRI and evaluated according to RECIST 1.1 criteria
Adverse events and concomitant medication	Assessed on an ongoing basis.

5.2.4 END OF TREATMENT

Patients who discontinue therapy for any reason must have and end of treatment (EOT) visit completed 30 days (± 7 days) after the last application of study drug. At the EOT visit, the patients will undergo the following assessments:

Physical examination and vital signs	Body weight Blood pressure, heart rate, respiratory rate, temperature Physical examination
ECOG performance status	Please refer to Appendix 4
Standard clinical neurological examination	A neurological exam will be performed to assess motor, sensory and balance functions
Hematology	Hemoglobin, white blood cell (WBC) count, neutrophils, lymphocytes, platelets, leukemic blasts
Clinical chemistry	Sodium, Potassium, Calcium, Creatinine, Total Bilirubin, Alkaline Phosphatase, alanine

	aminotransferase (ALT), aspartate aminotransferase (AST), Total Protein, Albumin, LDH
Urine dipstick	Urine bilirubin, glucose, hemoglobin, ketones, pH, protein
Cardiac evaluation	12-lead ECG
Tumor marker (if reason for EOT is not PD)	CEA, CA19-9
Assessment of disease status (if reason for EOT is not PD)	The disease status will be measured by CT/MRI and evaluated according to RECIST 1.1 criteria
Adverse events and concomitant medication	Assessed on an ongoing basis

5.2.5 FOLLOW-UP

Patients who discontinued for reasons other withdrawal of consent for participation in the trial will be followed every 3 months ± 28 days to assess the following:

- Overall survival
- Progression-free survival for patients discontinued for other reason than disease progression

Follow-Up will be continued for maximum of 24 months per patient or end of study as defined below, whichever is first.

5.2.6 END OF STUDY

The primary statistical analysis (i.e. primary endpoint and secondary endpoints RR and toxicity) will be performed when all patients have received treatment with study medication for 4 cycles i.e. after first in study tumor assessment of last patient. End of study will be defined 2 years after registration of last patient.

5.3 PLANNED TREATMENT OF THE PATIENT AFTER END OF TREATMENT PHASE

After completion of the study at routine follow-up (EOT), patients will generally be treated at the discretion of the investigator according to medical routine.

5.4 REMOVAL OF PATIENTS FROM TREATMENT

Subjects 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 subjects should be avoided. Patients who are withdrawn from the study and not evaluable for DLT will be replaced.

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

- Disease progression
- 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 the AEs have been resolved or declined to baseline values.

If a patient has failed to attend scheduled assessments in the study, the investigator must determine the reasons and circumstances as completely and accurately as possible.

In case of premature discontinuation of the study treatment, the investigations scheduled for the EOT and the follow-up visits should be performed, if possible. The CRF section entitled “End of Treatment” must be completed in all cases. Should a patient decide to withdraw, every effort will be made to complete and report the observations as thoroughly as possible. The investigator should contact the patient to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient’s withdrawal should be made, with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded on the CRF.

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

5.5 STUDY DISCONTINUATION

The whole study may be discontinued at the discretion of the sponsor in the event of any of the following:

- Medical or ethical reasons affecting the continued performance of the study

- Difficulties in the recruitment of patients

6 TREATMENT

6.1 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

An investigational medicinal product 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 authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

The IMP in this study is Selinexor. Oxaliplatin, 5-FU and LV are not considered IMP as the treatment is according to the standard of care.

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 drug provider.

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 per 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 CRF.

Tablets, including instructions for administration, are dispensed by study personnel on an outpatient or inpatient 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

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**) that specifically blocks nuclear export by binding irreversibly 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 tablet with strengths: of 10 mg.

Labelling: Each bottle of Selinexor tablets will be labelled in accordance with current ICH GCP and specific national requirements.

Storage: Selinexor tablets will be stored at ambient temperatures between 5 –30 °C in a locked and secured area with restricted access to study staff. The tablets should not be stored at freezer temperatures or allowed to freeze. Tablets will be supplied in white high density polyethylene (HDPE) bottles.

6.2.2 ROUTE OF ADMINISTRATION

Selinexor tablets will be taken on Day 1, 3 and 8 of each two–week cycle.

Selinexor is to be taken within approximately 30-minutes of solid food consumption together with >120 mL (8 ounces) of water.

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 CRF, 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 CRF 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 drug provider and in accordance with applicable regulatory requirements.

6.3 DOSE MODIFICATION OF SELINEXOR

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 ~12mg/m² to ≥50mg/m² orally twice weekly. At the present time, we cannot predict which patient's CRC will respond to lower doses, nor can tolerability be predicted. Therefore, in order to individualize and optimize safety and therapeutic benefit, study therapy will be initiated with 30mg/m² twice weekly by mouth of Selinexor. This dose is below the MTD of oral Selinexor when used as monotherapy and is associated with clinical benefit.

Toxicity will be graded according to NCI CTCAE, version 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.

Study medication cycles will be repeated every 2 weeks provided that on Day 1 of each cycle the laboratory parameters are deemed adequate and study medication-related toxicities have resolved to Grade < 2 or baseline. Dose modifications for Selinexor are permitted in the setting of non-life-threatening, reversible Grade 3-4 AEs that resolve to Grade ≤ 1 within one treatment cycle (approximately 2 weeks).

Flexible dose reductions and/or schedule modifications will be permitted. In patients with tolerability issues on Selinexor, it is recommended either: (1) reducing Selinexor dose by 30% or (2) reducing Selinexor dosing frequency to once weekly. Specific criteria for dose reductions or delays in the setting of various AEs are presented in Table 10.

Re-escalation of the study drug is 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 CRF, including the respective reason.

6.3.1 DOSE ADJUSTMENT GUIDELINES FOR SELINEXOR RELATED TOXICITIES

Table 3 Dose level

Dose Level 3	selinexor 80 mg on day 1, 3, and 8
Dose Level 2	selinexor 60 mg on day 1, 3, and 8
Dose Level 1	selinexor 40 mg on day 1, 3, and 8
Dose Level -1	selinexor 20 mg on day 1, 3, and 8

Dose adjustments should be made based on specific toxicities as shown in Table 10.

