KCP-330-004 (KING)

A PHASE 2 STUDY EVALUATING THE EFFICACY AND SAFETY OF SELINEXOR (KPT-330) IN PATIENTS WITH RECURRENT GLIOMAS

Study Name:	**KING (KPT-330 in Gliomas)**
Sponsor:	Karyopharm Therapeutics Inc.
Coordinating Investigator for Denmark:	PPD MD, PhD
Coordinating Investigator for U.S.:	PPD MD
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Karyopharm Therapeutics Inc.

13 November 2015

Date (dd Month yyyy)

PPD

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Karyopharm Therapeutics Inc.

13 November 2015

Date (dd Month yyyy)

Investigator's Agreement

I have read the attached protocol entitled

"A PHASE 2 STUDY EVALUATING THE EFFICACY AND SAFETY OF SELINEXOR (KPT-330) IN PATIENTS WITH RECURRENT GLIOMAS"

and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation 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 identifier no.	KCP-330-004
Protocol version (Date)	Version 6.0, 13 November 2015
Study name	KING (KPT-330 in Gliomas)
Title	A PHASE 2, STUDY EVALUATING THE EFFICACY AND SAFETY OF SELINEXOR (KPT-330) IN PATIENTS WITH RECURRENT GLIOMAS
EudraCT no.	2013-003668-30
Coordinating Investigator for Denmark	PPD MD, PhD
Coordinating Investigator for U.S.	PPD MD
Sponsor	Karyopharm Therapeutics Inc. 85 Wells Avenue Newton, MA 02459
Study design	• Open label, multicenter, Phase 2 study • Patients will be enrolled into either CCI [redacted] Medical Arm (Arm B, Arm C, and Arm D) for patients who are not eligible for surgery. CCI [redacted] Patients in the Medical Arm (Arms B, C, and D) will be treated with selinexor alone. Patients will be treated until progression of disease or the development of unacceptable toxicities. Patients will also be followed for survival status.
Start date	January 2014
Duration of study	Enrollment is anticipated to take approximately 36 months. The treatment period for an individual patient is expected to be up to 6 months, but there is no maximum duration for treatment. Treatment in all arms of the study will continue until disease progression or development of unacceptable toxicities. End of study will be when the last patient in the study has died, has been off study treatment for 12 months, has been lost to follow-up, or has withdrew consent, whichever occurs first.
Total number of sites	Approximately 6
Study populations	Primary Patient Population (Arms C CI B, C, and D): Patients with WHO Grade 4 gliomas (glioblastoma [GBM] and subvariants) at first diagnosis with recurrent disease, who have failed prior treatment with radiation therapy and temozolomide, and who meet the inclusion and none of the exclusion criteria are eligible for enrollment.
Objectives	
Primary objective (Arms, B, C, and D)	• To determine the efficacy of selinexor in adults with recurrent GBM as determined by the 6-month progression-free survival (6mPFS) rate
Secondary objectives (Arms, B, C, and D)	• To determine the efficacy of selinexor in adults with recurrent GBM as determined by response rate according to the Response Assessment in Neuro-Oncology (RANO) criteria • To determine the efficacy of selinexor in adults with recurrent GBM as estimated by median overall survival (OS) • To determine the efficacy of selinexor in adults with recurrent GBM as determined by median progression-free survival (PFS) • To evaluate safety and tolerability of selinexor

Exploratory objectives	CCI [redacted]
Planned sample size	Approximately 110 patients are planned to be enrolled. CCI [redacted] Although approximately 30 patients were planned to be enrolled in Arm B (medical arm, 50 mg/m^2 twice weekly), enrollment was stopped to explore alternative dosing in Protocol Versions ≥ 4.0 to potentially improve tolerability. The study is continuing with two randomized arms (Arms C and D, both using Simon's two-stage design) with flat dosing that were added in Protocol Version 4.0. Approximately 30 patients will be included in each of the randomized flat dosing medical arms: Arm C (60 mg twice weekly) and Arm D (80 mg weekly).
Inclusion criteria	1. Pathologically confirmed diagnosis of GBM (including all histologic variants) at first diagnosis with radiographic evidence of recurrent disease after treatment with radiotherapy and temozolomide. 2. Age ≥ 18 years; 3. Karnofsky Performance Status (KPS) ≥ 60; 4. Patients enrolling in the Medical Arm (Arms B, C, or D) must be on a stable or decreasing dose of corticosteroids (or none) for at least 5 days prior to the baseline CT/MRI. 5. Patients must have received prior treatment with radiation therapy and temozolomide (all Arms). 6. Measurable disease (according to RANO guidelines, within 14 days of starting treatment). Measurable disease CCI [redacted] is not required. 7. Written informed consent obtained prior to any screening procedures. Patients must be willing and able to comply with the protocol and aware of the investigational nature of this study. 8. Patients must have adequate bone marrow function and organ function within 2 weeks of study treatment as defined by the following laboratory criteria: o Hematopoietic function: total white blood cell (WBC) count ≥ 3000/mm^3, absolute neutrophil count (ANC) ≥ 1500/mm^3, platelet count ≥ 125,000/mm^3; hemoglobin ≥ 9 g/dL. o Hepatic function: bilirubin ≤ 2 times the upper limit of normal (ULN), ALT ≤ 2.5 times ULN, AST ≤ 2.5 times ULN; unless bilirubin elevation is related to Gilbert's Syndrome for which bilirubin must be < 4 times ULN. o Renal function: estimated creatinine clearance of ≥ 30 mL/min, calculated using the formula of Cockroft and Gault or other standard methods at the treating institution. 9. All female patients of childbearing potential must agree to use reliable methods of birth control during study treatment and for 3 months after the last dose of study drug and have a negative serum pregnancy test at screening. Reliable methods of contraception include intrauterine devices, hormonal contraceptives [contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release], abstinence or sterilization of the partner. 10. Fertile males must be willing to employ reliable methods of contraception during study treatment and for 3 months after the last dose of study drug.

	11. Archived paraffin-embedded tissue: approximately 10 unstained slides (if less, contact Sponsor) or a tumor block must be available for correlative studies. 12. CCI [redacted] 13. Patients enrolling in the medical arm (Arms B, C, or D) must have an interval of at least 12 weeks from completion of radiation therapy and study unless there is histologic proof of active tumor from intervening resection.
Exclusion criteria	1. Patients must not have 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. < 24 days from prior temozolomide, < 6 weeks from nitrosourea, < 4 weeks from other chemotherapy or investigational agents prior to start of treatment within study. 3. Unstable cardiovascular function. 4. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen); hepatitis testing is not required. 5. Known HIV infection; HIV testing is not required. 6. Markedly decreased visual acuity if attributed to other causes than GBM. 7. Active infection requiring parenteral systemic antibiotics. 8. Patients with coagulation problems and medically significant bleeding in the month prior to start of treatment (e.g., peptic ulcer, epistaxis, spontaneous bleeding). Prior history of DVT or PE is not exclusionary. 9. Patients who are pregnant or breast-feeding. 10. Other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission and off all therapy for that disease for a minimum of 3 years. 11. Patients must not have significantly diseased or obstructed gastrointestinal tract, malabsorption, uncontrolled vomiting or diarrhea, or inability to swallow oral medications. 12. Dehydration of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 1. 13. Patients must not have serious psychiatric or medical conditions that could interfere with treatment. 14. History of organ allograft. 15. Concurrent therapy with approved or investigational anticancer therapeutics. 16. Prior treatment with bevacizumab or other direct VEGF/ VEGFR inhibitors. For any question of the definition of a direct VEGF/VEGFR inhibitor, consult Sponsor. 17. Arms C and D only: body surface area < 1.2 m^2, to avoid a dose exceeding the maximum allowable dose of 70 mg/m^2. 18. Major surgery < 4 weeks prior to the start of study treatment
Treatment plan	Selinexor (taken orally) will be given once weekly (4 doses) or twice weekly (8 doses) during Weeks 1-4 of each 4-week cycle. Patients who are currently being treated twice weekly for Weeks 1-3 under a previous version of the protocol may, at the discretion of the investigator, have the frequency of selinexor dosing increased to twice weekly for Weeks 1-4. One cycle is defined as 28 days or 4 weeks. Selinexor should be taken with a light meal, and 120 mL (4 oz) of water. CCI [redacted]

CCI

Arms B, C, and D: Medical Arm (mITT and PP populations)

Arm B: Approximately 30 patients who were not eligible for surgery were planned to be treated with selinexor (50 mg/m^2) twice weekly. Enrollment in Arm B was stopped to explore alternative dosing in Protocol Versions ≥ 4.0 to potentially improve tolerability. Although enrollment in Arm B has been stopped, the study is continuing with two randomized arms (Arms C and D) with flat dosing that were added in Protocol Version 4.0. Patients previously enrolled in Arm B with mg/m^2 dosing who are at a dose of 35 mg/m^2 or greater will be converted to 60 mg twice weekly flat dosing; however, if the patient is currently at a lower dose the Investigator should contact the medical monitor to determine the starting dose for flat dosing.

GBM patients enrolled under Protocol Versions ≥ 4.0 (i.e., after cessation of Arm B enrollment) will be randomly allocated in a 1:1 ratio to one of the following treatment arms:

Arm C: Approximately 30 patients who are not eligible for surgery will be treated with selinexor (60 mg) twice weekly (e.g., Monday and Wednesday, Tuesday and Thursday, Wednesday and Friday, Thursday and Saturday) during Weeks 1-4 of each 4-week cycle. In the first stage, 12 patients will be accrued. If there is at most one 6mPFS response in the first 12 patients, no further enrollment will be allowed in Arm C.

	Arm D: Approximately 30 patients who are not eligible for surgery will be treated with selinexor (80 mg) once weekly. In the first stage, 12 patients will be accrued. If there is at most one 6mPFS response in the first 12 patients, no further enrollment will be allowed in Arm D. Treatment in all arms of the study will continue until disease progression or development of unacceptable toxicities.
Primary analysis parameter	6-months progression-free survival (6mPFS) rate (progression of disease defined according to the RANO criteria). Note that a window of ±14 days will be allowed around the 6-month visit and will be applied to the calculation of the point estimate of 6mPFS.
Secondary analysis parameters	• Response rate according to the RANO criteria • Median overall survival (OS) • Median progression-free survival (PFS) • Safety
Exploratory analysis parameters: supportive studies on blood and tumor samples	CCI [redacted]
Study procedures	Disease status will be measured by contrast-enhanced MRI (or CT), including pre-contrast T1, T2/FLAIR, and post-contrast T1- and T2-weighted FLAIR, and assessed using the RANO criteria at screening CCI [redacted] 8 weeks after Cycle 1 Day 1, and approximately every 8 weeks thereafter.
Safety assessment	Safety will be monitored by assessing vital signs and weight, performance status, neurological examinations, ophthalmic examinations, physical examinations, ECGs, and concomitant medication use. All adverse events occurring during the course of the trial and to the extent possible for up to 30 days after the last dose of study medication will be captured, documented, and reported. Toxicity is graded according to the current version of NCI-CTCAE version 4.03. Safety blood samples, including blood count, clinical chemistry (including liver function tests), TSH, and coagulation, will be collected.
Statistical considerations	This study will assess efficacy of selinexor in patients with gliomas. Efficacy will be defined as the proportion of patients in Arms B, C, and D with no progression and who are still alive 6 months after start of study drug treatment (6mPFS). The RANO criteria will be used. Based on histological information contained in the literature, the trial would be considered a success if there is evidence to suggest a 6mPFS rate as high as 30%.

	Enrollment in Arm B was stopped to explore alternative dosing in Protocol Versions ≥ 4.0 to potentially improve tolerability. An assessment of the efficacy data prior to the formal PFS analysis for the first 12 patients in Arm B revealed clinically meaningful efficacy in this challenging patient population. The study is continuing with two randomized arms (Arms C and D, both using Simon's two-stage design) with flat dosing that were added in Protocol Version 4.0. If there is no 6mPFS response in the first 12 patients accrued in Arms C or D no further enrollment will be allowed in that arm. CCI [redacted]
Randomization procedure	For the Medical Arm, patients who are enrolled under Protocol Version 4.0 or above and meet the enrollment criteria will be allocated by means of a computer-generated randomization list in a 1:1 ratio to Arms C and D. Patients enrolled prior to Protocol Version 4.0 and surgical patients will not be randomized.
Sample size calculation	CCI [redacted]

INFORMATION TO BE PROVIDED REGARDING SAES

In the case of a serious adverse event (SAE) the completed SAE form must be sent to:

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

Table 1: Schedule of Assessments During the Study

	Screening		CCI	Cycle 1-2	Cycle 3-5	Cycle ≥6	End of Treatment[23]	Follow-up[24]	Survival Follow-up[25]
Visit window [days]	Prior to start of study drug			Day 1 of each week	Day 1+15 of each cycle	Day 1 of each cycle	30 days post-last dose		
	≤ 14 days	≤ 7 days		± 2 days	± 2 days	± 2 days	± 7 days	± 7 days	± 14 days
Informed consent[1]	X								
Inclusion and exclusion criteria		X							
Demographics	X								
Medical history[2]	X								
Randomization[3]		X							
Pregnancy test (if applicable)[4]		X					X		
Body height and weight[5]		X		X	X	X	X		
BSA		X		X	X	X			
Vital signs[6]		X		X	X	X	X		
Physical examination and Karnofsky PS[7]		X		X	X	X	X		
Standard clinical neurological examination[8]	X			X	X	X	X		
Ophthalmic exam[9]	X								
Oxygen saturation[10]		X							
12-lead ECG[11]	X						X		
Urinalysis[12]		X							
Hematology (CBC)[13]	X			X	X	X	X		
TSH		X					X		
Complete serum chemistry[14]	X			X			X		
Limited serum chemistry[15]					X	X			
Coagulation tests[16]		X							
Assessment of disease status including CT/MRI[17]	X				X	X		X	
Chest radiograph[18]	X								
Selinexor dosing[19]				X	X	X			
Cytoreductive surgery[20]									

CCI

Adverse events			X	X	X	X		
Concomitant medication	X	X	X	X	X	X		
Information on survival status and anticancer therapy after end of selinexor treatment								X

1 Before the first study-specific measures are performed. Results from tests/scans performed before written informed consent is obtained may be used as specified in this table.

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 Only Arms C and D will be randomized. Randomization must occur ≤ 3 days before the start of dosing on Cycle 1 Day 1.

4 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. Urine pregnancy testing is to be performed as clinically indicated during the study. Any positive urine pregnancy test must be confirmed with a serum β-HCG test.

5 Body height will be measured at screening only.

6 Vital signs: blood pressure, pulse and temperature.

7 Full physical examination for baseline and end of treatment (EOT) visit. Physical examinations during the study should be symptom directed.

8 A complete neurological exam is to be completed at screening (baseline exam) and the EOT visit. Neurological examinations during the study should be symptom directed. Any neurological deficits noted during the baseline exam must be followed at subsequent visits. Any new neurological complaints reported by the patient and any deficits observed by the investigator should be assessed and followed at subsequent visits.

9 A full ophthalmic exam will be conducted by an optometrist or ophthalmologist at screening. Additional ophthalmic assessments will be completed during the study as clinically indicated: CCI The full ophthalmic assessments includes: *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 for newly enrolling patients or enrolled patients for whom no cataracts have been detected to date, the cataract will be graded using a Grade 1-4 scale (Section 16.5; Appendix 5). However, patients enrolled under a prior version of the protocol who had detectable cataracts graded according to the Lens Opacities Classification System (LOCS III) will continue to have their cataracts graded according to LOCS III and will not switch to the Grade 1-4 scale.

10 Pulse oximetry is performed for patients at rest breathing room air at screening then only if clinically indicated.

11 ECGs **t**o be performed pre-dose in a supine position. ECGs may be performed as clinically indicated during the treatment phase.