Table 4 Criteria for dose adjustments of Selinexor related toxicities

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Fatigue (common)		
Grade 1	Rule out other causes of fatigue. Insure adequate caloric intake and assess volume status. Consider addition of 4-12 mg dexamethasone or equivalent with each dose of selinexor +/- the day after selinexor.	Maintain dose.
Grade 2	Rule out other causes of fatigue. Insure adequate caloric intake and assess volume status. Consider addition of 4-12 mg dexamethasone or equivalent with each dose of selinexor +/- the day after selinexor. For additional support see NCCN guidelines a (appendix.	Maintain dose. Consult medical monitor for additional option such as temporary dose reduction or short dose interruptions.
Grade 3	See guidelines for Grade 2 fatigue.	Interrupt selinexor dosing until resolved to Grade ≤ 2, For first occurrence of Grade 3, if adequate supportive care resulted in fatigue improving to Grade ≤1 within 7 days, restart selinexor at current dose. Otherwise, restart selinexor at one dose level below (Table 3).
Anorexia or Weight loss		
Grade 1	Rule out other causes of anorexia. Assess dietary options (e.g., try a variety of other foods). Add high-calorie supplements (e.g., Ensure®). Consider addition of 4-12 mg dexamethasone or equivalent with each dose of selinexor +/- the day after selinexor.	Maintain dose.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 2	Rule out other causes of anorexia. Assess dietary options (e.g., try a variety of other foods). Add high-calorie supplements (e.g., Ensure®). Consider addition of 4-12 mg dexamethasone or equivalent with each dose of selinexor +/- the day after selinexor. Consider megesterol acetate 80-400 mg daily. Consider anabolic steroids such as oxandrolone, or dronabinol (Marinol®) or other cannabinoid, mainly for patients who can't tolerate steroids or at high risk to progress. For additional supportive care see NCCN guidelines[b](Appendix 6).	Selinexor may be skipped intermittently while supportive medications are instituted, usually for <1 week.
Grade 3	See guidelines for Grade 2 anorexia.	Interrupt dosing with selinexor. Restart selinexor at 1 dose level reduction (Table 3) once anorexia resolves to Grade ≤ 2 and patient is clinically stable.
Grade 4 (anorexia only)	See guidelines for Grade 2 anorexia.	Stop dosing of selinexor. Restart selinexor at 1 dose level reduction (Table 3) only if anorexia resolves to Grade ≤ 2, patient is clinically stable other contributing factors have been addressed.
Nausea/ - acute (common)		
Grade 1	Insure adequate caloric intake and assess volume status. Consider alternate 5-HT3 antagonists and/or D2 antagonists as needed. Consider addition of NK1 antagonists. Consider addition of 4-12 mg dexamethasone or equivalent with each dose of selinexor +/- the day after selinexor.	Maintain dose.
Grade 2	See guidelines for Grade 1 nausea For additional options see NCCN guidelines for antiemesis[c] (Appendix 6)	Selinexor may be skipped intermittently while supportive medications are instituted, usually for <1 week.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 3	See guidelines for Grade 1 nausea For additional options see NCCN guidelines for antiemesis[c] (Appendix 6)	Interrupt selinexor dosing until resolved to Grade ≤ 2, For first occurrence of Grade 3, if adequate supportive care resulted in nausea improving to Grade ≤1 within 3 days, restart selinexor at current dose. Otherwise, restart selinexor at one dose level below (Table 3). If nausea stabilizes for at least 4 weeks at Grade ≤1, then original dose of selinexor may be resumed.
Hyponatremia (common)		
Grade 1 (sodium levels <Normal to 130 nM)	Be certain sodium level is corrected for hyperglycemia (serum glucose >150mmol/L). Rule out other causes of low sodium (e.g., cardiac, hepatic, adrenal, renal and thyroid diseases, SIADH, Fanconi Syndrome, hyperglycemia, diuretic use). Consider salt supplementation one – two times per day.	Maintain dose.
Grade 3 (sodium levels 126-129nM) without Symptoms	Be certain sodium level is corrected for hyperglycemia (serum glucose >150mmol/L). Rule out other causes of low sodium (e.g., cardiac, hepatic, adrenal, renal and thyroid diseases, SIADH, Fanconi Syndrome, hyperglycemia, diuretic use). Initiate salt supplementation two-three times per day.	Hold selinexor until Grade ≤1 (≥130 nM), restart on the same dose level.
Grade 3 (120-125 nM) or Grade 4 or any Grade 3 with Symptoms	Correct sodium as per institutional guideline Initiate salt supplementation two-three times per day.	Hold selinexor until resolved to Grade ≤ 1 (≥130nM) then reduce selinexor dose by 1 level (Table 3). For Grade 3 hyponatremia, if serum sodium stabilizes to grade ≤1 for at least 4 weeks, then original dose of selinexor may be resumed.
Diarrhea (common)		
Grade 1+2	Diet recommendation as per guidelines (Benson, 2004)[d]. Institute standard anti-diarrheal therapy After the first occurrence of diarrhea, loperamide 2 mg should be considered prophylactically approximately 1-2 hours before the administration of selinexor and repeated every 4 hours for the first 12 hours.	For Grade 2 only, reduce selinexor one dose level (Table 3) until resolved to ≤ Grade 1, then re-start at the current dose level.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 3	Institute IV fluids Diet recommendation as per guidelines (Benson, 2004)[d]. Institute standard anti-diarrheal therapy. Once the symptoms resolve to ≤Grade 1, loperamide 2 mg should be considered prophylactically approximately 1-2 hours before the administration of selinexor and repeated every 4 hours for the first 12 hours.	Delay selinexor until resolved to ≤ Grade 1, then reduce selinexor dose by one dose level (Table 3). If diarrhea stabilizes for at least 4 weeks at Grade ≤1, then original dose of selinexor may be resumed.
Grade 4	Rule out other causes of diarrhea, including infectious agents. In case of opportunistic infection, withdraw all steroids (with tapering if medically appropriate) until culture is negative. Follow institutional guidelines for Grade 4 diarrhea.	Delay selinexor until resolved to ≤ Grade 1, then reduce selinexor dose by one dose level (Table 3).
Thrombocytopenia		
Grade 1	In cases of marked reduction in platelet numbers from baseline, consider implementing platelet growth factors (eltrombopag or romiplostim +/- oprelvekin [IL-11]).	Maintain dose.
Grade 2	Strongly consider implementing platelet growth factors (eltrombopag or romiplostim +/- oprelvekin [IL-11]). Monitor platelet counts weekly.	If Grade 2 thrombocytopenia persist > 14 days, hold selinexor dosing until platelet count returns to Grade 1 or baseline values, then re-start at the current dose level.
Grade 3 Thrombocytopenia Without bleeding	Initiate platelet growth factors (eltrombopag or romiplostim +/- oprelvekin [IL-11]). Monitor platelet counts at least weekly. Consider holding anti-platelet agents.	Hold selinexor dosing until the patient's platelet count returns to Grade ≤2 or baseline. For Grade 2, restart selinexor at same dose level taken once weekly only until platelet counts resolve to Grade ≤1 or baseline., then resume twice weekly dosing at current dose. Second occurrence: hold selinexor dosing until platelet counts return to Grade ≤2 or baseline. For Grade 2, restart selinexor at same dose level taken once weekly only until platelet counts resolve to Grade ≤1 or baseline, then resume twice weekly dosing at one dose level below (Table 3). If platelet counts stabilize at Grade ≤1 or baseline for at least 4 weeks, then original dose of selinexor may be resumed.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 4 Thrombocytopenia Without bleeding	Follow guidelines for Grade 3 thrombocytopenia without bleeding. Transfuse as per institutional guidelines.	Hold selinexor dosing until platelet counts return to Grade ≤2 or baseline. For Grade 2, restart selinexor at same dose level taken once weekly only until platelet counts resolve to Grade ≤1 or baseline, then resume twice weekly dosing at one dose level belowv(Table 3). If platelet counts stabilize at Grade ≤1 or baseline for at least 4 weeks, then original dose of selinexor may be resumed.
≥ Grade 3 Thrombocytopenia associated with bleeding	Transfuse as per institutional guidelines. Follow guidelines for Grade 3 thrombocytopenia without bleeding.	Hold selinexor dosing until platelet counts return to Grade ≤1 or baseline, then resume selinexor dosing at one dose level below (Table 3).
Neutropenia		
Grade 3 neutropenia without fever	Implement growth factors per institutional guidelines.	Hold dosing with selinexor until the patient's ANC returns to Grade ≤2 or baseline values. Resume dosing with selinexor at current dose.
Grade 4 neutropenia without fever	Implement growth factors per institutional guidelines.	Hold dosing with selinexor until the patient's ANC returns to Grade ≤2 or baseline values. Resume dosing with selinexor at current dose. Second occurrence: hold dosing with selinexor until the patient's ANC returns to Grade ≤2 or baseline values then reduce selinexor dose by one dose level (Table 3).
Grade 3 or 4 neutropenia with fever (febrile neutropenia)	Implement growth factors per institutional guidelines. Implement broad anti-microbial coverage per institutional guidelines. Please note that selinexor has not been associated to date with any opportunistic infections	Hold dosing with selinexor until the patient's ANC returns to Grade 1 or baseline values, fever has resolved and patient is stable, then reduce selinexor dose by one dose level (Table 3).
Other selinexor-related adverse events*		
Grade 1 or 2	Initiate standard supportive care and follow institutional guidelines.	Maintain dose.
Grade 3	Initiate standard supportive care and follow institutional guidelines.	Delay dose until resolved to Grade ≤ 1 or baseline, then reduce by one dose level (Table 3).

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 4	Initiate standard supportive care and follow institutional guidelines.	Delay dose until resolved to Grade ≤ 1 or baseline, then reduce by two dose levels (Table 3).
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.		
[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 1.2014. Fort Washington, NY. April 2014. Available at: http://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/generalcancer/pdf/facts.pdf. [c]**National Comprehensive Cancer Network®**. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Antiemesis, version 2.2014. Fort Washington, NY. April 2014. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. [d]Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Onc 2004; 22:2918.		

6.3.2 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 >170 patients treated as of 15 October 2013.

6.3.2.1 Missed or Vomited Doses

Missed doses

A maximum of two doses may be given per week. If the dose was missed for more than 24 hours, the dose will be skipped and the next dose will be taken as per schedule. If the dose was missed within 24 hours, then it will be replaced. Doses should not be administered in less than 36 hours apart and all missed doses should be documented in the patient diary and the CRF.

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.

6.4 GENERAL DOSE MODIFICATIONS: MFOLFOX6

Table 5

Drug	Dose Level		
	Starting Dose	**-1**	**-2 [a]**
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^{2,a}
5-FU bolus	400 mg/m^2	OMIT	OMIT
5-FU continuous infusion over 46-48 hours	2400 mg/m^2	1900 mg/m^2	1500 mg/m^{2,a}
Leucovorin[b]	400 mg/m^2	100%	100%

Abbreviations: 5-FU = 5-fluorouracil; DP = drug product; mFOLFOX6 = 5-FU), leucovorin, and oxaliplatin.

a. For 5-FU or oxaliplatin infusions, further dose levels (-3, -4, etc.) will be 20% dose reductions from the previous level for oxaliplatin and 5-FU continuous infusion. In addition, the bolus dose of 5-FU will continue to be omitted, and the leucovorin dose will remain unadjusted (100%).

b. Dosing of leucovorin will remain fixed at 100% of recommended dose.

6.4.1 MODIFICATIONS FOR FIRST TWO CYCLES

Strictly follow the modifications in the following tables for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to prevent side effects from exceeding a mild-to-moderate level, and minimize the incidence and duration of debilitating side effects.

If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed.

6.4.2 IMPLICATIONS OF DOSE REDUCTIONS FOR SUBSEQUENT CYCLES

If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for all subsequent cycles.