12 Urinalysis will include urine bilirubin, glucose, hemoglobin, ketones, pH, protein (screening) and then if clinically indicated.

13 Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell (WBC) count, WBC differential, lymphocytes, monocytes, neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated. During the treatment phase, labs can be done 3 days prior to visit.

14 Complete serum chemistry for baseline, Cycles 1 and 2 and EOT visit includes: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, LDH, total protein, albumin, amylase, lipase, creatine kinase, and urate. During the treatment phase, labs can be done 3 days prior to visit.

15 CCI

16 Coagulation test include prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT) (screening only) and if clinically indicated.

17 Disease status will be measured by contrast-enhanced MRI (or CT for patients unable or unwilling to undergo MRI) at baseline. A CT/MRI scan performed as part of clinical evaluation of disease status as part of standard of care can be used as baseline CT/MRI scan provided study treatment will start within 14 days (for all patients in Arms B, C, and D, CCI CCI

18 Both posteroanterior and lateral films should be obtained for baseline. Note: this test does not need to be repeated if results are available from a test performed 30 days prior to start of therapy. This test serves as a baseline in the event that patients develop any adverse events during the study.

19 CCI

CCI [redacted] Arms B and C: Oral selinexor (60 mg) will be given twice weekly (e.g., Monday and Wednesday, Tuesday and Thursday, Wednesday and Friday, Thursday and Saturday) during Weeks 1-4 of each 4-week cycle. Patients who are currently being treated twice weekly for Weeks 1-3 under a previous version of the protocol may, at the discretion of the investigator, have the frequency of selinexor dosing increased to twice weekly for Weeks 1-4. Arm D: Oral selinexor (80 mg) will be given once weekly. Dosing will be selected based on the first stage results for Arms C and D.

20 CCI [redacted]

21 CCI [redacted]

22 CCI [redacted]

23 Patients who discontinue therapy for any reason (other than withdrawal of consent) will be encouraged to have an EOT visit. The EOT visit should take place 30 days (±7 days) after their last dose, if possible.

24 Before disease progression, patients who discontinue for reasons other than progression of disease (and withdrawal of consent for participation in the trial) should be encouraged to visit the clinic for clinical evaluation of their disease every 4 weeks and assessment by CT/MRI every 8 weeks (± 7 days) until progression of disease is determined.

25 After disease progression all patients will be evaluated for survival and further anticancer therapy every 3 months (± 14 days) until the End of Study (Section 5.2.6). Patients who have not expired or progressed by the data analysis cutoff date for the 6mPFS rate will be censored at the date of their last disease assessment. Patients who have not expired by the data analysis cutoff date for OS will be censored at their last date known to be alive

GLOSSARY OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse event
ALT (SGPT)	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate aminotransferase
BCNU	Carmustine
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CCNU	Lomustine
CFR	Code of Federal Regulations
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CR	Complete response
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CYP450	Cytochrome P450
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of treatment
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
FLAIR	Fluid-Attenuated Inversion Recovery
GBM	Glioblastoma
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GSH	Glutathione
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	High-density polyethylene
HIV	human immunodeficiency virus
hr	Hour
HGG	High-grade glioma
IB	Investigator's Brochure
IC_{50}	Inhibitory concentration, 50% (half maximal inhibitory concentration)
ICH	International Conference on Harmonisation
IDH	isocitrate dehydrogenase
IEC	Independent ethics committee
IFN	Interferon
IMP	Investigational medicinal product
IRB	Institutional review board
K	Karnofsky Performance Status
LDH	Lactate dehydrogenase
LOCS III	Lens Opacities Classification System III

m^2	Square meter (body surface area)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified intent-to-treat
mL	Milliliter
MM	Multiple myeloma
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NAC	N-acetylcysteine
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCIC-CTG	National Cancer Institute of Canada – Clinical Trials Group
NK1	Neurokinin 1
OS	Overall survival
PCR	Polymerase chain reaction
PCV	Procarbazine and vincristine
PD	Progressive disease
PDGFR	Platelet-derived growth factor receptor
CCI	[redacted]
PE	Pulmonary embolism
PFS	Progression-free survival
C	[redacted]
PP	Per-protocol population
PR	Partial response
PTCL	Peripheral T cell lymphoma
qRT-PCR	Quantitative reverse-transcription, polymerase chain reaction
RANO	Response Assessment in Neuro-Oncology
RBC	Red blood cell
REB	Research ethics board
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAM	S-adenosylmethionine
SD	Stable disease
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SINE	Selective Inhibitor of Nuclear Export
SOC	System/Organ/Class
SUSAR	Suspected unexpected serious adverse reaction
TKI	Tyrosine kinase inhibitor
T_{max}	Time to maximum serum concentration
TSH	Thyroid-stimulating hormone
TSP	Tumor suppressor protein
TUNEL	Terminal deoxyribonucleotidyl transferase-dUTP nick end labeling
ULN	Upper limit of normal
V_d	Volume of distribution
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
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 Glioblastoma

High-grade gliomas (HGG) are defined as World Health Organization (WHO) Grade 3 and 4 tumors of glial origin. Grade 4 tumors are called glioblastoma (GBM). With approximately 70%, GBM is the most common type of malignant primary brain tumors. More than 14,000 cases are newly diagnosed in adults in the United States each year.[1]

The prognosis of GBM is very poor. An extensive infiltration of the surrounding brain tissue limits the accessibility in surgical resection. Aggravating the blood-brain barrier is an obstacle for many chemotherapeutic agents. Only small and lipophilic molecules, e.g. nitrosoureas, are able to reach their target. Furthermore, GBM is frequently refractory to cytotoxic agents. Median overall survival (OS) from first diagnosis is about 13-18 months.

First-line therapy

For a long time, standard therapy comprised surgical resection followed by radiotherapy. In a randomized Phase 3 trial by the EORTC (European Organisation for Research and Treatment of Cancer) and the NCIC-CTG (National Cancer Institute of Canada – Clinical Trials Group), a significant benefit of concomitant radiotherapy and temozolomide plus six cycles of adjuvant chemotherapy over radiotherapy alone could be demonstrated for the first time. With the addition of the oral alkylating agent temozolomide, a median survival of 14.6 versus 12.1 months with radiotherapy alone was achieved. Patients had a two-year survival rate of 25.6% with radiotherapy plus temozolomide versus 10.4% with radiotherapy alone.[2-4]

Recurrent disease

Irrespective of the first-line therapy, patients with HGG have a high risk for relapse within 6 to 11 months after the primary treatment.[5] There is still no established standard treatment for recurrent HGG. Nitrosourea-based regimens are commonly used, e.g. carmustine (BCNU) or lomustine (CCNU) alone or combined with procarbazine and vincristine (PCV). 6-months progression-free survival (6mPFS) rates of approximately 20% were seen.[6-9]

One other option is the treatment with temozolomide in a continuous dose-intense (50 mg/m²/d) regimen that could overcome resistance to standard therapy. In the RESCUE study, patients with GBM achieved a 6mPFS rate of 23.9% and the median overall survival (OS) was 9.3 months. Another Phase 2 study with 37 patients revealed a 6mPFS rate of 19% and a median OS of 7 months. However, the benefit of continuous temozolomide was only true for GBM patients who had not experienced progression while on extended adjuvant treatment, i.e. beyond six cycles. Also, the success of this treatment strategy seems to be dependent on previous treatment with bevacizumab. One advantage of the regimen is its tolerability with a lower hematologic toxicity and nausea/vomiting compared to other chemotherapies such as nitrosoureas or other temozolomide schedules.[6, 10, 11]

GBM was found to be one of the most vascularized human tumors with a high expression of vascular endothelial growth factor (VEGF). VEGF expression is associated with a poor prognosis.

Promising results were obtained with targeted therapies such as the monoclonal antibody bevacizumab that binds to VEGF inhibiting its activity, for which 6mPFS is 25% to 46%. Bevacizumab also showed a positive impact on quality of life.[12-18]

As high activity of signal transduction pathways such as PI3K, AKT and mTOR (mammalian target of rapamycin) is associated with a poor prognosis, many inhibitors targeting various objectives in these pathways have reached Phase 1and 2 clinical trials. For example, the effect of the mTOR inhibitor added to bevacizumab after failure of a bevacizumab-containing second-line treatment was investigated, but did not show sufficient activity.[19, 20]

Many other targets have recently been or are currently under investigation: Although amplification of epidermal growth factor receptor (EGFR) can be detected in approximately 40% of GBM, EGFR-inhibiting drugs such as erlotinib did not show sufficient activity in monotherapy.[21] The EGFR antibody nimotuzumab is currently under investigation due to its lack of toxicity, although first data have proven only modest efficacy.[22]

Similarly, nintedanib, a small, oral, triple angiokinase inhibitor targeting vascular endothelial growth factor receptor (VEGFR) 1-3, FGFR 1-3, and PDGFR-α/β, failed to show clinically relevant antitumor activity. In a Phase 2 study with 25 patients in second- or third-line therapy, best response was stable disease (SD) achieved by 12% of patients; one patient previously treated with bevacizumab had SD for more than 17 months. All other patients progressed within the first four 28-day cycles. Median progression-free survival (PFS) was 1 month and median OS was 6 months.[23]

Vandetanib is a multitargeted tyrosine kinase inhibitor (TKI) of VEGF-2, EGFR, and the rearranged-during-transfection oncogene. In a Phase 2 trial with 64 patients with recurrent GBM and recurrent anaplastic glioma (AG), the 6mPFS was 6.5% in the GBM arm and 7.0% in the AG arm. Median OS was 6.3 months in the GBM arm and 7.6 months in the AG arm. Only 12.5% of GBM patients had radiographic response. Seizures were an unexpected toxicity of this therapy.[24]

Another attempt was to investigate the activity of the TKIs imatinib combined with hydroxyurea. In a Phase 2 study with 231 patients, the combination therapy was, in fact, well tolerated, but its clinical antitumor activity was low with a 6mPFS of 10.6% and a median OS of 26 weeks.[25]

With the lipophilic oral camptothecin analogue gimatecan, a similar 6mPFS rate of 12% was achieved in a Phase 2 study with 29 patients with recurrent GBM.[26] Slightly better successes were achieved with the microtubule-destabilizing agent verubulin (MPC-6827) in combination with carboplatin, with a 6mPFS rate of 21% and a median PFS of 8 weeks. This combination was administered to 19 patients in one Phase 1 study.[27]

Another approach currently under investigation is treatment with the antiangiogenic agent pazopanib in combination with the ErbB inhibitor lapatinib. Although the regimen has already shown limited antitumor activity in Phase 1/2 studies, pharmacokinetic (PK) data has revealed subtherapeutic doses of lapatinib, so this combination is still a candidate for further trials.[28]

In summary, recurrent GBM still has poor outcome and treatment remains a challenge, as these data consistently show. Consequently, new treatment options for patients with recurrent GBM are desperately needed.

1.1.2 Selinexor

Selinexor is a Selective Inhibitor of Nuclear Export (SINE) compound that binds and inactivates Exportin 1 (XPO1), forcing the nuclear retention of key tumor suppressor proteins (TSPs). Transient retention of TSPs in the nucleus at high levels via XPO1 blockade activates their cell cycle checkpoint and genome surveying actions. This leads to the death of nearly all types of malignant cells, whereas normal cells undergo transient cell cycle arrest and recovery when the export block is released. The reactivation of multiple tumor suppressor pathways and inhibition of translation of key pro-survival proteins through inhibition of a non-redundant, single protein represents a novel approach to the treatment of neoplastic diseases including those with multiple genomic alterations and resistance mechanisms. More information about the mechanism of action, pharmacology, pre-clinical, and clinical studies with selinexor is available in the *Selinexor/KPT-330 Investigator's Brochure (IB).*

Selinexor is being evaluated in multiple Phase 1 and 2 studies in patients with heavily pretreated relapsed and/or refractory hematological and solid tumor malignancies. More than 1,100 patients have received selinexor to date (as of 01 October 2015). Evidence of anti-cancer activity has been observed in a substantial number of patients and selinexor has been sufficiently well-tolerated to allow many of these patients to remain on therapy for prolonged periods, including several patients who have remained on treatment for over 12 months, with the longest treatment duration thus far of > 24 months.

The main side effects of selinexor seen in heavily pretreated Phase 1 patients to date have been fatigue, nausea, anorexia, vomiting, and thrombocytopenia. These adverse events (AEs) are mainly Grades 1 and 2, and may be mitigated or eliminated with standard supportive care. Their prevalence and intensity typically decline after 4-8 weeks of treatment. Selinexor treatment is not associated with significant major organ toxicity.

1.1.2.1 Preclinical Data

A brief summary of preclinical data is provided below. More detailed information is available in the *Selinexor/KPT-330 IB*.

In vitro experiments with continuous (72 hr) exposure to selinexor demonstrated potent pro apoptotic activity across a broad panel of tumor-derived cell lines and patient samples in culture, with the majority of 50% inhibitory concentration (IC50) values for cytotoxicity < 800 nM and most hematologic tumor lines having IC50 values of 20 – 400 nM for selinexor. In contrast, normal cells typically underwent (or remained in) cell cycle arrest but were resistant to apoptosis-induction; cytotoxicity IC50 values were typically > 1 μM (based on results seen with MRC-5 cells). Maximum selinexor serum levels of 1-2 μM are typically achieved in cancer patients following selinexor oral doses of 40-100 mg (~25-60 mg/m^2).

Selinexor, as well as other SINE compounds, have been administered in non-clinical efficacy studies to mice and dogs and in toxicology studies to rats and monkeys, with every-other-day oral dosing regimens (2-3 doses per week). Dosing regimens were designed based on pharmacodynamic observations that the biological effects of oral selinexor have durations > 48 hours. Efficacy was seen with these intermittent dosing regimens at doses of selinexor 5-20 mg/kg (15-60 mg/m^2) in mouse models of myeloma, mantle cell lymphoma (MCL), T-cell acute lymphocytic leukemia (T-ALL) xenografts, and solid tumor models. Selinexor treatment resulted in significant survival

advantages in models of MM, NHL, CLL, AML and ALL, as well as solid-tumor models including prostate, breast, melanoma, colon cancer, ovarian cancer, neuroblastoma and several sarcomas. In addition, marked synergy was observed when selinexor was combined with a variety of chemotherapies and targeted therapies including platinums, taxanes, topoisomerase I and II inhibitors, dexamethasone, cytarabine, proteasome inhibitors, various tyrosine kinase inhibitors (TKIs), PD-1 inhibitors and BCL2 inhibitors.

Selinexor had little effect on normal (nonmalignant) lymphocytes or other nontransformed cells, which correlated with the low incidence in animals of the typical side effects seen with most anti-cancer therapies such as significant myelosuppression, alopecia, mucositis and other gastrointestinal (GI) dysfunction. Selinexor does induce a reduction in platelet counts without affecting platelet function, and with minimal effects on numbers of megakaryocytes. The effects of selinexor on platelet generation are primarily related to a slowing of maturation of stem cells to megakaryocytes.

The major side effects across all animal models studied were reduced appetite with anorexia-induced weight loss that was partially consistent with satiety induction. Similar effects are observed in humans, where high caloric foods and appetite stimulants, including glucocorticoids, are known to improve appetite and mitigate weight loss.

1.1.2.2 Clinical Data

1.1.2.2.1 Pharmacokinetics

Oral selinexor pharmacokinetics (PK) are predictable, approximately dose-proportional, and exhibit moderate- to moderately-high inter-patient variability across a wide dose range of doses in male and female patients with advanced hematological malignancies or solid tumors. Total exposure ($AUC_{0\text{-}inf}$) was significantly greater following selinexor administration with food so patients taking selinexor should be instructed to take selinexor with food in order to optimize selinexor absorption.