6.4.3 CONTINUATION OF THERAPY ON-STUDY IN THE SETTING OF DISCONTINUATION OF ONE COMPONENT OF STUDY THERAPY

If one therapeutic agent is permanently discontinued secondary to toxicity (for example, oxaliplatin discontinued secondary to neurotoxicity), then therapy with the other study agents should continue and the patient should remain on-study with full adherence to all protocol related requirements.

Omit:	Treatment is not given for this cycle
Hold/Delay:	Treatment can be made up as part of this cycle
Discontinue:	Treatment is totally stopped
Recommended Dose Modifications for Oxaliplatin+5-Fluorouracil/Leucovorin[a]	

Table 6

CTCAE v. 4.03 System Organ Class[b]	**Adverse Event**	**Dose Level for Subsequent Cycles Based on Interval Adverse Events**	**At Time of Retreatment**
All Adverse Events <1		Maintain dose level	Maintain dose level
Blood and lymphatic system disorders	***Hemolytic uremic syndrome (HUS)[c]*** *≥Grade 3*	Discontinue oxaliplatin	Discontinue oxaliplatin
Investigations:	**Neutrophil count decreased** Grade 1 (ANC <LLN-1500/mm^3) Grade 2 (ANC <1500-1000/mm^3) Grade 3 (ANC <1000 - 500/mm^3) Grade 4 (ANC <500/mm^3)	Maintain dose level Maintain dose level ⊕ 1 oxaliplatin dose level ⊕ 1 5-FU dose level ⊕ 1 oxaliplatin dose level	If ANC <1500 at start of cycle, hold and check weekly then treat based on interval adverse event. If ANC <1500 after 4 weeks, discontinue therapy.
	Platelet count decreased Grade 1 (PLT<LLN-75,000/mm^3) Grade 2 (PLT<75,000-50,000/mm^3) Grade 3 (PLT <50,000-25,000/mm^3) Grade 4 (PLT <25,000/mm^3)	Maintain dose level Maintain dose level ⊕ 1 oxaliplatin dose level ⊕ 2 oxaliplatin dose levels	If PLT <75,000 at start of cycle, hold and check weekly then treat based on interval adverse event. If PLT <75,000 after 4 weeks, discontinue therapy.

Gastrointestinal disorders:	**Diarrhea** Grade 1, 2 Grade 3 Grade 4 **Mucositis oral** Grade 1, 2 Grade 3 Grade 4 **Vomiting** Grades 1, 2 Grade 3 Grade 4	 Maintain dose level ⊕ One 5-FU dose level ⊕ Both 5-FU and oxaliplatin 1 dose level Maintain dose level ⊕ One 5-FU dose level ⊕ One 5-FU dose level Maintain dose level ⊕ 1 oxaliplatin dose level ⊕ Both 5-FU and oxaliplatin 1 dose level	If Grade ^{3}2 at start of cycle, hold and check weekly then treat based on interval adverse event. If Grade ^{3}2 after 4 weeks, discontinue therapy.
Neurology	Do not use CTCAE.	See xxx for adverse event scale and oxaliplatin dose modifications.	
Respiratory, thoracic, and mediastinal disorders	**Cough** ^{3} Grade 3 **Dyspnea** ^{3} Grade 3 **Hypoxia** ^{3} Grade 3 **Pneumonitis** ^{3} Grade 3	Hold oxaliplatin until interstitial lung disease is ruled out. If interstitial lung disease, oxaliplatin should be permanently discontinued.	
Other nonhematologic adverse events[d, e]	Grades 1, 2 Grades 3, 4	Maintain dose level ⊕1 5-FU dose level	

a. The dose of leucovorin will not be adjusted due to adverse event. It should remain at 400 mg/m^2 for all courses. Leucovorin will be given immediately prior to each 5-FU dose; thus, if 5-FU is delayed, leucovorin will be delayed.

b. For ≤ NCI CTCAE v. 4.03 Grade 2 toxicity not described, maintain dose level of agent.

c. Recommended evaluation of suspected HUS: Evaluation should include CBC differential, platelets, PT, PTT, fibrinogen, FDP, Anti thrombin III, Von Willebrand factor, anti-nuclear antibody, rheumatoid factor, Compliment Cascade C3, C4, and CH50, anti-platelet antibodies, platelet-associated IgG, and circulating immune complexes. Renal evaluation should include creatinine, BUN, and urinalysis with microscopic examination. Other laboratory and hematological evaluations as appropriate should also be obtained, including peripheral blood smear and free hemoglobin.

d. Exceptions: alopecia, fatigue, anorexia, nausea/vomiting if can be controlled by antiemetics, and viral infections.

e. Dose modifications for other nonhematologic adverse events at the start of subsequent courses of therapy, and at time of retreatment are also based on NCI CTCAE v. 4.03 criteria.

6.4.4 OXALIPLATIN DOSE MODIFICATIONS FOR NEUROLOGIC ADVERSE EVENTS

Adverse Events	Duration of Adverse Event		Persistent[b] Between Cycles
	1 - 7 Days	>7 Days	
Paresthesias/Dysesthesias			
Paresthesias/dysesthesias[c] of short duration that resolve and do not interfere with function (Grade 1)	No change	No change	No change
Paresthesias/dysesthesias[c] interfering with function, but not activities of daily living (ADL) (Grade 2)	No change	No change	⊕1 oxaliplatin dose level
Paresthesias/dysesthesias[c] with pain or with functional impairment that also interfere with ADL (Grade 3)	1st time: ⊕1 oxaliplatin dose level 2nd time: ⊕1 oxaliplatin dose level	1st time: ⊕1 oxaliplatin dose level 2nd time: ⊕1 oxaliplatin dose level	Discontinue
Persistent paresthesias/dysesthesias that are disabling or life-threatening (Grade 4)	Discontinue	Discontinue	Discontinue
Laryngeal Dysesthesias (investigator discretion used for grading):			
Grade 1 = mild	No change	– duration of infusion to 6 hours	– duration of infusion to 6 hours
Grade 2 = moderate. (Also recommended is administration of benzodiazepine and patient education. Management of patient if [3] Grade 2 laryngeal dysesthesias occurs while treatment is being administered.)	Stop oxaliplatin infusion. Administer benzodiazepine and give patient reassurance. At the discretion of the investigator, the infusion can be restarted at 1/3 the original rate of infusion.		
Grade 3 = severe			

Abbreviations: ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events.

a If oxaliplatin is discontinued, continue other study agents unless adverse events preclude their continuation.

b Not resolved by the beginning of the next cycle.

c May be cold-induced.

6.5 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. Patients should minimize the use of products containing acetaminophen, which can interfere with the metabolism of Selinexor. For combination painkillers containing acetaminophen it is recommended that single agent opiates or aspirin combinations (when clinically acceptable) be substituted.

6.5.1 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.

6.5.2 PREVENTION OF PREGNANCY

Female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening, and male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. For both, male and female patients, effective methods of contraception must be used throughout the study and for three-months following the last dose.

6.5.3 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. Appropriate anti-coagulation is allowed during the study (eg: LMW heparin, direct factor Xa inhibitors, etc).

6.5.4 GLUCOCORTICOID THERAPY

Glucocorticoids ≤ 10 mg oral prednisone (or equivalent) per day are permitted at baseline and during the study for non-malignant conditions (i.e., asthma, IBD, etc.) 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 (4-10mg) or prednisone (10-20mg) on days of (±1 day after) Selinexor dosing may improve appetite, reduce nausea or vomiting, and minimize fatigue.

6.5.5 PROHIBITED MEDICATIONS

Patients should minimize the use of products containing acetaminophen. For combination painkillers containing acetaminophen it is recommended that single agent opiates or aspirin combinations (when clinically acceptable) be substituted, particularly on the days of Selinexor dosing.

Concurrent therapy with an approved or investigational anticancer therapeutic, other than Oxaliplatin, 5-fU and Levamisol as specified herein, is not allowed.

Use of any immunosuppressive agents during the study must be confirmed by the medical monitor. Other investigational agents should not be used during the study.

Inactivation of Selinexor by glutathione conjugation is a significant metabolic pathway *in vitro* and *in vivo*, including in humans. This process can be mediated in the absence of proteins, indicating that it is thermodynamically favorable. *In vitro* studies using human liver microsomes confirm *in vivo* findings that Selinexor undergoes minimal CYP450 metabolism. Therefore, administration of Selinexor with drugs which undergo substantial glutathione conjugation should be minimized or avoided. These drugs include acetaminophen (paracetamol) and ethyl alcohol. It should be noted that studies of Selinexor in combination with acetaminophen are currently on-going and therefore that these recommendations are empirical. It should also be noted that recreational ethanol ingestion is associated with glutathione depletion; therefore, the use of products containing ethanol should be minimized or avoided on Selinexor dosing days.