The elimination (terminal) half-life ($t_{1/2}$) of selinexor is approximately 5-8 hours. The duration of pharmacodynamic effect, based on XPO1 mRNA increase due to XPO1 inhibition, is > 48 hours. Maximal serum concentrations (C_{max}) of 1-2 μM have been achieved at doses of 40-100 mg (25-60 mg/m^2), which are below the maximum tolerated dose (MTD) of 120 mg (65-70 mg/m^2).

An analysis of existing PK data from Phase 1 studies (KCP-330-001 and KCP-330-002) supports the use of fixed, rather than body surface area (BSA) based dosing. As a result, selinexor dose schedules will henceforth be based on flat doses. In a separate study in patients with advanced sarcomas (KCP-330-003), no detectable difference in selinexor exposure was observed in the presence of a high-fat or low-fat meal.

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Table 2: KPT-330 Concentration in Human Tumor Tissue and Plasma

PPD

BLQ = below limit of quantitation (< 1.0 ng/mL)
- = Data not available

1.1.2.2.2 Safety

Overall, AEs in patients receiving single-agent selinexor have been generally low-grade, consistent with events observed in patients with other hematological malignancies, and responsive to standard supportive care.

Fewer AEs have been reported in patients receiving selinexor plus dexamethasone, particularly levels of nausea, consistent with dexamethasone's reduction in selinexor's main side effects of nausea, anorexia, and fatigue.

Potential Risks

Preliminary clinical safety results for > 730 patients have been evaluated as of 31 May 2015 and the entire safety profile is not fully known at this time. In the current study, measures will be taken to ensure the safety of patients, including the use of stringent inclusion and exclusion criteria and close monitoring.

If toxicities are encountered, adjustments will be made to study treatment as detailed below. All AEs and serious adverse events (SAEs) will be recorded during the trial and for up to 30 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first.

In ongoing clinical trials (as of 31 May 2015), the most common AEs suspected to be related to selinexor (incidences in parentheses) have been low-grade nausea (55%), fatigue (54%), anorexia (43%), vomiting (35%), and mild/moderate thrombocytopenia (30%). Most of these side effects can be managed effectively with dose modification and/or supportive care initiated prior to first dosing. In a previous study, one patient, heavily pre-treated for recurrent pancreatic cancer, developed acute cerebellar syndrome following 3 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 date of the initial reported event, this patient is recovering, with both speech and mobility recovered to near baseline over ~6 weeks. No other patients have reported similar symptoms to date.

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

Reproductive Risks

Macroscopic and microscopic changes in reproductive organs were noted during rat and monkey toxicology studies; most resolved or partially resolved during the recovery period. The long term

effects of these changes on reproductive potential are unknown. Secondary developmental effects due to reduced maternal body weights were also noted during a study on rat embryo/fetal development. Please see the *Selinexor/KPT-330 IB* for additional information. As it is unknown if selinexor produces any reproductive toxicity in humans, all patients must agree to use effective contraception (see Section 6.4.1.1) during the study and for 3 months after the end of treatment.

1.1.2.2.3 Efficacy

Clinical Evidence of Anti-Cancer Activity

Hematologic Malignancies: In the dose escalation phase of study KCP-330-001, tumor load reductions and disease stabilization have been noted across many tumor types, consistent with the broad anti-tumor mechanism and results observed in preclinical studies. Responses have been documented in patients with MM, mantle cell lymphoma and DLBCL, CLL, Richter's Syndrome, and AML. Durability for 6-12 months has been observed. The safety and tolerability of selinexor in patients with relapsed peripheral T-cell lymphomas (PTCL and CTCL) are being evaluated in a separate arm. Optimal twice-weekly dosing (e.g., dosing on Days 1, 2 vs. 1, 3 vs. 1, 4) is being explored in additional arms.

Solid Tumor Malignancies: In the dose escalation phase of study KCP-330-002, disease stabilization or responses for > 4 months has been observed in patients with colon cancer, cervical adeno- and squamous cancers, and endometrial stromal sarcoma. Tumor shrinkage has also been observed in patients with melanoma, head and neck cancers, Ewing sarcoma, and others. Dose expansion in patients with prostate, ovarian, squamous (head and neck, lung, and cervical), colon, and high-grade malignant gliomas is ongoing. Optimal twice-weekly dosing as described above is being explored in additional arms.

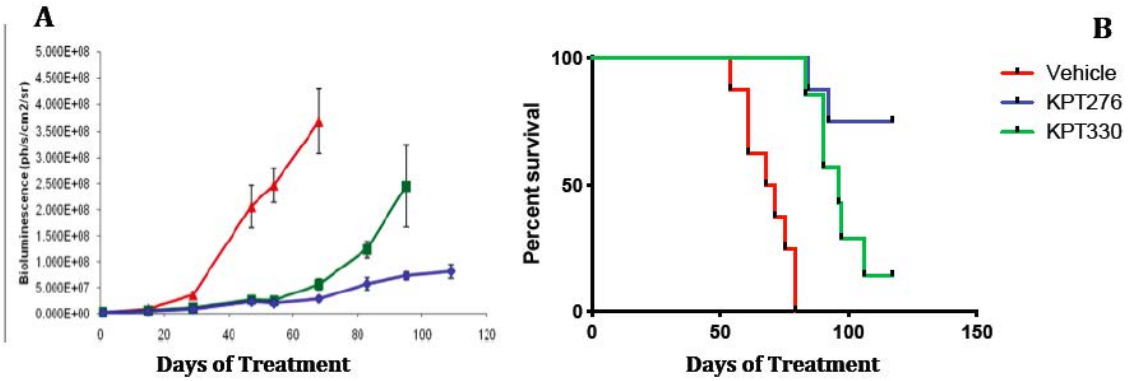
1.1.3 XPO1 and Selinexor in High-Grade Gliomas (HGG)

XPO1 is overexpressed in HGG, and the degree of over-expression correlates with tumor grade and survival. One substrate of XPO1 is p27, which functions as a tumor suppressor through cell cycle control[29] and requires phosphorylation at its Ser10 site in order to interact with XPO1.[30] *In vitro* studies have shown that in glioma, the expression of Ser10-phosphorylated p27 correlates directly with XPO1 expression; both are overexpressed in higher-grade lesions. The expression of total p27 correlates indirectly with XPO1 expression, and increase in total p27 protein levels is associated with lower-grade tumors. In contrast, low p27 levels are associated with a poor prognosis. These findings strengthen the rationale for studying the use of XPO1 inhibition in HGG and offer a point of entry into investigation of a disease-specific mechanism of action.

The XPO1 inhibitors KPT-276 and KPT-330 (selinexor) were evaluated in a murine orthotopic patient-derived xenograft (PDX) model of GBM.[35] Adult primary human glioma cells infected with a luciferase-expressing virus to allow serial imaging were injected into three groups of 10 mice each. When the bioluminescence level of the tumors reached 1,000 times its starting value, treatment of two of the groups with KPT-276 and KPT-330 (selinexor) began, with the third group acting as a control.

As shown in Figure 1, over time the inhibitors had a significant effect on the rate of tumor growth (A) and survival (B). The main side effect in the mice was weight loss, but this could be overcome with dosing adjustments.

Figure 1: Rate of Tumor Growth (A) and Survival (B) of Mice over Time with XPO1 Inhibitors KPT-276 and KPT-330 (Selinexor)



Investigation of a mechanism of efficacy for XPO1 inhibition in HGG has shown an increase in apoptosis, but not cell cycle arrest, *in vitro* and *in vivo*. Preliminary results indicate that this effect may be mediated through sequestration of mRNA for Mcl1, an anti-apoptotic member of the Bcl2 family, in the nucleus through inhibition of XPO1. This leads to failure of translation of Mcl1 and restoration of apoptosis; these inquiries are ongoing. Luxol Fast Blue/Cresyl Violet staining of sectioned mice brains of treated animals revealed no significant abnormalities in myelin health, and the treated mice had no significant neurologic side effects.

1.2 Study Rationale

Patients with GBM have a high risk for recurrence shortly after first-line therapy. The overall survival times of patients with recurrent GBM are poor, approximately 10 months at the highest despite various new treatment approaches within recent years. Consequently, new treatment options are desperately needed.

The cytotoxicity of selinexor against glioma (LN-229, U87MG, T-98G) cell lines was evaluated in MTT assays. IC_{50} values for selinexor ranged from 40 to 80 nM. Following this, seven patient-derived HGG lines (four adult, three pediatric) were treated with selinexor in culture conditions where dose-responsive growth inhibition in all seven HGG lines (IC_{50} range 6-354 nM) was observed.[35] Given these results, the ability of selinexor to inhibit *in vivo* growth of various glioma tumors was tested. In a xenograft model of glioma, U87MG cells were inoculated into severe combined immunodeficiency disease mice and selinexor was orally administered at 15 mg/kg three times weekly. Mean tumor weight and volume were significantly reduced with selinexor treatment ($p<0.001$). Selinexor has shown significant activity in multiple in-vitro glioma models. In a patient-derived orthotopic model of HGG, BT145-wt-mCLP cells were injected intracranially into nude mice and tumor growth was measured by bioluminescence imaging and MRI at discrete time points.[35] Selinexor at 20 and 25 mg/kg was administered via oral gavage three times a week (Monday, Wednesday, and Friday). All vehicle-treated mice were sacrificed by treatment day 79 due to tumor progression and neurological symptoms. A significant prolongation in survival was observed in selinexor treatment groups ($p < 0.0001$). Tumor growth was markedly suppressed, based on bioluminescence imaging, and verified by MRI imaging. In addition, the number of $TUNEL^+$ cells was significantly higher with selinexor treated tumors. These studies demonstrate

potent *in vitro* and *in vivo* efficacy of selinexor against a variety of glioma tumor models as a single agent. These data further support the development of selinexor for the therapy of glioma.

A maximum tolerated dose (MTD) of 65 mg/m^2 twice weekly (Days 1 and 3) was determined in the ongoing dose escalation Phase 1 study (KCP-330-002/OZM-043) in patients with advanced solid tumors. The MTD was based on two dose-limiting toxicities (DLTs) in 2 patients treated at 85 mg/m^2 twice weekly ('probably related' asymptomatic Grade 3 hyponatremia and 'possibly related' acute cerebellar syndrome with ataxia and dysarthria). No patients in any study may receive doses above 70 mg/m^2 once or twice weekly. As a selinexor dose of 50 mg/m^2 twice weekly was tolerated and cleared DLT evaluation in KCP-330-002, the same dose and schedule was initially chosen for the current study. However, analysis of prolonged dosing results in KCP-330-002 demonstrated that a dose of 35 mg/m^2 (~60 mg) twice weekly had acceptable efficacy and improved long-term tolerability. Therefore, the revised recommended Phase 2 dose (RP2D) of KPT-330 as single agent for use in this study is 60 mg twice weekly and 80 mg once weekly (~35 to ~45 mg/m^2, respectively).

Enrollment in Arm B was stopped to explore alternative dosing in Protocol Versions ≥ 4.0 to potentially improve tolerability. An assessment of the efficacy data prior to the formal PFS analysis for the first 12 patients in Arm B revealed clinically meaningful efficacy in this challenging patient population. Two patients in Arm B have had partial response (PRs) with PFS >160 days. C
CI
ased on the data to date, the study team has concluded that patient enrollment should continue notwithstanding the results of formal PFS analysis, but at a reduced starting dose. Although enrollment in Arm B has been stopped, the study is continuing with two randomized arms (Arms C and D, both using Simon's two-stage design[36]) with flat dosing that were added in Protocol Version 4.0. Based on the prolonged dosing results in KCP-330-002, patients in Arm C will receive 60 mg selinexor twice weekly, while patients in Arm D will receive 80 mg once weekly. Patients continuing in Arms CCI B who are at a dose of 35 mg/m^2 or greater will be converted to 60 mg twice-weekly flat dosing, however, if the patient is currently at a lower dose the Investigator should contact the medical monitor to determine the starting dose for flat dosing.

Patients will be treated until progression of disease or unacceptable toxicities occur. Safety data obtained in Phase 1 studies to date have shown that patients being on study for a time period of several months do not have an increased risk for developing adverse effects. No cumulative toxicities have been observed so far and adverse effects have generally been manageable with supportive measures. Thus, we consider that safety of the patients will not be affected even when study medication will be administered for a longer time period.

It is believed that selinexor may be of benefit in patients who require cytoreductive surgery for recurrent disease as part of their routine care. While determination of PFS in patients with no imaging evidence of tumor post-surgery is problematic, selinexor may benefit these patients by treating the small amount of residual cancer not detectable by imaging. CCI

[redacted]

2 OBJECTIVES OF THE STUDY

2.1 Primary Objectives

The aim of the study is to determine the efficacy of selinexor in adults with recurrent GBM as determined by the 6-months progression-free survival (6mPFS) rate (Arms B, C, and D).

2.2 Secondary Objectives

Secondary objectives of the study (Arms B, C and D) are:

- To determine the efficacy of selinexor in adults with recurrent GBM as determined by response rate according to the Response Assessment in Neuro-Oncology (RANO) criteria (see Table 4).[37]
- To determine the efficacy of selinexor in adults with recurrent GBM as determined by median overall survival (OS).
- To determine the efficacy of selinexor in adults with recurrent GBM as determined by median progression-free survival (PFS).
- To evaluate safety and tolerability of selinexor.

2.3 Exploratory Objectives

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3 INVESTIGATIONAL PLAN

3.1 Overview of Study Design and Dosing Regimen

This is an open-label, multicenter, Phase 2 study to evaluate the efficacy and safety of oral selinexor in patients with recurrent gliomas.

Initially, the study included 2 arms: CCI [redacted] medical arm (Arm B) for patients who are not eligible for surgery. The starting dose for Arms CCI [redacted] B was 50 mg/m^2 twice weekly, with one cycle defined as 28 days or 8 doses.

Enrollment in Arm B was stopped to explore alternative dosing in Protocol Versions ≥ 4.0 to potentially improve tolerability. Two arms (Arms C and D) were added to the Medical Arm in Protocol Version 4.0. Patients in the primary population enrolled under Protocol Version 4.0 or above will be randomized to Arm C and Arm D (approximately 30 patients per arm) to explore alternative dosing to potentially improve tolerability. See Section 1.2 for rationale. A schematic of the study design is provided in Figure 2.

After screening and registration/randomization in the study, patients enrolling CCI [redacted] randomized to Arm C will receive 60 mg selinexor orally twice weekly (e.g., Monday and Wednesday, Tuesday and Thursday, Wednesday and Friday, Thursday and Saturday) during Weeks 1-4 of each 4-week cycle. Patients who are currently being treated twice weekly for Weeks 1-3 under a previous version of the protocol may, at the discretion of the investigator, have the frequency of selinexor dosing increased to twice weekly for Weeks 1-4. Patients randomized to Arm D will receive 80 mg selinexor orally weekly. One cycle is 28 days (4 weeks) and should include either 4 (weekly) or 8 (twice weekly) doses. Patients continuing in Arms CCI [redacted] B who are at a dose of 35 mg/m^2 or greater will be converted to 60 mg twice-weekly flat dosing; however, if the patient is currently at a lower dose the Investigator should contact the medical monitor to determine the starting dose for flat dosing. The dose may be reduced due to AEs related to study drug to a minimum dose of 20 mg once weekly (see Table 5).

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Patients will be treated until progression of disease or the development of unacceptable toxicities. All patients will then undergo the End of Treatment (EOT) visit.

Enrollment in Arms C and D is based on Simon's two-stage design.[36] Formal statistical analyses for efficacy will pertain only to the medical arms in the primary population (Arms B, C, and D).

CCI [redacted]

3.1.1 CCI [redacted]

CCI [redacted]

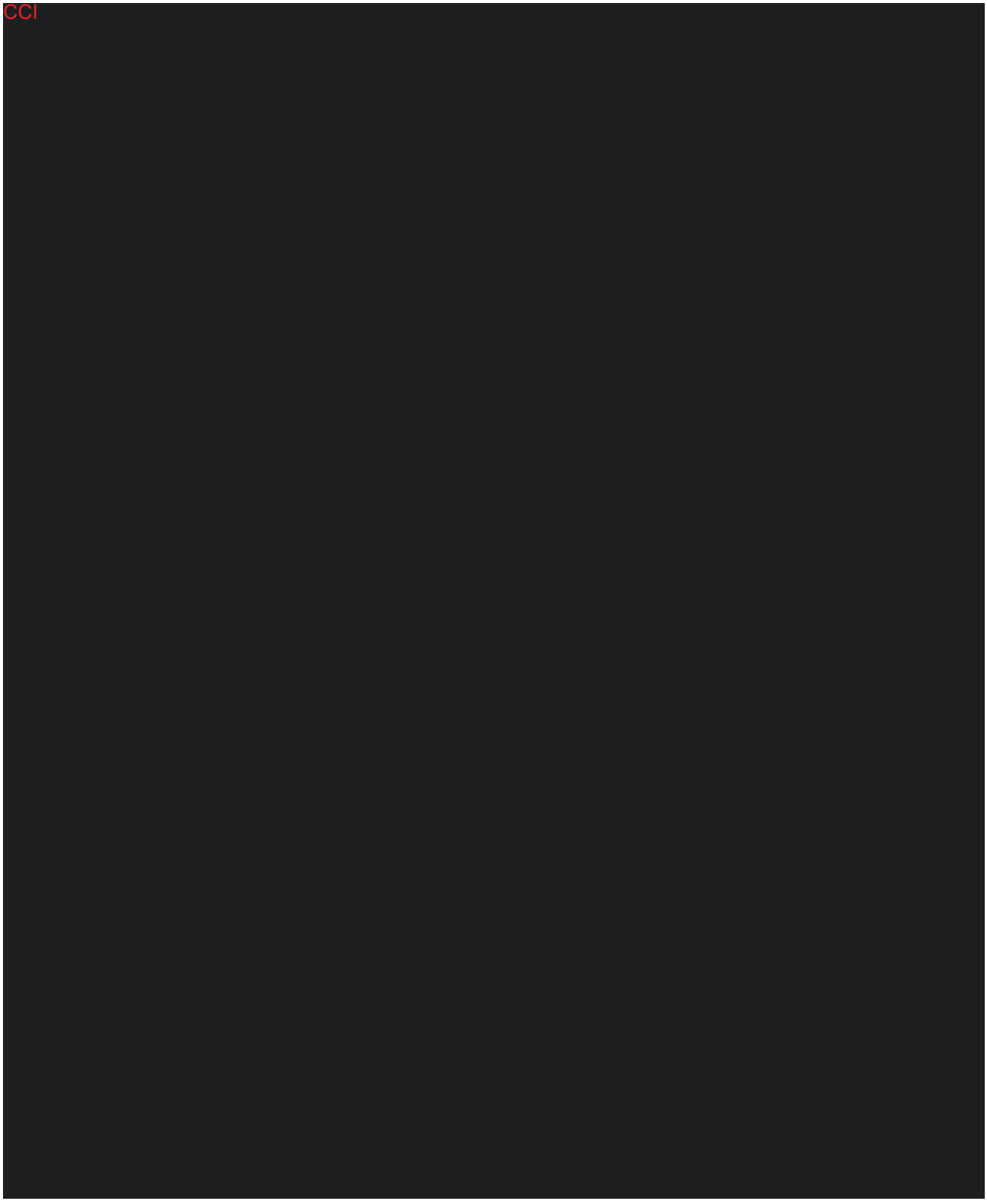
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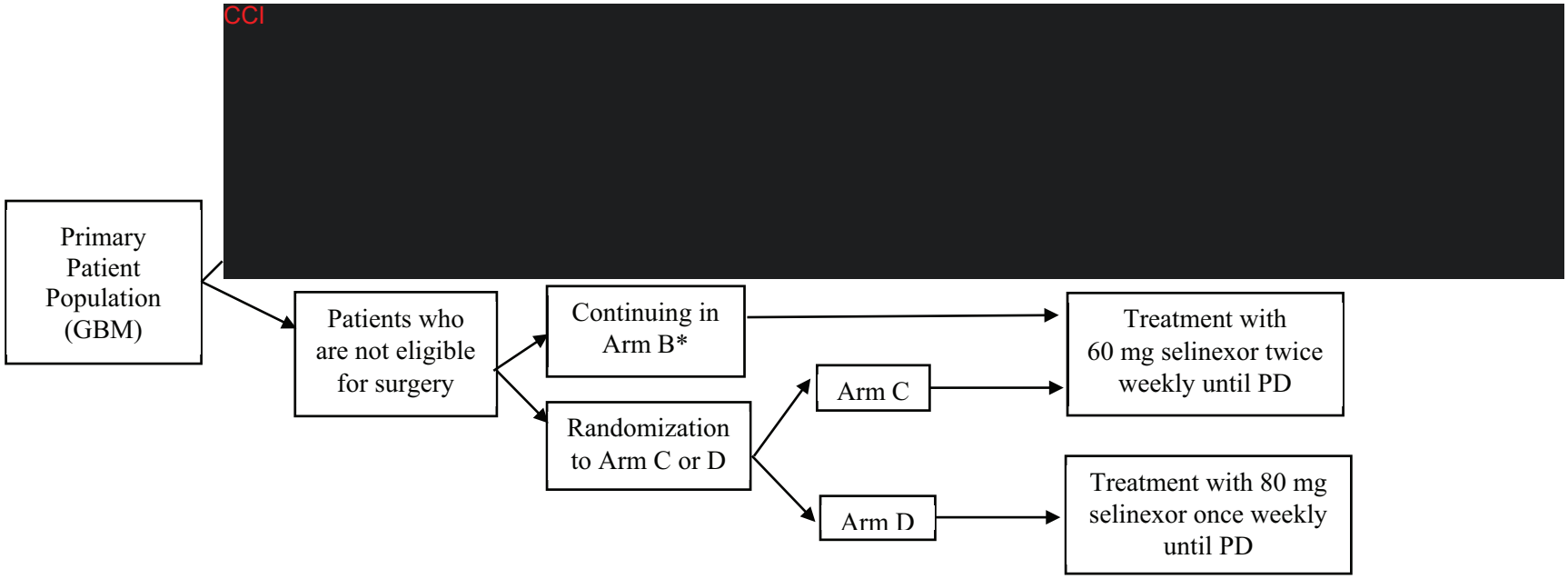
Figure 2: Overview of study design



Abbreviations: AG = anaplastic glioma; GBM = glioblastoma; PD = progressive disease.
*If the dose for a patient continuing in Arm CCI B is <35 mg/m^2, the Investigator should contact the medical monitor to determine the starting dose for flat dosing. Refer to Table 5 for dose modifications.

3.1.2 Definitions of Treatment Cycles

Twice-weekly Dose Schedules:

- Selinexor will be taken orally twice weekly during Weeks 1-4 of each 4-week cycle.
- Includes patients in Arms CCI C (who enrolled under Protocol Version 4.0 or above) and Arms CCI B (continuing patients who started on mg/m^2 dosing)
- CCI [redacted]

Once-weekly Dose Schedules:

- Arm D: Selinexor will be taken orally once weekly during Weeks 1-4 of each 4-week cycle.

All Dose Schedules:

- All cycles are 28 days (4 weeks) long.
- Study drug administration may be delayed for toxicity according to protocol Section 6.3.

3.1.3 Treatment Duration

Patients may continue to receive treatment with selinexor until either progression of disease is determined according to the RANO criteria[37], unacceptable toxicities occur which precludes further treatment with selinexor, patient's consent is withdrawn, or if the Investigator feels it is in the patient's best interest. The treatment period for an individual patient is expected to be up to 6 months, but there is no maximum duration for treatment. Clinically stable patients with CT/MRI scan showing borderline progression are allowed to continue on study at the discretion of the Investigator provided that re-evaluation is performed within 4 weeks. If progression is confirmed, the date of the first CT/MRI scan should be considered time of progression. Details of the study schedule are illustrated in the study flow chart (Table 1).

3.1.4 End-of-Treatment Visit

Patients who discontinue treatment will be encouraged to undergo an EOT visit, unless they withdraw consent to participate in the trial.

3.1.5 Follow-Up Phase

Before progression of disease, patients who discontinue for reasons other than progression of disease (and withdrawal of consent for participation in the trial) should be encouraged to visit the clinic for clinical evaluation of their disease every 4 weeks (± 7 days) and assessment by CT/MRI scan every 8 weeks (± 7 days) until progression of disease is determined.

After disease progression, all patients will be evaluated for survival and further therapy every 3 months (± 14 days). Patients who have not expired or progressed by the data analysis cutoff date for the 6mPFS rate will be censored at the date of their last disease assessment. Patients who have

not expired by the data analysis cutoff date for OS will be censored at their last date known to be alive.

3.2 Registration/Randomization of Patients

Patients who meet the enrollment criteria will be registered in the study in the CCI [redacted] Medical Arm (Arms C and D), dependent on the requirement for surgery. Enrollment is anticipated to take approximately 36 months. Enrollment in Arm B was stopped to explore alternative dosing in Protocol Versions ≥ 4.0.

For the Medical Arm, patients in the primary population who enrolled under Protocol Version 4.0 or above will be randomized via the EDC system in a 1:1 ratio to Arms C and D.

Patient eligibility will be reviewed by the Medical Monitor for each patient participating in the study after the patient completes all screening procedures and before the patient receives study treatment. There will be no exceptions. Any questions should be addressed to the Sponsor prior to registration/randomization. The eligibility check form/Patient Registration Form will be sent from the site to Karyopharm Therapeutics by email for evaluation. Upon confirmation of eligibility, Karyopharm Therapeutics will assign a patient number and return the signed eligibility check form/Patient Registration Form via email to the site. The Patient Registration Form will confirm the treatment arm in which the patient will participate.

The first planned dose of study drug will be administered CCI [redacted] no more than 3 days following randomization (Arms C and D).

3.3 Investigational Sites

Approximately 6 sites will participate in the study. Recruitment will be competitive at each site until the planned total number of approximately 110 patients is reached. A list of all participating investigational sites including information regarding names of the Principal Investigators and contact details (address, phone, fax email) will be handled separately.

4 SELECTION OF THE STUDY POPULATION

4.1 Target Patient Populations

Primary Patient Population:

Patients with pathologically confirmed GBM (including all histologic variants) with radiographic evidence of recurrent disease after failure of radiation therapy and temozolomide will be eligible for enrollment in Arms CCI C, and D of the study. Enrollment in Arm B was stopped to explore alternative dosing in Protocol Versions ≥ 4.0.

CCI [redacted]

4.2 Inclusion Criteria

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

1. Pathologically confirmed diagnosis of GBM (including all histologic variants) at first diagnosis with radiographic evidence of recurrent disease after treatment with radiotherapy and temozolomide;
2. Age ≥ 18 years.
3. Karnofsky Performance Status (KPS) ≥ 60.
4. Patients enrolling in the Medical Arm (Arms B, C, or D) must be on a stable or decreasing dose of corticosteroids (or none) for at least 5 days prior to the baseline CT/MRI.
5. Patients must have received prior treatment with radiation therapy and temozolomide (all Arms).
6. Measurable disease (according to RANO guidelines[37], within 14 days of starting treatment). Measurable disease CCI [redacted] is not required.
7. Written informed consent obtained prior to any screening procedures. Patients must be willing and able to comply with the protocol and aware of the investigational nature of this study.
8. Patients must have adequate bone marrow function and organ function within 2 weeks of study treatment as defined by the following laboratory criteria;
    - Hematopoietic function: total white blood cell (WBC) count ≥ 3000/mm³, absolute neutrophil count (ANC) ≥ 1500/mm³, platelet count ≥ 125,000/mm³; hemoglobin ≥ 9 g/dL.
    - Hepatic function: bilirubin ≤ 2 times the upper limit of normal (ULN), ALT ≤ 2.5 times ULN; AST ≤ 2.5 times ULN; unless bilirubin elevation is related to Gilbert's Syndrome for which bilirubin must be < 4 times ULN.
    - Renal function: estimated creatinine clearance of ≥ 30 mL/min, calculated using the formula of Cockroft and Gault (Section 16.3, Appendix 3) or other standard methods at the treating institution.
9. All female patients of childbearing potential must agree to use reliable methods of birth control during study treatment and for 3 months after the last dose of study drug and have

a negative serum pregnancy test at screening. Reliable methods of contraception include intrauterine devices, hormonal contraceptives [contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release], abstinence or sterilization of the partner.

10. Fertile males must be willing to employ reliable methods of contraception during study treatment and for 3 months after the last dose of study drug.
11. Archived paraffin-embedded tissue: approximately 10 unstained slides (if less, contact Sponsor) or a tumor block must be available for correlative studies.
12. CCI [redacted]
13. Patients enrolling in the Medical Arm (Arms B, C, or D) must be on a stable or decreasing dose of corticosteroids (or none) for at least 5 days prior to the baseline CT/MRI.

4.3 Exclusion Criteria

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

1. Patients must not have 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. < 24 days from prior temozolomide, < 6 weeks from nitrosourea, < 4 weeks from other chemotherapy or investigational agents prior to start of treatment within study.
3. Unstable cardiovascular function.
4. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen); hepatitis testing is not required.
5. Known HIV infection; HIV testing is not required.
6. Markedly decreased visual acuity if attributed to other causes than GBM.
7. Active infection requiring parenteral systemic antibiotics.
8. Patients with coagulation problems and medically significant bleeding in the month prior to start of treatment (e.g., peptic ulcer, epistaxis, spontaneous bleeding). Prior history of DVT or PE is not exclusionary.
9. Patients who are pregnant or breast-feeding.
10. Other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission and off all therapy for that disease for a minimum of 3 years.
11. Patients must not have significantly diseased or obstructed gastrointestinal tract, malabsorption, uncontrolled vomiting or diarrhea, or inability to swallow oral medications.
12. Dehydration of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade ≥1.
13. Patients must not have serious psychiatric or medical conditions that could interfere with treatment.
14. History of organ allograft.
15. Concurrent therapy with approved or investigational anticancer therapeutics.

16. Prior treatment with bevacizumab or other direct VEGF/ VEGFR inhibitors. For any question of the definition of a direct VEGF/VEGFR inhibitor, consult Sponsor.
17. Arms C and D only: BSA <1.2 m^2, to avoid a dose exceeding the maximum allowable dose of 70 mg/m^2.
18. Major surgery < 4 weeks prior to the start of study treatment

5 SCHEDULE OF ASSESSMENT AND PROCEDURES

Please refer to the Schedule of Assessments at the end of the synopsis for an overview (Table 1).

Data will be collected via the completion of an electronic Case Report Form (eCRF) for each enrolled patient. The Investigator should confirm eligibility of the patient according to the inclusion and exclusion criteria of the study. Written Informed Consent must be obtained before any study-specific assessment is performed. A study-specific assessment is defined as a procedure that is not part of the routine assessments performed for diagnostic purposes or standard care. Screening assessments should occur within 14 days of the first administration of study drug.

Patients who do not meet the eligibility criteria will not be enrolled in the study. Patients should receive their first dose of study treatment as soon as possible after registration/randomization, but not later than CCI 3 days after randomization (Arms C and D).

5.1 Study Assessments

5.1.1 Tumor Assessment

The disease status will be measured by contrast-enhanced MRI (or CT for patients unable or unwilling to undergo MRI) scans including pre-contrast T1, T2/FLAIR and post-contrast T1 and T2-weighted FLAIR and assessed using the RANO criteria (Table 4).[37]

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Radiographic response will be determined by comparison to the tumor measurement obtained at baseline (Arms B, C and D) CCI for patients. Tumor progression may also be determined by comparison with baseline tumor measurement. CCI

See Table 4 for the definition of response.