6.6 SUPPORTIVE CARE GUIDELINES

Supportive measures for optimal medical care shall be provided during participation in this clinical trial. Supportive care including anti-nausea / anti-emetic therapy, acid suppression (proton pump inhibitors and/or H2-blockers), glucocorticoids, and other standard treatments may be administered as per institutional guidelines for symptomatic patients. As needed and per individual study site institutional guidelines, prophylactic therapies, including antivirals,

antifungals, and antibiotics, may be administered to ameliorate risks associated with non-malignant disorders or of immune system compromise.

6.6.1 ANOREXIA

Based on clinical observations on Schedules 1-3 with over 200 patients treated with Selinexor across phase 1 clinical trials (KCP-330-001 and KCP-330-002), the dose limiting toxicities (DLTs) are primarily related to anorexia with poor caloric and fluid intake leading to weight loss, fatigue and nausea. Therefore, it is strongly recommended that patients at risk for anorexia, weight loss, and/or fatigue receive strong nutritional counseling, high caloric beverages with adequate electrolyte levels (e.g., Ensure®), prophylaxis with appetite-stimulating agent(s), and anti-emetic agents. Patients with proper nutritional support and counseling have remained on Selinexor for >11 months. There is no correlation between initial BMI or weight and the development of anorexia.

In patients with problematic food/liquid/caloric intake, a patient log of food and drink should be considered and monitored by the treatment team.

Fresh juices, simple carbohydrates, as well as ginger can improve appetite before the meal; ginger may also improve dysgeusia.

Since the duration of treatment is short and most of the patients are hospitalized during induction treatment patients with anorexia nutrition is usually provided by infusion directly into the circulatory system

If constipation occurs, then laxatives should be given as constipation can contribute to anorexia and loss of appetite.

6.6.2 FATIGUE

Fatigue may be related to underlying malignancy, Selinexor side effects, side effects of other agents or concurrent morbidities. Fatigue may also be related to anorexia and/or dehydration, so caloric and fluid intake should be optimized in all patients (please see above aggressive guidelines for maintenance of food and fluid intake). Acid suppression (proton pump inhibitors and/or H2-blockers) may be beneficial in some patients with fatigue.

6.6.3 EMESIS

Supportive care for nausea and vomiting should be given promptly. The site can consider prophylactic treatment in case of previous side effect of nausea and vomiting with prior anti-

cancer therapy. The treatment should start with the first sign of nausea. Standard anti-emetics are allowed and strongly recommended.

6.6.4 ACUTE EMESIS

Acute emesis is not a major observation with Selinexor but has been reported. Selinexor associated nausea/emesis generally responds to D2-antagonists, 5-HT3 antagonists, or combinations of agents.

5-HT3 receptor antagonists (Zofran® 8 mg od on days of dosing) — First-generation 5-HT3 receptor antagonists all appear equally effective at preventing nausea/emesis at the recommended doses. A single dose of a 5-HT3 receptor antagonist prior to therapy is equivalent to a multiple dose schedule. The efficacy of 5-HT3 receptor antagonists is significantly improved when they are combined with glucocorticoids. As QTc prolongation is the main side effect, magnesium and potassium should be corrected prior to use. If first-generation 5-HT3 receptor antagonists+dexamethasone do not adequately control emesis, second generation 5-HT3 receptor antagonists (e.g., palonosetron) should be considered. Second generation 5-HT3 receptor antagonists also improve delayed nausea/emetic response.

Neurokinin-1 receptor antagonists (e.g., aprepitant or fosaprepitant, Emend®) – should be considered in case of uncontrolled emesis with standard treatments as described above. Neurokinin-1 receptor antagonists should be given with combination of dexamethasone and first or second generation 5-HT3 receptor antagonists.

Additional treatment: Metoclopramide Hydrochloride 10mg, 30 min before meal (up to 4 time a day) or prochlorperazine (standard doses) have been effective in many patients. Dronabinol (Marinol) has shown some activity in both nauea/emesis and anorexia in patients treated with Selinexor. Lorazapeam can be added to the combination treatment of 5-HT3 receptor antagonists +dexamethasone, e.g., at night, but has been less effective in Selinexor associated nausea/emesis.

6.6.5 DELAYED EMESIS - > 24H AFTER TREATMENT

Management — Selinexor is infrequently associated with delayed, resistant emesis. Many of the regimens associated with delayed emesis are classified as high-emetic risk, and professional guidelines recommend the use of an NK1 receptor antagonist (either NK-1 blockers e.g., aprepitant on days 1 to 3 or fosaprepitant on day 1 only), plus a glucocorticoids on days 1 to 4, along with a 5-HT3 receptor antagonist (particularly second generation

agents) on day 1. This regimen is effective against both acute and delayed emesis. The data supporting the individual components of this regimen are reviewed below.

Olanzapine — Conventional antiemetics are more successful at preventing emesis than in preventing nausea, particularly delayed nausea. Olanzapine 10 mg once daily (typically given at night to mitigate sedative effects) was proven effective in both anti emesis and nausea control. It may also be useful for management of breakthrough emesis, and to improve food intake in patients with anorexia.

Glucocorticoids are also consistently useful and should be administered as described above.

Granisetron transdermal patch — A transdermal preparation of granisetron should be consider in patients that have uncontrolled emesis/nausea >grade 2 under best supportive treatment

Ginger — Supplemental ginger added to foods or at doses of 0.5, 1.0gm powder daily total dose, usually in divided doses. Ginger may also improve dysgeusia.

Additional agents can be added, including lorazepam or alprazolam, olanzapine, a dopaminergic D2-antagonist (eg, prochlorperazine, thiethylperazine, haloperidol), or substituting high-dose intravenous metoclopramide for the 5-HT3 antagonist.

6.6.6 DIARRHEA

Diarrhea is common at up to 32% (mostly Grade 1), which responds to standard anti-diarrheal agents. Fluid replacement is important to prevent dehydration, fatigue and electrolyte abnormalities (e.g., hyponatremia).

6.6.7 HYPONATREMIA

Hyponatremia (Grade 3) has been reported in about 9% of patients. One of these cases was pseudohyponatremia due to hyperglycemia (not associated with Selinexor). None of these cases have been symptomatic. Most of the patients had anorexia, nausea, vomiting and/or diarrhea. Two of the patients with Grade 3 hyponatremia had third-space fluid accumulation or resolution (e.g., ascites, edema). Adequate fluid and caloric intake, including electrolyte rich beverages rather than free water, has led to reversal of the hyponatremia.

7 SAFETY REPORTING

The Investigator's Brochure will be used as reference document for KPT-330 (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 is defined in the International Conference on Harmonization (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.

7.1.2 ADVERSE DRUG REACTION

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 adverse event 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 SERIOUS ADVERSE EVENT

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.

7.1.4 NOT TO BE REPORTED AS SAEs

For this study, the following is **not** classified as serious adverse event:

- 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 unrelated 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.

7.1.5 SUSAR/ UNEXPECTED SERIOUS ADR

A SUSAR/ Unexpected Serious ADR is a suspected unexpected serious adverse reaction. A suspected adverse reaction is an adverse event for which there is a reasonable possibility that the drug caused the event. An unexpected adverse reaction is any adverse reaction with a reasonable possibility that the study drug caused the event and the specificity or severity is not consistent with the current investigator's brochure for Selinexor. Also, reports that provide significant information on the specificity or severity of a known, already documented adverse event constitute unexpected adverse events. An event more specific or more severe than described in the investigator's brochure would be considered "unexpected". All suspected adverse reactions related to Selinexor which occur in the trial and that are both unexpected and serious (SUSARs/ Unexpected Serious ADR) are subject to expedited reporting.

7.2 REPORTING OF SAES

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 the sponsor and the drug provider within 24 hours of knowledge (expedited reporting). For each patient, all serious adverse events must be reported up to 30 days after the last dose of investigational product. Serious adverse events 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 faxed to:

SAE reporting forms will be completed within 24 hours of the event and faxed to:

Clinical Trial Manager	**Dr. Anne L. Kranich**
Address:	**GSO mbH** Harvestehuder Weg 21 20148 Hamburg Germany
Phone:	**0049-40-44 19 54 60**
Fax:	**0049-40-44 19 54 78**

The drug provider will medically review all SAEs.

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

- A description of the AE in medical terms

- The severity grade as assessed by the investigator according to the definitions in NCI-CTC 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 treatment procedures necessary for the SAE, concomitant medications, relevant lab tests and relevant medical history

If in any one subject 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.

7.3 REPORTING OF SUSARS/ EXPEDITED REPORTING OF UNEXPECTED SERIOUS ADRS

The sponsor will via coordinating CRO ensure the notification of the appropriate ethics committees, competent authorities and participating investigators of all SUSARs events occurring at the sites in accordance with local legal requirements, statutes and the European Clinical Trial Directive as follows:

- Reporting of the SUSAR to the Competent Authorities and Ethics Committees within 15 days (or within 7 days for fatal and life-threatening events)
- Sending the event to all participating Investigators for information (with confirmation of receipt).