Table 4: Summary of the Proposed RANO Response Criteria

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑ [1]
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑ [1]
New lesions	None	None	None	Present [1]
Corticosteroids	None	Stable or ↓	Stable or ↓	NA [2]
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓ [1]
Requirement for response	All	All	All	Any [1]

Notes:
Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
↓ decrease
↑ increase
[1] Progression occurs when this criterion is present.
[2] Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

The baseline CT/MRI scan must be recorded and measured within 14 days prior to treatment start. A CT/MRI scan performed as part of standard of care can be used as the baseline CT/MRI scan provided study treatment will start within the 14-day window. CCI

[redacted]

5.1.2 Exploratory Assessments

CCI

[redacted]

CCI

5.1.3 Safety and Tolerability Assessments

Safety will be monitored by assessing laboratory parameters, physical examinations, vital signs and weight, performance status, neurological examinations, and concomitant medication use. Information regarding AEs will be collected and each AE will be graded according to the NCI CTCAE (current edition version 4.03; Section 16.4, Appendix 4) beginning at day of first administration of study drug, throughout the treatment period and to the extent possible until 30 days after last dose of study drug.

5.1.3.1 Laboratory Assessments

The standard clinical laboratory analysis is to be performed by the study site's local laboratories according to the Schedule of Assessments. More frequent examinations may be performed at the Investigator's discretion if medically indicated; results should be recorded on the eCRFs.

At any time during the study, abnormal laboratory parameters that are clinically relevant (e.g. interruption or delay of study treatment, lead to clinical symptoms, or require therapeutic

intervention) must be recorded in the eCRF. When abnormal laboratory values or test results constitute an AE, they must be recorded on the eCRF Adverse Events page.

Every effort must be made to follow the schedule outlined in the Schedule of Assessments. Safety laboratory assessments on the day of a study visit must be completed prior to study drug administration.

5.2 Study Procedures

5.2.1 Screening Procedures

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

Procedure	Notes
Signed written informed consent	Obtained prior to any study specific assessments are performed
Confirmation of eligibility (Days -7 to -1)	Please refer to Section 4.
Demographics and medical history	• Age, gender, ethnic background • Details on tumor diagnosis • Details on prior cancer therapy, including start and stop dates, disease progression during or after therapy, as well as discontinuation due to toxicities • Previous and concurrent relevant diseases • Current symptoms and/or residual toxicities from prior therapies
Pregnancy test (if applicable) (Days -7 to -1)	A serum pregnancy test will be performed in pre-menopausal women and women who are post-menopausal for < 2 years.
Physical examination and vital signs (Days - 7 to -1)	• Body height and weight • BSA (to ensure no patient exceeds the maximum allowable dose of 70 mg/m^2) • Blood pressure, pulse, temperature • Physical examination
Karnofsky performance status (Days - 7 to -1)	Please refer to Section 16.2; Appendix 2
Standard clinical neurological examination	A complete neurological exam will be performed (baseline exam).
Ophthalmic exam	A full ophthalmic exam will be conducted by an optometrist or ophthalmologist at screening. Additional ophthalmic assessments will be completed during the

	study if clinically indicated. CCI [redacted] 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 for newly enrolling patients or enrolled patients for whom no cataracts have been detected to date, the cataract will be graded using a Grade 1-4 scale (Section 16.5; Appendix 5). However, patients enrolled under a prior version of the protocol who had detectable cataracts graded according to the Lens Opacities Classification System (LOCS III) will continue to have their cataracts graded according to LOCS III and will not switch to the Grade 1-4 scale.
Oxygen saturation (Days -7 to -1)	Pulse oximetry is performed for patients at rest breathing room air
Cardiac evaluation	12-lead electrocardiogram (ECG)
Urinalysis (Days -7 to -1)	Urine bilirubin, glucose, hemoglobin, ketones, pH, protein
Hematology (CBC)	Hemoglobin, hematocrit, RBC count, WBC count, WBC differential, lymphocytes, monocytes, neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated
Complete clinical chemistry	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, amylase, lipase, creatinine kinase, urate, LDH
Coagulation (Days -7 to -1)	Prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT)
TSH (Days - 7 to -1)	Thyroid stimulating hormone (TSH)
Assessment of disease status	The disease status will be measured by CT/MRI scan including pre-contrast T1, T2/FLAIR and post-contrast T1 and T2-weighted FLAIR. Note: the CT/MRI scan does not need to be repeated if results are available from a scan performed 14 days prior to start of therapy.
Chest radiograph	Both posteroanterior and lateral films should be obtained for baseline. Note: this test does not need to be repeated if results are available from a test performed 30 days

	prior to start of therapy. This test serves as a baseline in the event that patients develop any AEs during the study.
CCI	[redacted]
Randomization (Day -3 to prior to first dose of study drug on Day 1)	Please refer to Section 3.2
Concomitant medication	Concomitant medication currently used
Supportive care	Initiated prior to first selinexor dose (see Section 6.5)

5.2.2 Treatment Phase

During the treatment phase the following assessments are to be performed as listed in the schedule of assessments (Cycles 1 and 2, weekly Day 1 [± 2 days]; Cycles 3-5, Days 1 and 15 [± 2 days]; Cycles ≥6, Day 1 [± 2 days]; CCI [redacted]

Procedure	**Notes**
Physical examination and vital signs	• Body weight • BSA (to ensure no patient exceeds the maximum allowable dose of 70 mg/m^2) • Blood pressure, pulse, temperature • Physical examination (symptom directed)
Karnofsky performance status	Please refer to Section 16.2; Appendix 2
Standard clinical neurological examination	A symptom-directed neurological exam will be performed. Any neurological deficits noted during the baseline exam must be followed. Any new neurological complaints reported by the patient and any deficits observed by the investigator should be assessed and followed.
Cardiac evaluation	12-lead ECG (as clinically indicated during the treatment phase)
Hematology	Hemoglobin, hematocrit, RBC count, WBC count, WBC differential, lymphocytes, monocytes, neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated. Labs can be done 3 days prior to visit.
CCI [redacted]	

CCI

CCI

Selinexor dosing	Please refer to Section 3.1.2
CCI	
AEs and concomitant medication	Assessed on an ongoing basis
Supportive care	Supportive measures for optimal medical care will be provided during the Treatment Phase (see Section 6.5).

CCI

5.2.3 End of Treatment

Patients who discontinue therapy for any reason (other than withdrawal of consent) will be encouraged to have an EOT visit. The EOT visit should take place 30 days (± 7 days) after their last dose, if possible. At the EOT visit, the patients will undergo the following safety assessments:

Procedure	Notes
Pregnancy test (if applicable)	A serum pregnancy test will be performed in pre-menopausal women and women who are post-menopausal for < 2 years to exclude that a pregnancy occurred under treatment
Physical examination and vital signs	• Body weight • Blood pressure, pulse, temperature • Physical examination
Karnofsky performance status	Please refer to Section 16.2; Appendix 2
Standard clinical neurological examination	A complete neurological exam will be performed
Cardiac evaluation	12-lead ECG
Hematology	Hemoglobin, hematocrit, RBC count, WBC count, WBC differential, lymphocytes, monocytes, neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated.
Complete clinical chemistry	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, amylase, lipase, creatinine kinase, urate, LDH.
TSH	TSH.
AEs and concomitant medication	Assessed on an ongoing basis until 30 days after the last dose of study medication (EOT visit).

5.2.4 Follow-up Before Progression of Disease

Patients who discontinue for reasons other than progression of disease (and withdrawal of consent for participation in the trial) should be encouraged to visit the clinic for clinical evaluation of their disease every 4 weeks (±7 days) and assessment by CT/MRI every 8 weeks (±7 days) until progression of disease is determined.

Patients lost to follow up should be recorded as such on the eCRF. For patients who are lost to follow-up, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

5.2.5 Survival Follow-up

After disease progression all patients will be evaluated for survival and further anticancer therapy every 3 months (±14 days). Patients who have not expired or progressed by the data analysis cutoff date for the 6mPFS rate will be censored at the date of their last disease assessment. Patients who

have not expired by the data analysis cutoff date for OS will be censored at their last date known to be alive.

5.2.6 End of Study

End of study will be when the last patient in the study has died, has been off study treatment for 12 months, has been lost to follow-up, or has withdrawn consent, whichever occurs first

5.3 Planned Treatment of the Patients after End of Treatment Phase

After completion of the EOT visit, patients will generally be treated at the discretion of the Investigator according to standard medical routine.

5.4 Removal of Patients from Treatment

Patients will be free to discontinue treatment or withdraw from the study at any time, for any reason, or they may be withdrawn/removed if necessary in order to protect their health (see reasons for withdrawal below). It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

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

- Disease progression
- Adverse Event (unacceptable toxicity)
- Non-compliance
- 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 for any reason
- Pregnancy
- Termination of the study by the Sponsor

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

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

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 INVESTIGATIONAL PRODUCT

6.1 Investigational medicinal product

An investigational medicinal product (IMP) is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing 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 (KPT-330).

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

6.2 Preparation and Administration of Selinexor

6.2.1 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 eCRF.

Tablets, including instructions for administration, are dispensed by study personnel on an outpatient basis. Patients will be provided with an adequate supply of study drug for self-administration at home until at least their next scheduled study visit.

6.2.1.1 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

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Tablets:

Selinexor (KPT-330) for oral administration will be supplied as either 10 and 25 mg tablets (supplied in bottles) or 20 mg tablets (supplied in blister packs). The initial drug product for the study will be the 10 and 25 mg tablets, with transition to the 20 mg tablets as these supplies become available.

Labelling:

Each bottle/blister pack of selinexor tablets will be labelled in accordance with current ICH GCP, FDA and specific national requirements.

Storage:

10 and 25 mg Tablets in Bottles

- Tablets of selinexor drug product will be stored at ambient temperature in white high-density polyethylene (HDPE) bottles, in a locked and secured area with restricted access.
- CCI
- Storage of tablets: selinexor tablets can be stored at room temperature or refrigerated, from 5-30 ˚C, do not freeze. Room temperature storage is recommended.

20 mg Tablets in Blister Packs

- CCI
- All selinexor tablets must be kept in an appropriate, limited access, secure place until dispensed, destroyed or returned to Karyopharm Therapeutics Inc. or designee for destruction.
- Selinexor tablets can be stored at room temperature or refrigerated, at or below 86 ˚F or 30 ˚C, do not freeze. Room temperature storage is recommended. The study site will be required to maintain a log of the temperature where the study medication is stored.

6.2.1.2 Route of Administration

Selinexor is to be taken orally within approximately 30 minutes of a light meal together with 120 mL (4 oz) of water. When taken on day of surgery, the patient should take selinexor while fasting using 4 oz of water.

Patients continuing in Arms CCI B who are at a dose of 35 mg/m^2 or greater will be converted to 60 mg twice weekly flat dosing, however, if the patient is currently at a lower dose the Investigator should contact the medical monitor to determine the starting dose for flat dosing.

For Arms CCI B, and C, selinexor will be given at an oral fixed dose of 60 mg twice weekly ([e.g., Monday and Wednesday, Tuesday and Thursday, Wednesday and Friday, Thursday

and Saturday] during Weeks 1-4 of each 4-week cycle); doses should not be administered less than 36 hrs apart. CCI [redacted]

For Arm D, selinexor will be given at an oral fixed dose or 80 mg once weekly (e.g., Monday of each week).

6.2.1.3 Compliance

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

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

6.3 Dose Modifications for Selinexor

Toxicity will be graded according to NCI-CTCAE, version 4.03 (Section 16.4, Appendix 4); the therapy modifications described below are applied according to this severity grading.

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

Re-escalation of the study drug is only allowed as outlined in the sections that apply for the specific toxicity. If toxicity requires a treatment delay of more than 28 days the patient will be taken off study treatment.

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

Based on preliminary observations from the ongoing Phase 1 studies in patients with advanced hematological and solid tumors, selinexor (KPT-330) shows a reasonably wide therapeutic range, with activity from ~6 mg/m^2 to ≥60 mg/m^2 (approximately 10 mg to 120 mg) orally. Therefore, in order to optimize specific anti-tumor activity and tolerability, dose reductions and/or schedule modifications will be allowed as described in Table 5 and Table 6. Patients should also be treated aggressively with supportive care to reduce toxicities.

Table 5: Prespecified Dose/Schedule Modifications for Adverse Events Related to Study Drug

Dose Level	Starting Dose of Selinexor	
	Arms CCI C	Arm D
Dose level 0	60 mg twice per week	80 mg once per week
Dose level -1	40 mg twice per week	60 mg once per week
Dose level -2	40 mg once per week	40 mg once per week
Dose level -3	20 mg once per week	20 mg once per week
Dose level -4	Discontinue dosing	Discontinue dosing

Patients will continue to receive selinexor until they need to be have their dose reduced below 20 mg once per week, at which time study treatment will be discontinued.

If patients who were being treated twice weekly for Weeks 1-3 under a previous version of the protocol are continuing with the Weeks 1-3 schedule, the dose modifications in Table 5 should be made based on the Weeks 1-3 schedule.

Table 6: Supportive Care and Dose Adjustment Guidelines

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Fatigue (common)		
Grade 1	• Rule out other causes of fatigue. • Ensure adequate caloric intake and assess volume status. • Consider addition of ≤ 4 mg dexamethasone or equivalent with each dose of selinexor +/- the day after selinexor.	Maintain dose.
Grade 2 (If intolerable Grade 2, follow guidelines for Grade 3 below)	• Rule out other causes of fatigue. • Ensure adequate caloric intake and assess volume status. • Consider addition of ≤ 4 mg dexamethasone or equivalent with each dose of selinexor +/- the day after selinexor. • For additional support see NCCN guidelines[a].	• Maintain dose. • Consult medical monitor for additional options such as temporary dose reduction or short dose interruptions (e.g., skip 1-2 doses). Original dose may be resumed when patient's condition improves.
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 5).

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
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 mg dexamethasone or equivalent with each dose of selinexor +/- the day after selinexor.	Maintain dose.
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 mg dexamethasone or equivalent with each dose of selinexor +/- the day after selinexor. • Consider megesterol acetate 80-400 mg daily (divided doses). • 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] (Section 16.7; Appendix 7).	Selinexor may be skipped intermittently (e.g., skip 1-2 doses) 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 5) 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 5) only if anorexia resolves to Grade ≤ 2, patient is clinically stable, and other contributing factors have been addressed.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Nausea/- acute (common)		
Grade 1	• Ensure 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 mg dexamethasone or equivalent with each dose of selinexor +/- the day after selinexor.	Maintain dose.
Grade 2 (If intolerable Grade 2, follow guidelines for Grade 3 below)	• See guidelines for Grade 1 nausea • For additional options see NCCN guidelines for antiemesisc (Section 16.6; Appendix 6).	Selinexor may be skipped intermittently (e.g., skip 1-2 doses) while supportive medications are instituted, usually for < 1 week.
Grade 3	• See guidelines for Grade 1 nausea • For additional options see NCCN guidelines for antiemesisc (Section 16.6; 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 5). • If nausea stabilizes for at least 4 weeks at Grade ≤ 1, then the 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 to two times per day.	Maintain dose.
Grade 3 (sodium levels 126-129 nM) without symptoms	• Be certain sodium level is corrected for hyperglycemia (serum glucose > 150mmol/L). • Consider immediate IV rehydration with appropriate saline solution. • 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 to three times per day.	• Consider administration of appropriate saline solution and remeasure serum sodium levels. If (corrected) sodium is Grade ≤ 1, then patient may receive standard dosing. • If immediate sodium correction is not successful, skip one dose of selinexor, implement recommendations, and reassess sodium within 48 hours. Resume selinexor dosing at the same dose level when sodium is Grade ≤1 (≥130 nM).