In addition, all events that require a new assessment of the risk-benefit ratio will be reported to the Ethics Committee and the Competent Authority of each concerned Member State within 15 days. This includes:

- Single reports of expected serious adverse reactions with unexpected outcome.
- An increase in the rate of occurrence of expected serious adverse reactions which is judged to be clinically relevant
- Post-study SUSARs that occur after the patient has completed a clinical trial
- New events related to the conduct of the trial or the development of the investigational medicinal products and likely to affect the safety of the subjects

The sponsor is responsible to ensure that the latest investigator's brochure is used as the source document for determining the expectedness of an SAE.

7.4 RECORDING OF ADVERSE EVENTS

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

The following adverse event attributes must be assigned by the investigator:

- Adverse event term according to the NCI-CTC criteria Version 4.03 and verbatim term
- Severity grade according to the NCI-CTC 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 unrelated)
- Any action taken

Adverse events will be followed until they resolve to baseline or considered stable. It will be left to the investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

Pre-existing diseases, when worsening during study therapy, have to be considered as adverse events. They can lead to serious adverse events, if the meet the criteria described in section 7.1.3.

Intensity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. If an adverse event occurs which is not described in the CTCAE version 4.03, the four-point scale below will be used.

Pre-existing diseases, when worsening during study therapy, have to be considered as adverse events. They can lead to serious adverse events, if the meet the criteria described in Section 7.1.3.

Intensity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 . If an adverse event occurs which is not described in the CTCAE version 4.03, the four-point scale below will be used.

Mild:	Discomfort noticed but no disruption of normal daily activity
Moderate:	Discomfort sufficient to reduce or affect daily activity
Severe:	Inability to work or perform normal daily activity
Life-threatening:	Represents an immediate threat to life

7.5 LABORATORY TEST ABNORMALITIES

Laboratory test results will be recorded on the laboratory results pages of the CRF. In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately 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 CRF as adverse events unless they are judged clinical significant by the investigator.

7.6 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 to GSO. 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.

7.7 ADVERSE DRUG REACTIONS WITH CONCOMITANT MEDICATION

The investigators must be aware that for all concomitant medications the regulations of post-marketing reporting for suspected adverse drug reactions apply, i.e. reporting to the marketing authorization holder or the local regulatory bodies.

8 BIOSTATISTICAL ASPECTS

Based on the phase I design no sample size calculation will be performed, as sample size will be determined by the respective dose escalations.
However, secondary endpoints will be analyzed. Overall response rate, and secondary resection rate will be summarized using frequency tables. For the time-to-event variables PFS and OS, the Kaplan-Meier method will be used to estimate the event free survival. Toxicity will be documented in a descriptive way.
All secondary efficacy analyses will be based on the ITT population and the corresponding statistical testing results will be interpreted in the exploratory sense.

8.1 SAMPLE SIZE ESTIMATION

Due to the sequential nature of the traditional 6+3-design described in section 3.1, the exact number of patients in the trial is unknown. The number of evaluable patients that will be needed depends on the number of times the dose is escalated or possibly de-escalated and consequently varies between 6 and 27.

8.2 ANALYSIS POPULATION

Within this phase I trial all patients enrolled who started study treatment with Selinexor and mFOLFOX6 will be evaluable for statistical analysis.

8.3 STATISTICAL ANALYSIS

8.3.1 GENERAL STATISTICAL CONSIDERATIONS

Statistical analysis is based on the International Conference on Harmonization (ICH) Guidelines “Statistical Principles for Clinical Trials”.

Standard descriptive methods will be used to present all relevant data. All data recorded in the case report forms describing the sample, the efficacy and the safety will first be analyzed descriptively. Categorical data will be presented in contingency tables with frequencies and percentages.
Continuous data will be summarized with at least the following: frequency (n), median, quartiles, mean, standard deviation (standard error), minimum and maximum. Summary tabulations will be provided. Time-to-event data will be analyzed by Kaplan-Meier methods.

Number of patients with protocol deviations during the study and listings describing the deviations will be provided.

Safety analysis will be presented stratified by dose level. Since no other covariates of prognostic relevance are pre-specified within this protocol, an adjustment for co-variables will not be performed. Due to the small sample size, no site-specific analyses will be performed.

In case that the trial is prematurely stopped after enrollment of merely six evaluable patients, no aggregated tables and figures will be presented and statistical analysis is restricted to data listings only.

8.3.2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

All demographic and clinical characteristics recorded at baseline will be submitted to descriptive analyses using descriptive statistics by means of listing, tables and figures, if applicable.

8.3.3 PRIMARY VARIABLE

The primary study endpoint is defined as the maximally tolerated dose of Selinexor in combination with a dose of mFOLFOX6 defined by means of the rate of patients experiencing dose-limiting toxicity. A patient is considered to have experienced a DLT if at least one of the toxicity listed in section 3.1.1 has occurred within 28 days from start of treatment. For descriptive purposes, each individual adverse event fulfilling the definition of a DLT will be listed by dose level and patient.

The statistical decision strategy for dose (de-)escalation is outlined in section 3.1.

8.3.4 SECONDARY VARIABLES

Overall safety profile:

The incidence of patients experiencing adverse events will be analyzed as follows:

- All information recorded such as onset date, stop date, duration, maximum intensity, seriousness, relationship to study drug will be listed.
- Adverse event tables will be produced presenting the total number of patients reporting at least one specific event and the maximum toxicity grade. Thus, patients reporting more than one episode of the same event are counted only once by the worst grade per patient. Tabulations consist of the number and percentages of patients involved per CTC category and CTC term, the highest relation to study drug and the maximum severity.

- Special tables will be displayed for severe and life threatening adverse events and for adverse events resulting in discontinuation of the trial or reduction of the study medication or death.
- Additionally, analysis will be restricted to adverse events judged to be at least possibly related to study drug.
- Furthermore, summary tables with patient identification will be presented. These tables provide the number and percentage of patients with adverse events and also includes the subject identification in the table.
- Subset-tables will be provided for toxicity of special interest, i.e. ophthalmological events, thromboembolic events and bleeding.

The above mentioned analyses will be presented for all (pooled) evaluable patients together and stratified by dose level. Furthermore, subset-tables will be presented for those adverse events occurring within 4 weeks after start of treatment in order to be consistent with the time span defined for DLT-evaluation.

Safety laboratory parameters will be evaluated stratified by visit. For each parameter, the distribution over time as well as the mean values at baseline and changes from baseline will be computed and reported with descriptive statistics. Values outside normal ranges will be displayed and tabulated. In addition, for applicable laboratory parameters, NCI-CTCAE version 4.03 grades will be provided and incorporated in the patient laboratory listings.

Response rate:

Best response is defined as the best clinical response, as per RECIST version 1.1, documented during treatment phase. Patients without any documented tumor assessments are considered to have experienced a progressive disease, in case of therapy discontinuation due to progressive disease or early death (defined as death prior to first scheduled tumor assessment after start of treatment). The frequency distribution of response categories will be presented.

In addition the response rate, i.e. the percentage of patients experiencing partial or complete response during study, will be presented.

Progression-free survival:

Progression-free survival is defined as the time from start of therapy to the first observation of disease progression or death due to any cause. If a patient has not progressed or died, progression-free survival is censored at the time of last documented efficacy. The distribution

of progression-free survival will be estimated by Kaplan-Meier methods. 90% confidence limits for specific time points will be extracted together with their 90% confidence intervals.

Due to sparse data, progression-free survival will merely presented on all evaluable patients; no dose level stratifications are planned.

8.4 INTERIM AND FINAL ANALYSIS

No formal interim analyses are planned. A continuous monitoring of both safety and efficacy data will be performed.

9 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be assured by verification and cross–check of the CRFs 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 CRF. It will be transcribed by the site from the source documents onto the CRF. 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 DECLARATION OF HELSINKI / GOOD CLINICAL PRACTICE

The Declaration of Helsinki is the accepted basis for clinical study ethics, and must be fully followed and respected by all those engaged in research on human beings. Any exceptions must be justified and stated in the protocol. The latest version of the Declaration of Helsinki is available at www.wma.net.

Additionally it is the responsibility of all those engaged in research on human beings to ensure that the study is performed in accordance with the international standards of Good Clinical Practice and according to all local laws and regulations concerning clinical studies.

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 trial and that it may be transferred to the sponsor in pseudonymized form.

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

The informed consent form personally signed and dated by the patient must be kept on file by the investigator(s) and documented in the CRF and the subject's medical records. The investigator must confirm with the sponsor/coordinating CRO 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 doctors 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 subjects in accordance with the applicable local law. The sponsor provides appropriate insurance.

10.3.2 NOTIFICATION OF THE STUDY

The sponsor is responsible for notifying the competent regional authority about the study and all principal 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 ongoing studies must be made via amendment. The sponsor is responsible for obtaining independent approval for substantial amendments from the applicable regulatory authority 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 subjects 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 authorisation 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 and laboratory reports, ECG, EEG, X-ray, etc.), signed informed consent forms and patient screening and eligibility screening forms.

The investigator must keep these two categories of documents on file for at least 15 years (or longer, as legally required, e.g. 20 years in Belgium) 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 authorised 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 case report form 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 must be completed and signed by the principal investigator or an authorised 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 CRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to document the outcome clearly.