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 3 (120-125 nM) or Grade 4 or any Grade 3 with symptoms	• Correct sodium as per institutional guidelines • Initiate salt supplementation two to three times per day.	• Delay selinexor until resolved to Grade ≤ 1 (≥ 130 nM) then reduce selinexor dose by 1 level (Table 5). Sodium should be reassessed after one dose of selinexor is skipped (i.e., within 48 hours) and corrective measures implemented. • 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 hrs before the administration of selinexor and repeated every 4 hrs for the first 12 hrs.	For Grade 2 only, reduce selinexor one dose level (Table 5) until resolved to Grade ≤ 1, then re-start at the current dose level.
Grade 3	• Institute intravenous 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 hrs before the administration of selinexor and repeated every 4 hrs for the first 12 hrs.	• Delay selinexor dosing until resolved to Grade ≤ 1, then reduce selinexor dose by one dose level (Table 5). • 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 dosing until resolved to Grade ≤ 1, then reduce selinexor dose by one dose level (Table 5).
Thrombocytopenia		
Grade 1	In cases of marked reduction in platelet numbers from baseline, consider implementing platelet growth factors (e.g. eltrombopag or romiplostim ± oprelvekin [IL 11]).).	Maintain dose.
Grade 2	• Strongly consider implementing platelet growth factors (e.g. eltrombopag or romiplostim ± oprelvekin [IL 11]). • Monitor platelet counts weekly.	If Grade 2 thrombocytopenia persists > 14 days, delay selinexor dosing until platelet count returns to Grade ≤, then re-start at the current dose level.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 3 Thrombocytopenia without bleeding	• Initiate platelet growth factors (e.g. eltrombopag or romiplostim ± oprelvekin [IL 11]).). • Monitor platelet counts at least weekly. • Consider holding anti-platelet agents.	• Delay selinexor dosing until the patient's platelet count returns to Grade ≤ 2. • For Grade 2, restart selinexor at same dose level taken once weekly only until platelet counts resolve to Grade ≤ 1, then resume twice-weekly dosing at current dose. • Second occurrence: delay selinexor dosing until platelet counts return to Grade ≤ 2. For Grade 2, restart selinexor at same dose level taken once weekly only until platelet counts resolve to Grade ≤ , then resume twice-weekly dosing at one dose level below (Table 5). • If platelet counts stabilize at Grade ≤ 1 for at least 4 weeks, then original dose of selinexor may be resumed.
Grade 4 Thrombocytopenia without bleeding	• Follow guidelines for Grade 3 thrombocytopenia without bleeding. • Transfuse as per institutional guidelines.	• Delay selinexor dosing until platelet counts return to Grade ≤ 2. For Grade 2, restart selinexor at same dose level taken once weekly only until platelet counts resolve to Grade ≤ 1, then resume twice-weekly dosing at one dose level (Table 5). • If platelet counts stabilize at Grade ≤1 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.	Delay selinexor dosing until platelet counts return to Grade ≤ 1, and then resume selinexor dosing at one dose level below (Table 5).
Neutropenia		
Grade 3 neutropenia without fever	Implement growth factors per institutional guidelines.	Delay dosing with selinexor until the patient's ANC returns to Grade ≤ 2. Resume dosing with selinexor at current dose.
Grade 4 neutropenia without fever	Implement growth factors per institutional guidelines.	• Delay dosing with selinexor until the patient's ANC returns to Grade ≤ 2. Resume dosing with selinexor at current dose. • Second occurrence: delay dosing with selinexor until the patient's ANC returns to Grade ≤ 2 then reduce selinexor dose by one dose level (Table 5).

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
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	Delay dosing with selinexor until the patient's ANC returns to Grade ≤1, fever has resolved and patient is stable, then reduce selinexor dose by one dose level (Table 5).
Anemia		
Grade 1 or 2	Initiate standard supportive care and follow institutional guidelines.	Maintain dose.
Grade 3		Delay dosing with selinexor until resolved to Grade ≤ 2, then resume dosing with selinexor at current dose.
Grade 3 (symptomatic) or Grade 4		Delay dosing with selinexor until resolved to Grade ≤ 2, then reduce selinexor dose by one dose level.
Other clinically significant selinexor-related AEs*		
Grade 1 or 2	Initiate standard supportive care and follow institutional guidelines.	Maintain dose.
Grade 3		Delay dose until resolved to Grade ≤ 1, then reduce by one dose (Table 5).
Grade 4		Delay dose until resolved to Grade ≤ 1, then reduce by two dose levels (Table 5).
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. Note: for combinations of Grade 1 or 2 adverse events (e.g., nausea, fatigue, anorexia) that significantly impair the patient's quality of life, 1-2 doses of selinexor may be skipped and aggressive supportive care implemented. Selinexor may then be restarted at the original dose.		
[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.pdf31 [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[32] [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. [33] [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. [34]		

If the patient tolerates a reduced dose for at least four weeks, patients may be dose escalated to the dose they received prior to the reduction after authorization from medical monitor and Principal Investigator.

6.3.1 Selinexor Dose Reduction for Decreased Glomerular Filtration Rate

Selinexor is not significantly eliminated by the kidney; therefore, no dose alteration of selinexor is required with renal dysfunction. If dialysis is implemented during selinexor treatment, then selinexor should always be given after dialysis.

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. Dexamethasone should be adjusted per institutional guidelines, and adrenal suppression considered. 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.

6.3.3 Dose Adjustments with Changes in BSA

Patient BSA will be assessed to ensure that the 60 mg or 80 mg dose does not result in a dose >70 mg/m^2. If a patient's dose will exceed this limit, the Investigator should contact the medical monitor prior to administration to discuss appropriate dosing.

6.3.4 Missed or Vomited Doses

A maximum of two doses may be given per week; doses should not be administered less than 36 hrs apart. Every effort should be made to avoid missed doses.

- *Missed doses:* Doses held due to AE will not be considered missed.
- *Vomited doses:* If a dose is vomited within 1 hr of ingestion, it will be replaced. If vomiting occurs more than 1 hr after dosing, it will still be considered a complete dose.

6.4 Concomitant Medication and Treatment

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

6.4.1 Permitted Concomitant Medication

Patients will receive concomitant medications to manage cancer symptoms, AEs, intercurrent illnesses, and supportive care agents, such as, pain medications, anti-emetics, short courses of low dose oral steroids, and anti-diarrheal agents are allowed that are medically necessary as standard care. Medications to treat concomitant diseases like diabetes, hypertension, etc. are allowed.

6.4.1.1 Prevention of Pregnancy

Patients should not become pregnant or father a child while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important patients understand the need to use birth control while on this study. Female patients of child-bearing potential must have a negative serum pregnancy test at screening and agree to use reliable methods of contraception for three months after their last dose of medication. Such methods include intrauterine devices, hormonal contraceptives [contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release], abstinence or sterilization of the partner. Male patients must use a reliable method of contraception (abstinence or contraception with one of the above-described methods for your partner) if sexually active with a female of child-bearing potential. Total (true) abstinence (when this is in line with the preferred and usual lifestyle of the patient), is an acceptable method of contraception. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post- ovulation methods) and withdrawal are not

acceptable methods of contraception. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.

6.4.1.2 Use of Blood Products

During the administration of selinexor, patients may receive RBC or platelet transfusions, if clinically indicated, per institutional guidelines. Patients who require repeated transfusion support should be discussed with the Primary Investigator, Sponsor, and medical monitor.

Appropriate anti-coagulation is allowed during the study (e.g.: low molecular weight heparin, direct factor Xa inhibitors, etc.).

Patients may receive supportive care with erythropoietin, darbepoetin, G-CSF or GM-CSF, pegylated growth factors, and platelet stimulatory factors, in accordance with clinical practice or institutional guidelines or as recommended in Table 6 prior to entry and throughout the study.

6.4.2 Restrictions and Prohibited Medications

Concurrent therapies: Concurrent therapy with glucocorticoids as specified herein is allowed. Concurrent therapy with any other approved or investigative anticancer therapeutic is not allowed. Other investigational agents should not be used during the study. Use of any immunosuppressive agents during the study must be confirmed by the medical monitor.

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

Diet: There are no dietary restrictions on this study. Patients should maintain adequate caloric and fluid intake.

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

Patients should not take GSH-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products during their participation in this study as these products may enhance the metabolism of selinexor. See Section 16.8; Appendix 8 for a list of representative products. Patients must report all prescription and non-prescription medicines to their physicians during this study.

Concurrent warfarin or other Coumadin-derived anticoagulants are prohibited.

6.5 Supportive Care Guidelines

6.5.1 Required 5-HT3 Antagonists

In order to minimize nausea, unless contraindicated, all patients must receive 5-HT3 antagonists (ondansetron 8 mg or equivalent), starting before the first dose of selinexor and continued 2-3 times daily thereafter, as needed. Alternative treatment may be provided if the patient does not tolerate 5-HT3 antagonists.

6.5.2 Supportive Care Recommendations for Selinexor-Related Adverse Events

Supportive measures for optimal medical care shall be provided during participation in this study. Based on clinical observations in over 730 adult patients treated with selinexor as of 31 May 2015, the main side effects have been primarily related to anorexia with poor caloric and fluid intake, fatigue and nausea. Thrombocytopenia also occurs, although it is rarely associated with bleeding.

In addition to required 5-HT3 prophylaxis, supportive care including additional anti-nausea/anti-emetic therapy, acid suppression (proton-pump inhibitors [PPI] and/or H2-blockers) and other treatments may be administered as follows:

- Glucocorticoids: ≤4 mg dexamethasone [or equivalent] on the day of, and the day after, each selinexor dose, with a maximum of 16 mg/week) may also be used as needed to improve appetite, reduce nausea or vomiting, and minimize fatigue.
- Appetite stimulants: megesterol acetate at a dose of 80-400 mg daily.
- Centrally acting agents: per National Comprehensive Cancer Network® [NCCN] Clinical Practice Guidelines® see, respectively, Section 16.6; Appendix 6 and Section 16.7; Appendix 7.
- Neurokinin-1 receptor antagonist (NK1R antagonist): Aprepitant or equivalent should be considered and will be covered for selected patients who have severe nausea and vomiting

Supportive care guidelines for managing AEs are provided in Table 6.

6.5.2.1 Infection

Appropriate broad-spectrum intravenous antibiotics and antifungal agents should be started immediately in patients who develop fever or other signs of systemic infection. Selinexor should be suspended in any patient with Grade 4 infection or clinical sepsis (in the absence of documented infection) until the condition is stabilized. Selinexor can then be re-started at the same dose. See also Table 6.

6.5.3 Liver Function Test Abnormalities

Since selinexor is metabolized by GSH conjugation, hepatic GSH depletion might occur. Therefore, in patients who develop liver function test abnormalities, supportive measures such as SAM 400 mg orally 1-4 times per day or other drugs that can replace GSH should be considered.

7 ASSESSMENT OF SAFETY

The *Selinexor/KPT-330 IB* will be used as reference document for selinexor and will be provided to the Investigators.

7.1 Adverse Events and Laboratory Abnormalities Reporting

7.1.1 Adverse Event

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

An AE 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.

The Investigator will make a judgment regarding whether or not the AE was related to study drug, as outlined below in Table 7.

Table 7: Classification of Adverse Events by Causality

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

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

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 AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

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

7.1.3 Serious Adverse Event

A serious adverse event (SAE) is defined as an AE that

- Is fatal
- Is life threatening (places the patient 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 AE that does not meet one of the definitions of serious (e.g., visit to an emergency room, outpatient surgery, or requires urgent investigation) may be considered by the Investigator to meet the "other significant medical hazard" criterion for classification as an SAE. 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 patient or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical judgment should be exercised in deciding whether such an AE should be considered serious.

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

7.1.4 NOT to be reported as SAEs

For this study, the following conditions or planned events are **not** classified as SAEs:

- Progression, deterioration or other events secondary to 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 AE (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 defined as a suspected unexpected serious adverse reaction. An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current *Selinexor/KPT-330 IB*. Also, reports that provide significant information on the specificity or severity of a known, already documented AE constitute unexpected AEs. An event more specific or more severe than described in the IB 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 AE or abnormal laboratory test value that is serious occurring during the course of the study from the date of signing the informed consent, irrespective of the treatment received by the patient, must be reported to the Sponsor within 24 hrs (expedited notification). For each patient, all SAEs must be reported up to 30 days after the last dose of investigational product. SAEs occurring more than 30 days after a patient is discontinued from the study treatment may be reported at the discretion of the Investigator.

The completed SAE form must be sent to:

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

The Sponsor will medically review all SAEs.

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

- A description of the AE
- The severity grade as assessed by the Investigator according to the definitions in NCI-CTCAE Version 4.03 (Section 16.4, Appendix 4)
- The date of becoming serious and the date of becoming known (if different)
- The reason for seriousness
- The outcome of the SAE at the time of the report
- Information on administration of the study drug and any action taken
- Information on any treatment procedures necessary for the SAE, concomitant medications, relevant lab tests and relevant medical history

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

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

7.3 Reporting of SUSARs/Expedited Reporting of Unexpected Serious ADRs

Sites within the EU:

Karyopharm Therapeutics will 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.

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 patients.

Sites in the United States:

Karyopharm Therapeutics will ensure Expedited reporting of unexpected Serious ADR to FDA in accordance with local legal requirements, statutes and ICH topic E2A (Section 16.1, Appendix 1) as follows:

- Reporting of the unexpected Serious ADR to FDA 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).

Investigators must notify their Institutional Research Board (IRB) or Research Ethics Boards (REBs) in accordance with local regulations and file the report with their Investigator Site File.

The Sponsor is responsible to ensure that the latest *Selinexor/KPT-330 IB* 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 AEs observed by the Investigator or reported by patients are properly and no later than 7 days after patients visit recorded in the patient's medical records and the eCRF.

The following AE attributes must be assigned by the Investigator:

- Severity grade according to the NCI-CTCAE criteria Version 4.03 (Section 16.4, Appendix 4)
- 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 with study medication
- Any treatment administered to the patient or procedure performed due to the adverse event

AEs will be followed until they resolve to baseline or are considered stable. It will be left to the Investigator's clinical judgment to determine whether an AE is related and of sufficient severity to require the patient's removal from treatment or from the study. A patient may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these situations arises, the patient 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 AEs. They can lead to SAEs, if the meet the criteria described in Section 7.1.3.

Intensity of AEs will be graded using the NCI-CTCAE, version 4.03 (Section 16.4, Appendix 4). If an AE 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 eCRF. In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately (within 24 hrs) and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

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

1. Accompanied by clinical symptoms.

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

Please note: Any laboratory result abnormality fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

7.6 Pregnancy

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

Female patients must be instructed to immediately inform the Investigator if they become pregnant during the study. If a patient becomes pregnant, 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 should counsel the patient and 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 male patient participating in the study should also be reported to the Investigator. The partner should be counselled and followed as described above.

The investigator must report all pregnancies within 24 hours of knowledge to the Karyopharm Pharmacovigilance Department.

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 ADRs apply, i.e. reporting to the marketing authorization holder or the local regulatory bodies.

7.8 Safety Surveillance

Regular safety teleconferences between the site Investigators and the Sponsor will be conducted. Any safety issues will be discussed and minutes recorded and distributed to all attendees.

8 STATISTICAL METHODS

8.1 Trial Design and Hypotheses

This trial has been designed as an open label, multiple arm, multicenter, Phase 2 study. CCI [redacted] Patients in Medical Arms B and C will be treated with selinexor alone (twice weekly). Patients in Medical Arm D will be treated with selinexor once weekly.

The primary trial objective is to determine the efficacy of selinexor in adults with recurrent GBM as determined by the 6mPFS. Based on histological information contained in the literature, the trial would be considered a success if there is evidence to suggest a 6mPFS rate as high as 30%. Simon's two-stage design[36] will be used to address the primary objective, with the following hypothesis to be tested for the primary efficacy endpoint of 6mPFS:

H_0: true PFS rate at 6-months ≤ 0.09 versus H_1: true PFS rate at 6-months ≥ 0.30.

PFS is defined as the time from start of treatment until the first documented progression using the RANO criteria[37] or death from any cause.