13 MONITORING THE STUDY

The monitor is responsible for familiarising the investigator(s) and the entire centre staff involved in the study with all study procedures, including the administration of the study drug.

The monitor will visit the clinical study centre 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 CRFs (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 CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The investigator and the sponsor (or designated person) must ensure that all data obtained in the course of a clinical study is treated with discretion in order to guarantee the rights of the patient's privacy, according to the standards of the data protection law. CRFs or other documents should be submitted to the sponsor in pseudonymised 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.

15 STUDY REPORT AND PUBLICATION POLICY

This study will be entered into a clinical trial protocol registry and clinical results database. The sponsor is responsible for the timely reporting of study data. An integrated clinical study report (CSR) has to be completed one year after the end of the study (whether completed or prematurely terminated). The report has to be approved by the responsible specialist chosen by the sponsor, the project manager of the CRO, the statistician and the coordinating investigator by provision of their signatures. In this multi-center study, the main publication will be a full publication of all 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.

16 APPENDICES

Appendix 1: Overview of current CRC studies

Appendix 2: Definitions According to ICH Topic E2A Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, (CPMP/ICH/377/95)

Appendix 3: ECOG Performance Status

Appendix 4: Cockroft-Gault Formula

Appendix 5: National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

16.1 APPENDIX 1 – OVERVIEW OF CRC STUDIES

Authors	Indication	Treatment line	Number of patients enrolled (evaluable)	Drug	ORR (CR / PR)	SD	PFS (months)	OS (months)
Saltz et al.[11]	metastatic CRC	first-line	699	FOLFOX4 or XELOX plus bevacizumab	38%	(-)	9,4	21,3
			701	FOLFOX4 or XELOX plus placebo	38%	(-)	8	19,9
Hurwitz et al.[12]	mCRC	first line	411 (-)	placebo plus bolus- IFL	34,80%	(-)	6,2	15,6
			402 (-)	bevacizumab plus bolus- IFL	44,80%	(-)	10,6	20,3
Bennouna et al.[13]	metastatic CRC	second-line	53 (-)	bevacizumab plus FOLFIRI, FOLFOX, irinotecan or XELIRI	32%	55%	6,5	19,3
Bennouna et al.[14]	mCRC	second-line	409 (-)	bevacizumab + Oxaliplatin-or Irinotecan-based chemotherapy	(-)	(-)	5,7	11,2
			411 (-)	Oxaliplatin-or Irinotecan-based chemotherapy alone	(-)	(-)	4,1	9,8
Van Cutsem et al.[15]	unresectable mCRC	first-line	1965 (1914)	bevacizumab plus 5-FU/LV+oxaliplatin or irinotecan+5-FU/LV or capecitabine+oxaliplatin or monotherapy	44,80%	(-)	10,8	22,7
van Cutsem et al.[16]	mCRC	first-line	599 (533 KRAS population)	FOLFIRI	38,5% (39,7% WT-KRAS)	46,2% (46,3% WT-KRAS)	8,1 (9,1 WT-KRAS)	18,7 (20,0 WT-KRAS)
			599 (530 KRAS population)	Cetuximab plus FOLFIRI	46,8% (57,3% WT-KRAS)	37,9% (31,6% WT-KRAS)	8,4 (9,9 WT-KRAS)	20,2 (23,5 WT-KRAS)
Bokemeyer et al.[17]	mCRC	first-line	169 (113 KRAS population)	cetuximab plus FOLFOX4	48% (61% WT-KRAS)	41% (31% WT-KRAS)	7,3 (7,7 WT-KRAS)	(-)
			168 (120 KRAS population)	FOLFOX4 alone	42% (37% WT-KRAS)	39% (41% WT-KRAS)	7,2 (7,2 WT-KRAS)	(-)

Authors	Indication	Treatment line	Number of patients enrolled (evaluable)	Drug	ORR (CR / PR)	SD	PFS (months)	OS (months)
Authors	**Indication**	**Treatment line**	**Number of patients enrolled (evaluable)**	**Drug**	**ORR (CR / PR)**	**SD**	**PFS (months)**	**OS (months)**
Carrato et al.[18]	wild-type KRAS mCRC	second-line	53 (-)	panitumumab plus irinotecan	23% (PR 12)	41%	4,5	15,1
Douillard et al.[19]	mCRC	first-line	1183 (-)	panitumumab-FOLFOX4	55% (WT-KRAS) 40% (mutant)	(-)	9,6 (WT-KRAS)	23,9 (WT-KRAS) 15,5 (mutant)
				FOLFOX4 alone	48% (WT-KRAS) 40% (mutant)	(-)	8 (WT-KRAS)	19,7 (WT-KRAS) 19,3 (mutant)
Peeters et al.[20]	mCRC	second line	1186 (-)	panitumumab-FOLFIRI	36% (WT-KRAS)	(-)	6,7 (WT-KRAS)	14,5 (WT-KRAS)
				FOLFIRI	10% (WT-KRAS)	(-)	4,9 (WT-KRAS)	12,5 (WT-KRAS)
Saltz et al.[21]	metastatic CRC	first-line	124 (118)	mFOLFOX6 plus bevacizumab	52%	35%	(12-months PFS 45%)	21
			123 (121)	5-FU, leucovorin, bevacizumab, cetuximab (FOLF-CB)	41%	42%	(12-months PFS 32%)	19,5
Tol et al.[22]	metastatic CRC	first-line	124 (118)	XELOX plus bevacizumab	50%	44%	10,7	20,3
			123 (121)	XELOX plus bevacizumab and cetuximab	53%	42%	9,4	19,4
Grothey et al.[23]	Metastatic CRC (progressed after all standard therapy)		505 (-)	Regorafenib +BSC	1% (0+5 patients)	(-)	59 days	6,4
			255 (-)	Placebo +BSC	0.4% (0+1 pt)	(-)	52 days	5

Authors	Indication	Treatment line	Number of patients enrolled (evaluable)	Drug	ORR (CR / PR)	SD	PFS (months)	OS (months)
Schultheis et al.[24]	metastatic CRC	first- or second-line	45 (38)	FOLFOX or FOLFIRI plus regorafenib	18,40%	71%	4,0 (119 days)	(-)
Tabernero et al.[25]	mCRC	first-line	198 (-)	sorafenib plus mFOLFOX6	45%	(-)	9,1	17,8 (535 days)
				placebo plus mFOLFOX6	61%	(-)	8,7	18,4 (552 days)
Van Cutsem et al. [26]	previously treated metastatic colorectal adenocarcinoma	second line	855 (-)	PTK787/ZK 222584 plus FOLFOX4	(-)	(-)	5,6	13,1
				placebo plus FOLFOX4	(-)	(-)	4,2	11,9
Schmoll et al.[27]	advanced mCRC	first-line	709 (-)	mFOLFOX6 plus cediranib	46%	(-)	9,9	22,8
			713 (-)	mFOLFOX6 plus bevacizumab	47%	(-)	10,3	21,3
Van Cutsem et al. (J Clin Oncol. 2012 [28])	mCRC, previously treated with oxaliplatin	second line	612 (-)	aflibercept plus FOLFIRI	19,80%	(-)	6,9	13,5
			614 (-)	placebo plus FOLFIRI	11%	(-)	4,7	12,1

(-) not assessed

16.2 APPENDIX 2 – DEFINITIONS ACCORDING TO ICH TOPIC E2A CLINICAL SAFETY DATA MANAGEMENT, DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING, (CPMP/ICH/377/95)

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 fulfils 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 (unrelated; 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 11.

16.3 APPENDIX 3 – ECOG PERFORMANCE STATUS

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

16.4 APPENDIX 4 – COCKROFT-GAULT FORMULA

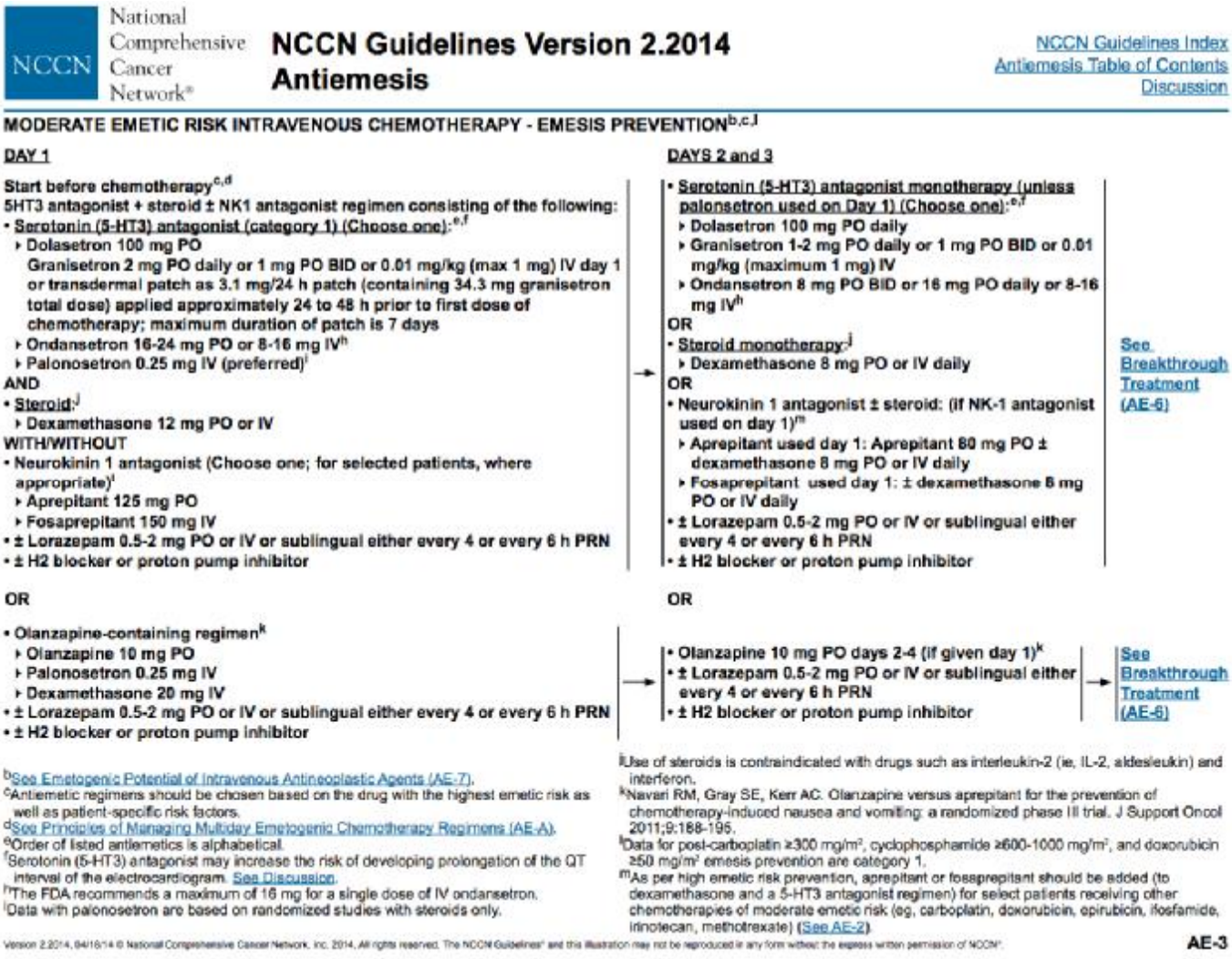
$$\text{Calculated } CL_{CR} \text{ (ml/min)} = \frac{[(140 - \text{subject's age in years}) \times \text{subject's actual body weight in kilograms}]}{72 \times \text{subject's serum creatinine (in mg/dL)}} *$$

*: x 0.85 for females

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

K*: 1.23 for males, 1.05 for females

16.5 APPENDIX 5 – NCCN PRACTICE GUIDELINES IN ONCOLOGY: NAUSEA/VOMITING



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Antiemesis

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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)[l]**

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**

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**

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)

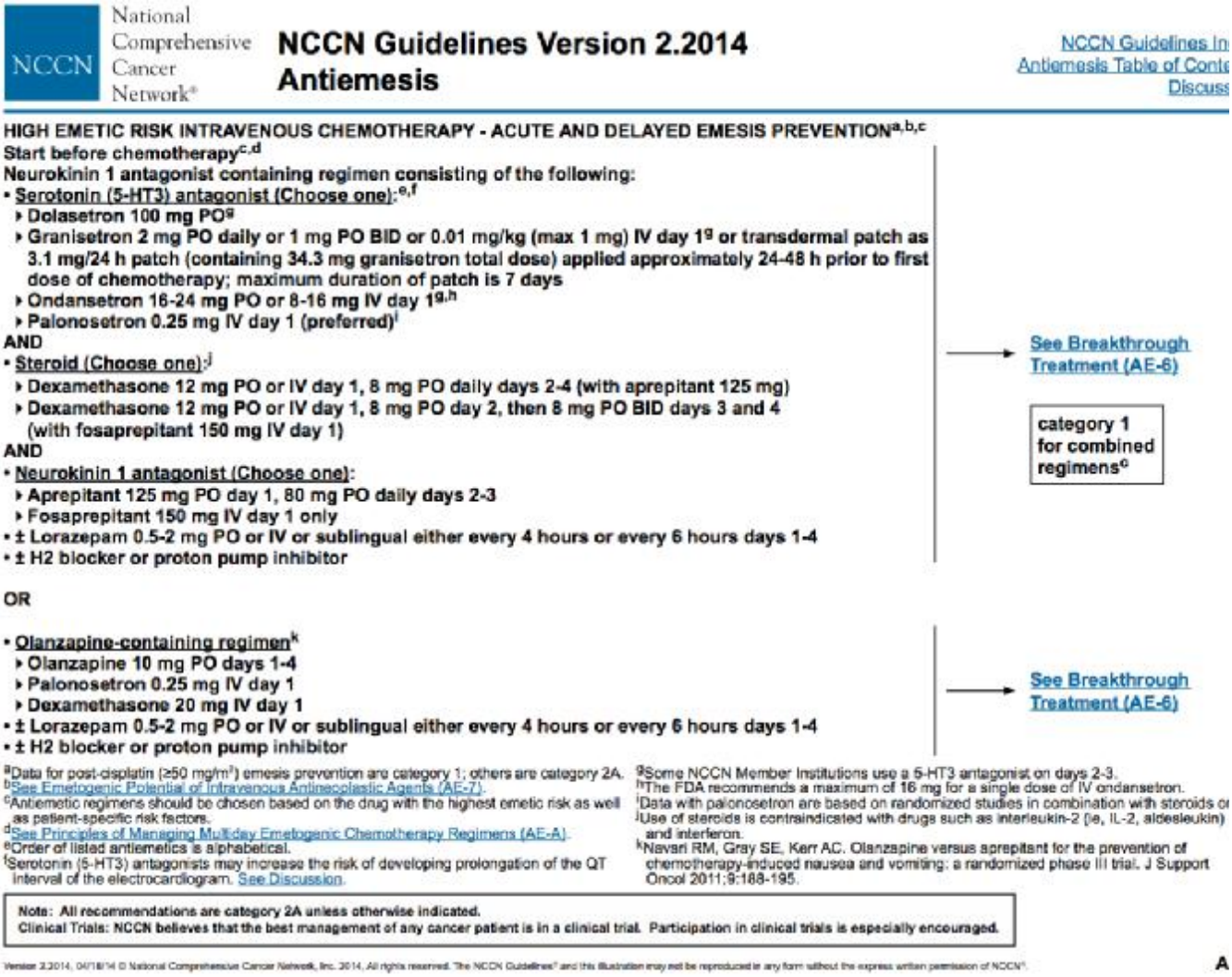
OR

- **Olanzapine 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.
[l] Data with palonosetron are based on randomized studies with steroids only.
[i] 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.
[j] 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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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

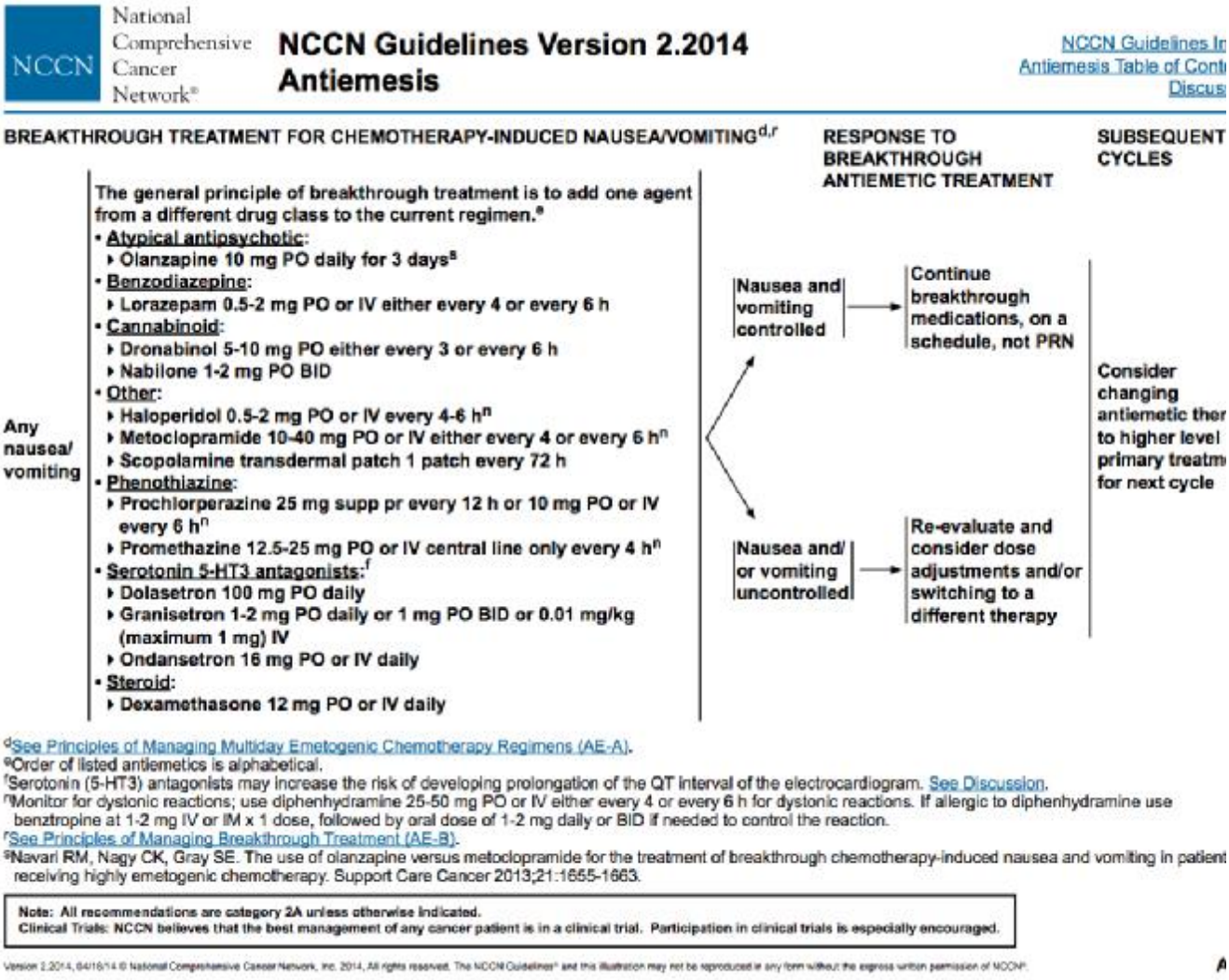
- **Olanzapine-containing regimen[k]**
  - **Olanzapine 10 mg PO days 1-4**
  - **Palonosetron 0.25 mg IV day 1**
  - **Dexamethasone 20 mg IV day 1**
- **± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 hours or every 6 hours days 1-4**
- **± H2 blocker or proton pump inhibitor**