Secondary objectives include the following:

- To determine the efficacy of selinexor in adults with recurrent GBM as determined by response rate according to the RANO criteria[37]
- To determine the efficacy of selinexor in adults with recurrent GBM as determined by median overall survival (OS)
- To determine the efficacy of selinexor in adults with recurrent GBM as determined by median progression-free survival (PFS)
- To evaluate safety and tolerability of selinexor

It is believed that selinexor may be of benefit in patients who require cytoreductive surgery for recurrent disease as part of their routine care. CCI [redacted]

8.2 Sample Size Calculation

8.2.1 Arm B (50 mg/m^2 twice weekly)

CCI [redacted]

CCI

[redacted]

8.2.2 Flat Dosing Arms (Arm C and Arm D)

CCI

[redacted]

8.3 Evaluation Categories for Patients

8.3.1 Modified Intent-to-Treat Population

The treated population (modified intent-to treat population [mITT]) will consist of all patients in Arms B, C and D who receive at least one dose of study medication and have at least one post-baseline efficacy follow-up assessment, unless the patient discontinued treatment prior to the first post-baseline assessment due to death, toxicity, or disease progression. . This population will be used for primary analyses of efficacy; additional sensitivity analyses will be performed on this population, as described in Section 8.4.3. CCI

[redacted]

8.3.2 Per Protocol Population

The per-protocol population (PP) will consist of all Arms B, C and D patients who have been administered at least 2 months of study drug treatment, who are compliant with study assessments and have received at least 80% of their prescribed study medication, and who have no major protocol violations that would compromise the assessment of efficacy. Major violations will be determined independently of knowledge of response to therapy. This population will be used for supportive inferences concerning efficacy, however, if there are major differences between the

results in this population and those obtained in the mITT population, this will be taken into consideration in the decision to continue to later phase studies, or in the design of further studies.

8.3.3 CCI

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8.3.4 Safety Population

The safety population will consist of all patients who have received any amount of study medication. The safety population will include both the non-surgical and surgical patient groups; analyses of safety will be produced for both the pool of surgical and non-surgical patients, as well as each group separately.

8.4 Methods of Statistical Analysis

8.4.1 General Statistical Considerations

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

No imputation of missing efficacy data is planned. For time to event analyses, patients who have no efficacy evaluations for disease recurrence will be considered censored at time 0. For OS, patients will be censored on the date they were last known to be alive regardless of disease status.

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

Formal statistical analyses for efficacy, as described in the following sections and consistent with Simon's two-stage design[36], will pertain only to the primary patient populations (mITT and PP) that include non-surgical GBM patients. Descriptive statistics only will be presented for the surgical group.

8.4.2 Demographics and Baseline Characteristics

The demographic characteristics to be summarized will include gender, race, ethnicity (Hispanic origin), and age at time of consent. For gender, race, and Hispanic origin, the summary statistics will be the number and percentage of patients within each category. The categories for race will be

those recorded in the database. For age at time of consent, the mean, median, minimum, maximum, and standard deviation will be provided for each group and the total sample.

Baseline characteristics include: Performance Status; duration from initial diagnosis; response to previous therapy (Y/N). Demographics and baseline characteristics will be summarized separately for patients in each treatment arm.

8.4.3 Efficacy Evaluation

8.4.3.1 Primary Analysis: Rate of 6mPFS

The analysis of 6mPFS will be performed by calculating the point estimate of the percentage of non-surgical GBM patients who have neither progressed nor died at 6 months following the start of therapy, where progression will be determined by the RANO criteria.[37] In order to accommodate potential changes in individual patient visit schedules, a window of ±14 days will be allowed around the 6-month visit for the primary analysis of rate of 6-month PFS. This window will be applied to the calculation of the point estimate of 6mPFS; actual times of events (progression or death) will be used for the Kaplan-Meier statistical summary of PFS. The primary analysis will be performed when all patients have died, completed 6 months of study treatment, have withdrawn, or have been lost to follow-up.

To be consistent with Simon's design[36], a lower one-sided 90% CI will be presented on rate of 6mPFS; additionally, for descriptive purposes a two-sided 95% CI will also be calculated. The 6mPFS results will be presented for the first stage of the study (separately for Arms B, C and D) and for both stages combined (separately for Arms C and D), consistent with Simon's design.[36]

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8.4.3.2 Secondary Analyses:

(1) Response to therapy: Response will be determined as objective response rate (ORR), defined as either complete response (CR) or partial response (PR) using the RANO criteria[37], calculated as a proportion and including a two-sided 95% CI. In addition, to assist in evaluating the evidence of efficacy and to be consistent with the approach used for rate of 6mPFS, a lower one-sided 90% CI on response rate will be calculated. Based on prior studies, preliminary evidence of efficacy would be provided if this lower limit were to exceed 0.10.

(2) Median Overall Survival: OS will be calculated from the date of start of study therapy to the date of death. Patients who are still alive prior to the data cutoff for final efficacy analysis, or who dropout prior to study end, will be censored at the day they were last known to be alive. The analysis of OS will be based on the Kaplan-Meier method for estimation of summary statistics, and include the 25th, 50th (median) and 75th percentiles and associated 95% CIs. A lower one-sided 90% CI on median OS will also be calculated. The secondary analysis for OS will be performed when all patients have died, have been off study treatment for 12 months, have been lost to follow-up, or have withdrawn.

(3) Median Progression-free Survival: PFS will be calculated from the date of start of study therapy to the date of progression based on RANO criteria[37], or date of death should progression not have

occurred. The analysis of median PFS will be similar to that of OS, using the Kaplan-Meier method; as noted above, actual event times will be used in this analysis.

8.4.3.3 Sensitivity Analyses:

A sensitivity analysis of the primary endpoint of 6mPFS will be performed to assess the potential influence of causality of deaths on study, where deaths due to causes that are clearly unrelated to the disease or study drug would be excluded from the definition of PFS. Sensitivity analyses will be performed on the data obtained from both stages of Simon's two-stage design[36], and will consist of one-sided, lower 90% CIs on the rate of 6mPFS.

8.4.3.4 Exploratory Analyses:

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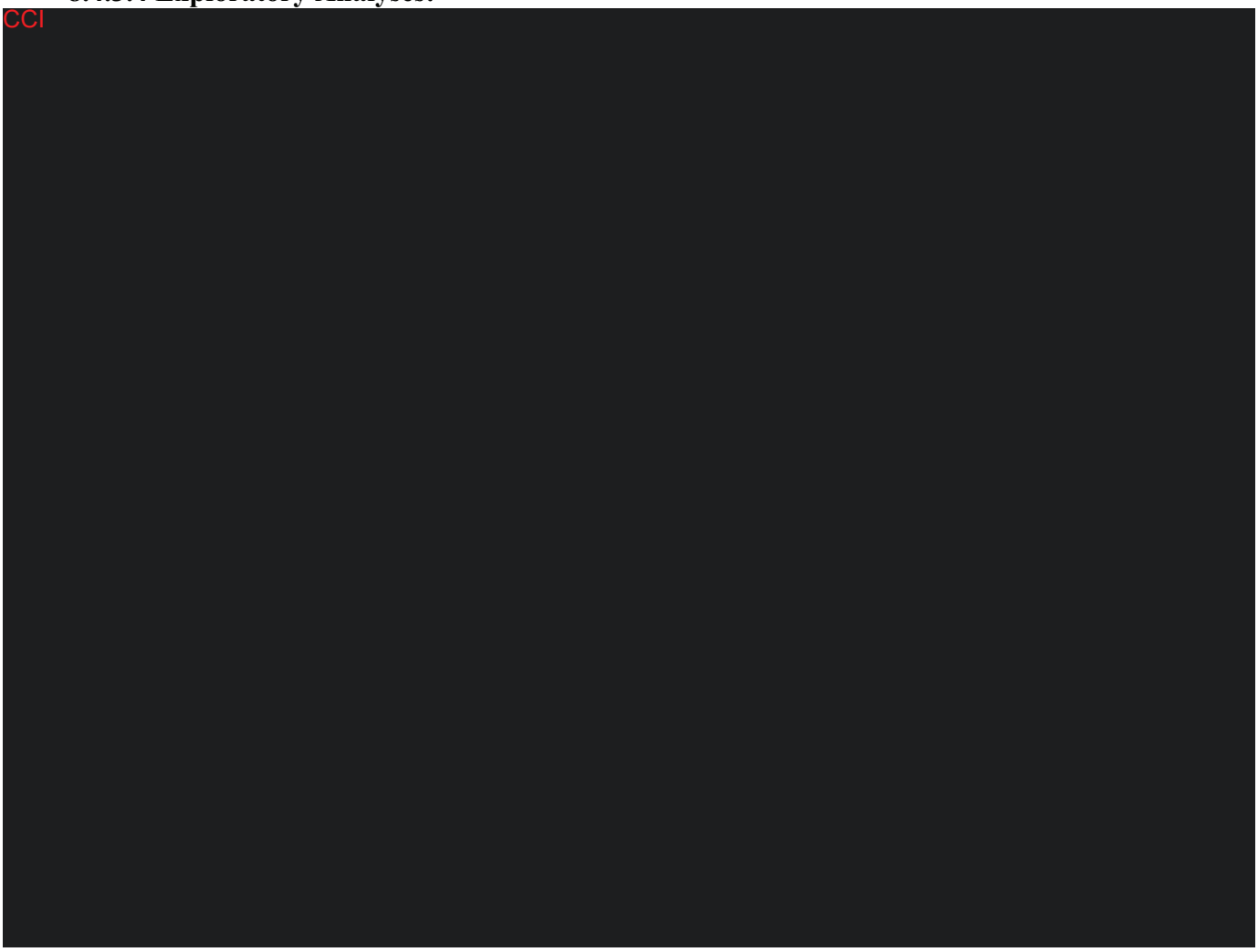

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[redacted]

8.4.4 Safety Evaluation

Safety analyses will be conducted using the Safety Population. Categories for summarization will consist of each individual arm, as well as a category for GBM non-surgical (consisting of Arms B, C and D), and an overall total.

The comparison of safety and tolerability of selinexor in Arms B, C, and D will be assessed using a descriptive review of the endpoints described in this section, in addition to the following:

- Difference in incidence of common AEs (occurring in ≥10% of the safety population) using Fisher's exact test. Similarly, the difference in the grading of common AEs will be assessed using Fisher' exact test as appropriate (e.g. the distribution of the grades is not sparse) , different grades may be collapsed for the feasibility of performing Fisher's test
- Incidence of dose reduction and incidence of dose interruption will be assessed by Fisher's exact separately (when there are many 0 values in the number of dose reduction or number of dose reduction). If dose reduction and dose interruption are common in all arms, the number of dose reductions and number of dose interruptions will be compared among treatment arms using Kruskal-Wallis test.

8.4.4.1 Adverse Events

AEs will be coded using the MedDRA dictionary and displayed in tables and listings using System/Organ/Class (SOC) and Preferred Term.

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

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

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

- Serious AEs will also be tabulated.
- No formal hypothesis-testing analysis of AE incidence rates will be performed.
- All AEs (treatment emergent and post-treatment) will be listed in patient data listings.
- By-patient listings will be provided for the following: patient deaths; serious AEs; and AEs leading to withdrawal.

8.4.4.2 Laboratory Data

The actual value and change from baseline to each on study evaluation will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry. In the event of repeat values, the last non-missing value per study day/time will be used.

Severity of select clinical lab measures will be determined using CTCAE v.4.03 criteria (e.g. those measures that have a corresponding CTCAE grade classification). Labs with CTCAE grades greater than or equal to 3 will be presented in a data listing. Shift tables that present changes from baseline to worst on-study values

8.4.4.3 Vital Signs and Physical Examinations

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

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

8.4.4.4 Concomitant Medications

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

8.5 Interim and Final Analysis

In accordance with Simon's two-stage optimal design[36], there will be a preliminary assessment of efficacy for Arms B, C, and D after the first 12 non-surgical patients enrolled in each arm have 6-month data available to assess PFS. Note that this initial analysis may take place sooner than when the 12th patient has available data, should there be 2 or more PFS responders after fewer than 12 patients. Should the trial be terminated at the first stage for Arms B, C, and D, all efficacy and safety analyses as noted above will be performed. Patient enrollment into the trial will continue while the first stage analysis is being conducted.

The final analysis of the primary endpoint will take place after there are 30 patients evaluable for analysis of 6mPFS separately in Arm C and Arm D, as enrollment in Arm B was stopped to explore alternative dosing in Protocol Versions ≥ 4.0 (see details in Section 8.2). Additional data summarization may take place after all available survival data are collected, or after Sponsor decision, as appropriate.

9 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be assured by verification and cross–check of the eCRFs against the Investigator's records by the study monitor (source document verification), and the maintenance of a drug–dispensing log by the Investigator. Data for this study will be recorded via eCRF. It will be transcribed by the site from the source documents onto the eCRF. Data are reviewed and checked for omissions, apparent errors, and values requiring further clarifications using computerized and manual procedures. Data queries requiring clarification are communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database and an audit trail will document all corrections.

10 ETHICAL ASPECTS

10.1 Good Clinical Practice

The Investigator will ensure that the study is performed in accordance with the international standards of GCP 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, or their legally authorized representative, 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 the collection of 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 patient also agrees to allow the monitor/auditor health authorities to verify the patient data collected against the patient's original medical records for the purpose of source data verification.

The informed consent form personally signed and dated by the patient, or their legally authorized representative, must be kept on file by the Investigator(s) and documented in the eCRF and the patient's medical records. The Investigator must confirm with the Sponsor that he/she has obtained written informed consent.

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

If family 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 by Regulatory Authorities and Independent Ethics Committees

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

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

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 patients or when the changes are non-substantial and involve only logistical or administrative aspects of the trial (e.g. change of telephone numbers).

12 STUDY DOCUMENTATION, CRFS AND RECORD-KEEPING

12.1 Investigator's Files/Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories: Investigator's study file and 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, electroencephalogram, 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 as long as legally required by local and national regulations, or local IRB/ethics board policies whichever is longer, after completion or discontinuation of the study. The documents must be archived in a secure place and treated as confidential material.

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

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

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

12.2 Source Documents and Background Data

The Investigator shall supply the Sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when 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 eCRF data must be done via direct inspection of the source documents. The Investigator agrees to comply with the Sponsor and regulatory authority requirements regarding the auditing of the study.

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

12.4 Case Report Forms

This study will use Electronic Data Capture (EDC). The designated Investigator site staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the Investigator site staff.

The Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

13 MONITORING OF STUDY

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

The monitor will visit the clinical study center before the first patient has been enrolled (initiation visit). During the study, the monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs (source data verification), the adherence to the protocol to GCP, 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. eCRFs 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.

Study data may be analyzed and submitted to regulatory authorities in one or more interim clinical study reports (CSR) when ≥ 75% of patients have potentially completed ≥ 2 cycles of treatment or discontinued from the study. Any additional data for patients continuing to receive study treatment past the data cutoff, as allowed by the protocol, will be reported in a final CSR once all patients have discontinued from the study. The final, integrated CSR will be completed approximately 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 statistician, and the coordinating Investigator by provision of their signatures.

The results from this study will be submitted for publication and made available through an on-line clinical results database. 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 Investigators. The two coordinating Investigators will have the opportunity to be the first and the last authors and corresponding authors for the main publication, unless they choose otherwise. 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 Investigators 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 Investigators.

16 APPENDICES

Appendix 1: Definitions According to ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

Appendix 2: Karnofsky Performance Status

Appendix 3: Cockroft-Gault Formula

Appendix 4 National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03

Appendix 5: Ophthalmic Examination

Appendix 6: NCCN Clinical Practice Guidelines in Oncology: Antiemesis

Appendix 7: NCCN Clinical Practice Guidelines in Oncology: Anorexia/Cachexia

Appendix 8: Glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing Products (Representative List)

Appendix 9: Summary of Changes and Rationale for Changes to Protocol KCP-330-004

16.1 Appendix 1 – Definitions According to ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient 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 IMP related to any dose administered.