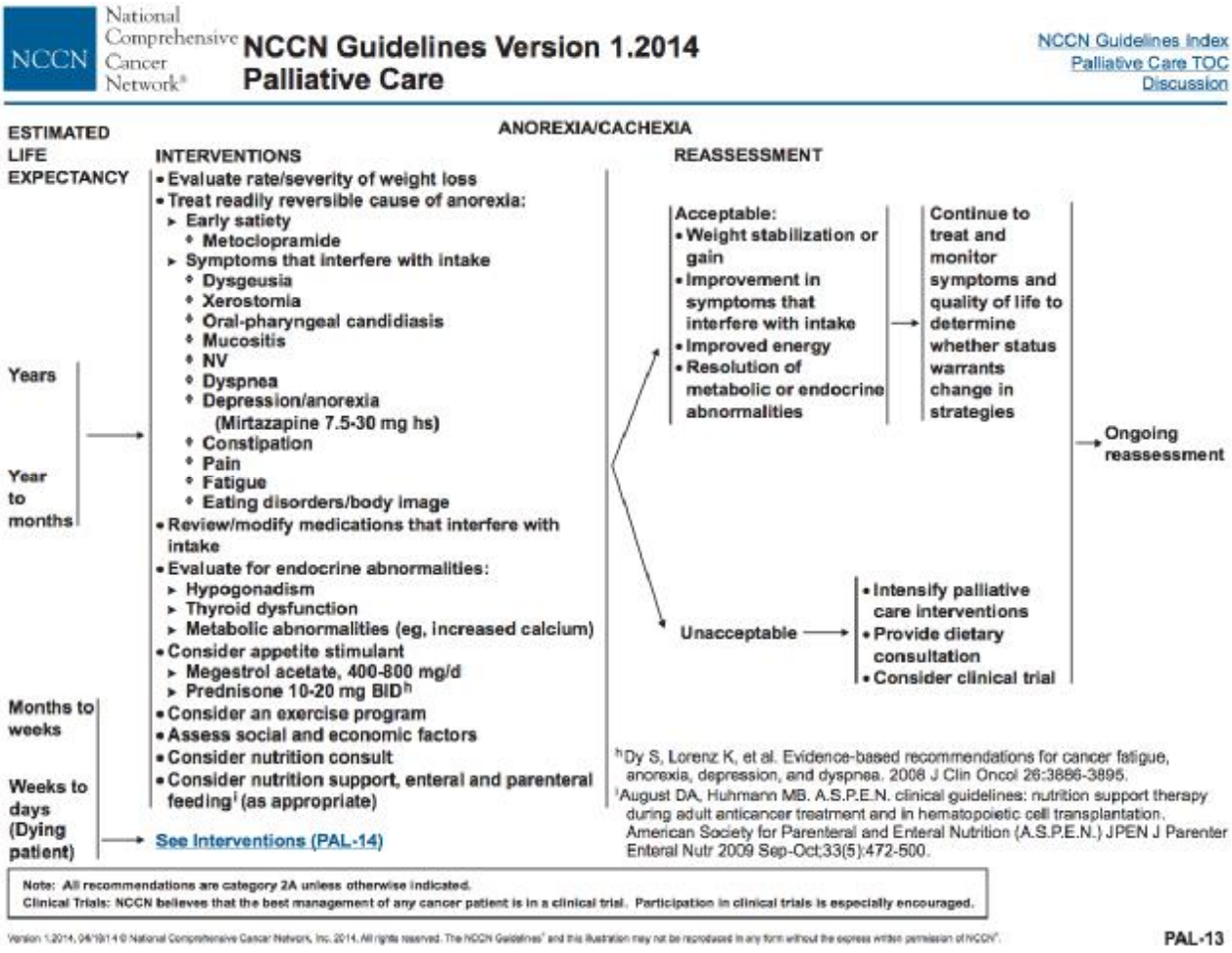
→ See Breakthrough Treatment (AE-6)

[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 or
[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.

A

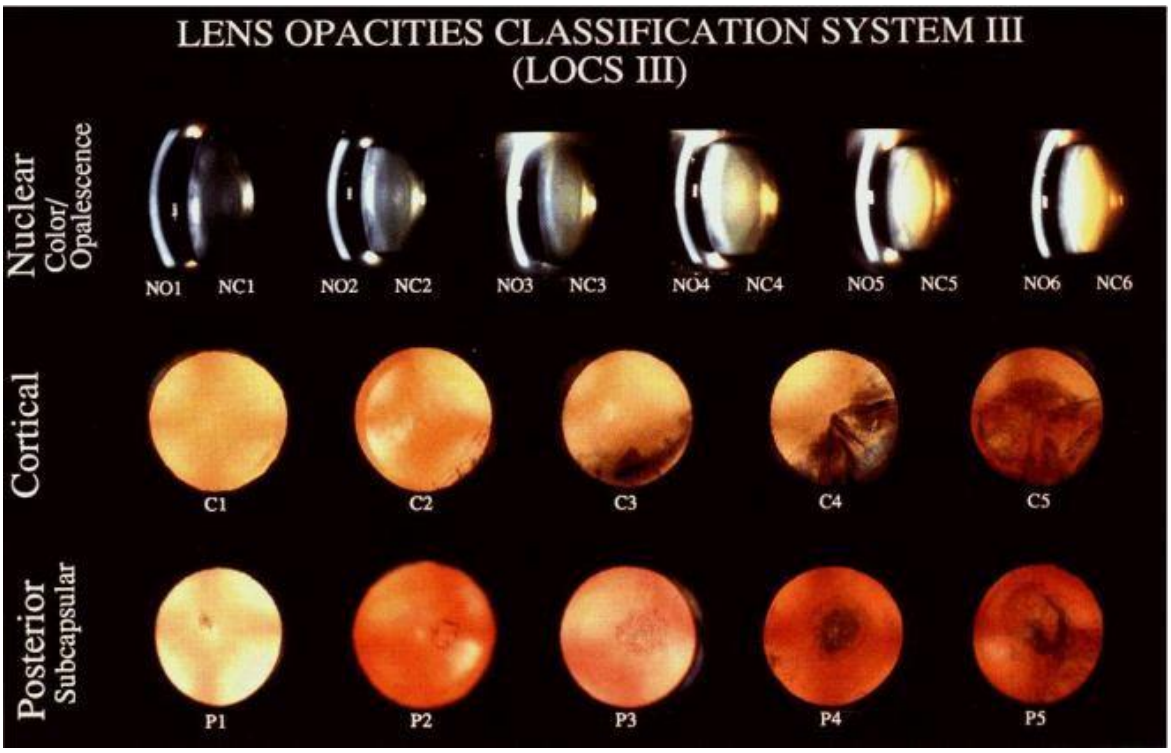




16.6 APPENDIX 6- RESPONSE CRITERIA

16.7 APPENDIX 7- LENS OPACITIES CLASSIFICATION SYSTEM III (LOCS III)

If a cataract is seen during the slit lamp examination to document lens clarity, the cataract will be graded according to the LOCS III.



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