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

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

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

Examples of such events are intensive treatment in an emergency room 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 is one where the nature or severity is not consistent with the applicable product information.

Causality is initially assessed by the Investigator. With respect to the obligation to report and document SAEs (i.e., to regulatory authorities, ethics committees, and other Investigators), 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 ADRs.

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 an SAE. On the other hand, stroke which results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

An SAE occurring during the study or which comes to the attention of the Investigator during the protocol-defined follow-up period, must be reported, whether considered treatment-related or not. In addition, SAEs 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 SAEs, at a minimum the following must be assessed and recorded on the adverse events page of the eCRF: intensity (severity), 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 reporting, please refer to page 10.

16.2 Appendix 2 – Karnofsky Performance Status

100%	Normal, no complaints, no signs of disease
90%	Capable of normal activity, few symptoms or signs of disease
80%	Normal activity with some difficulty, some symptoms or signs
70%	Caring for self, not capable of normal activity or work
60%	Requiring some help, can take care of most personal requirements
50%	Requires help often, requires frequent medical care
40%	Disabled, requires special care and help
30%	Severely disabled, hospital admission indicated but no risk of death
20%	Very ill, urgently requiring admission, requires supportive measures or treatment
10%	Moribund, rapidly progressive fatal disease processes
0%	Death

Source: Karnofsky DA, Burchenal JH. The Clinical Evaluation of Chemotherapeutic Agents in Cancer. In: MacLeod CM (Ed), Evaluation of Chemotherapeutic Agents. Columbia Univ Press 1949:196

16.3 Appendix 3 – Cockroft-Gault Formula

Calculated CL_{CR} (ml/min) =

$$\frac{[(140 - \text{patient's age in years}) \times \text{patient's actual body weight in kilograms}]}{72 \times \text{patient's serum creatinine (in mg/dL)}} *$$

*: x 0.85 for females

Calculated CL_{CR} (ml/min) =

$$\frac{[(140 - \text{patient's age in years}) \times \text{patient's actual body weight in kilograms}] \times K*}{\text{Patient's serum creatinine (in } \mu\text{mol/L)}}$$

K*: 1.23 for males, 1.05 for females

16.4 Appendix 4 – NCI-CTCAE version 4.03

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

16.5 Appendix 5 Ophthalmic Examination

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

The examination is to include the following:

Prior to dilation:

- best corrected visual acuity
- slit lamp examination
- tonometry

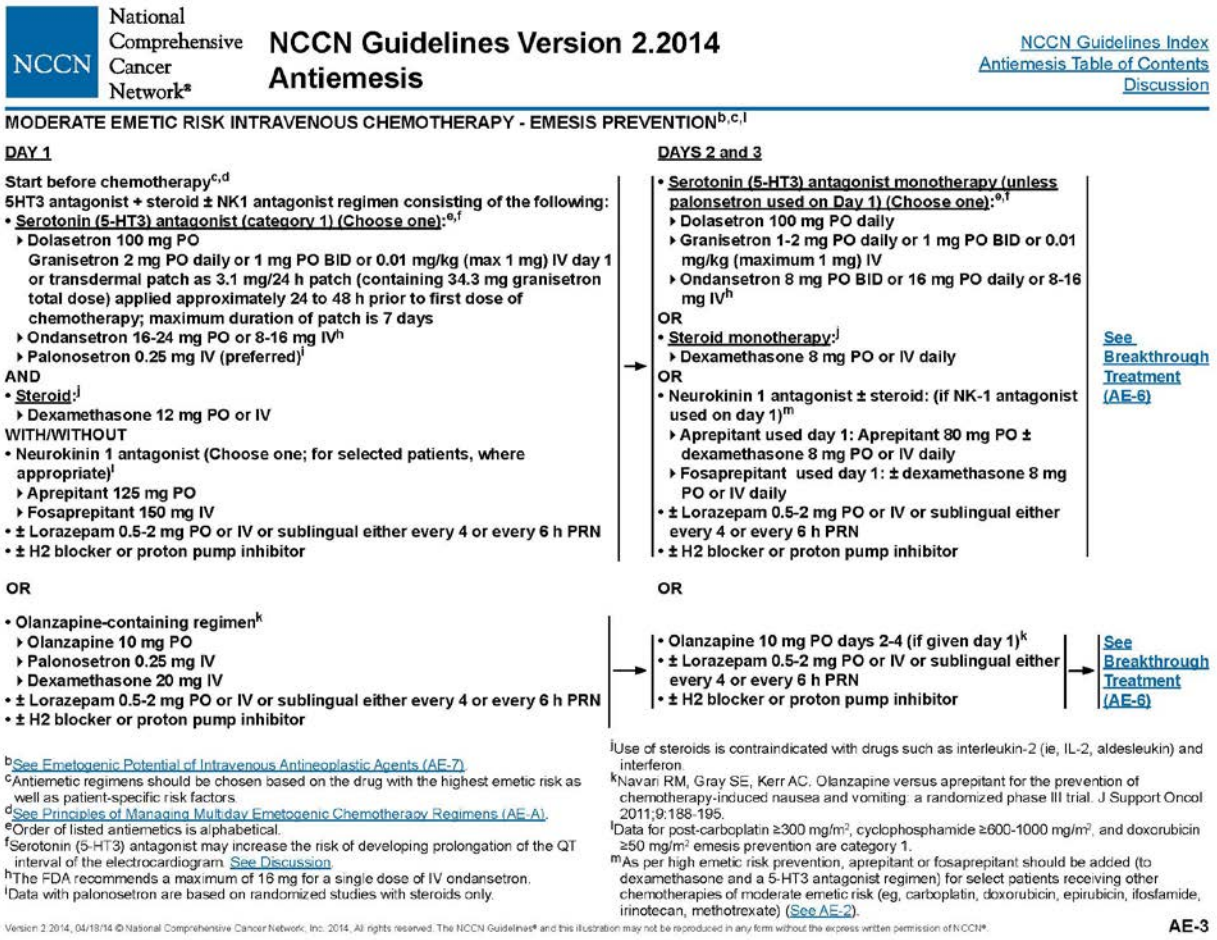
Following dilation:

- fundoscopy
- slit lamp examination to document lens clarity

If a cataract/lens opacity is seen during the examination for newly enrolling patients or enrolled patients for whom no cataract/lens opacity have been detected to date, the cataract/lens opacity will be graded according to a Grade 1-4 system (modified from Optometric Clinical Practice Guideline: Care of the Adult Patient with Cataracts: available on the American Optometric Association website: www.aoa.org). However, patients enrolled under a prior version of the protocol who had detectable cataracts graded according to the LOCS III will continue to have their cataracts graded according to LOCS III and will not switch to the Grade 1-4 scale.

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

16.6 Appendix 6 NCCN Clinical Practice Guidelines in Oncology: 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)[i]

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

WITH/WITHOUT
- Neurokinin 1 antagonist (Choose one; for selected patients, where appropriate)[l]
  - 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.
[i] Data with palonosetron are based on randomized studies with steroids only.
[j] Use of steroids is contraindicated with drugs such as interleukin-2 (ie, IL-2, aldesleukin) and interferon.
[k] Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. J Support Oncol 2011;9:188-195.
[l] Data for post-carboplatin ≥300 mg/m², cyclophosphamide ≥600-1000 mg/m², and doxorubicin ≥50 mg/m² emesis prevention are category 1.
[m] As per high emetic risk prevention, aprepitant or fosaprepitant should be added (to dexamethasone and a 5-HT3 antagonist regimen) for select patients receiving other chemotherapies of moderate emetic risk (eg, carboplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, methotrexate) (See AE-2).

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AE-3

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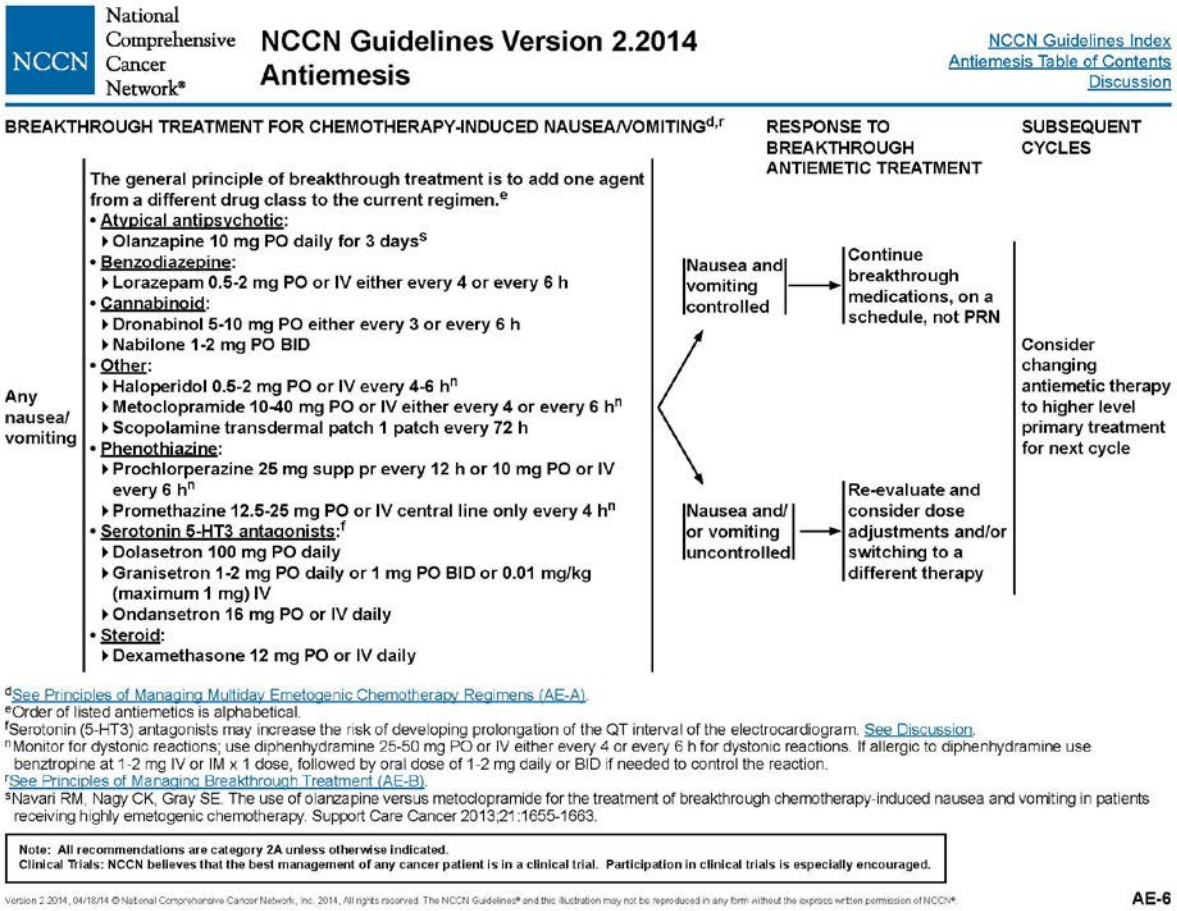

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BREAKTHROUGH TREATMENT FOR CHEMOTHERAPY-INDUCED NAUSEA/VOMITING[d,r]

RESPONSE TO BREAKTHROUGH ANTIEMETIC TREATMENT

SUBSEQUENT CYCLES

Any nausea/ vomiting

The general principle of breakthrough treatment is to add one agent from a different drug class to the current regimen.[e]

- Atypical antipsychotic:
  - Olanzapine 10 mg PO daily for 3 days[s]
- Benzodiazepine:
  - Lorazepam 0.5-2 mg PO or IV either every 4 or every 6 h
- Cannabinoid:
  - Dronabinol 5-10 mg PO either every 3 or every 6 h
  - Nabilone 1-2 mg PO BID
- Other:
  - Haloperidol 0.5-2 mg PO or IV every 4-6 h[n]
  - Metoclopramide 10-40 mg PO or IV either every 4 or every 6 h[n]
  - Scopolamine transdermal patch 1 patch every 72 h
- Phenothiazine:
  - Prochlorperazine 25 mg supp pr every 12 h or 10 mg PO or IV every 6 h[n]
  - Promethazine 12.5-25 mg PO or IV central line only every 4 h[n]
- Serotonin 5-HT3 antagonists:[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 16 mg PO or IV daily
- Steroid:
  - Dexamethasone 12 mg PO or IV daily

Nausea and vomiting controlled → Continue breakthrough medications, on a schedule, not PRN

Nausea and/ or vomiting uncontrolled → Re-evaluate and consider dose adjustments and/or switching to a different therapy

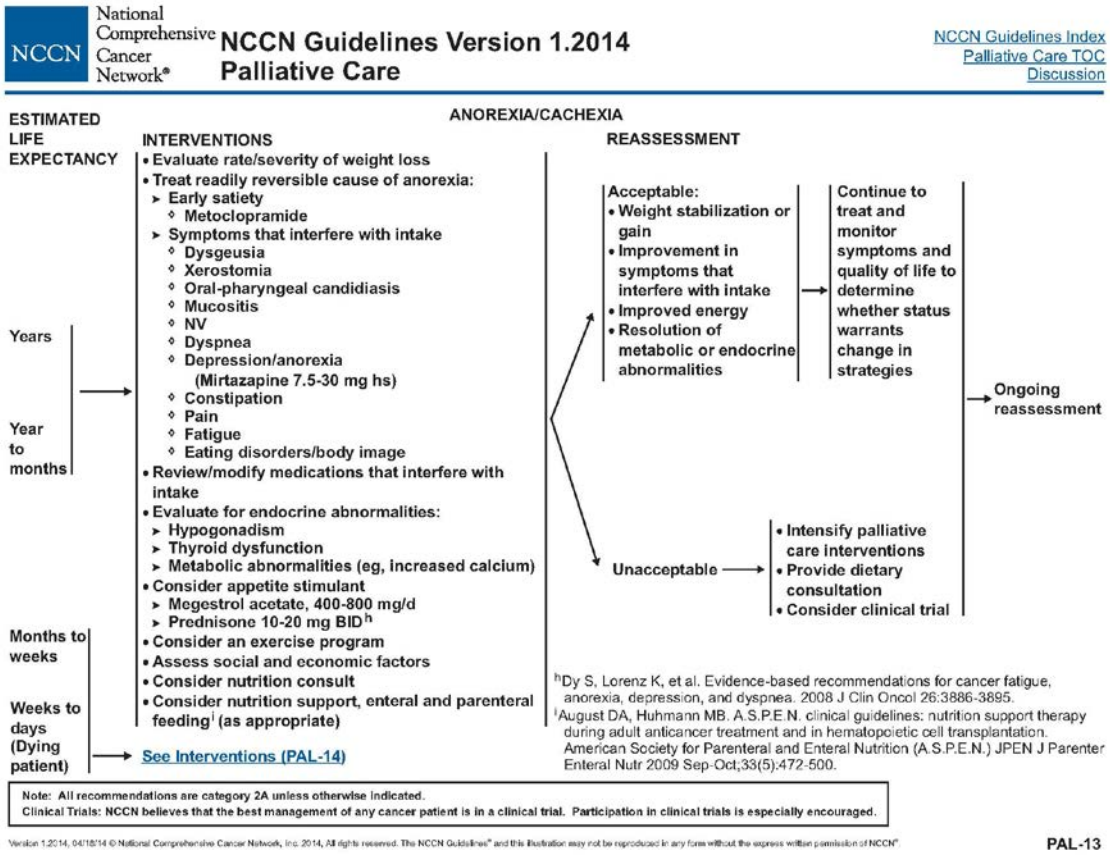
Consider changing antiemetic therapy to higher level primary treatment for next cycle

[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.
[n] Monitor for dystonic reactions; use diphenhydramine 25-50 mg PO or IV either every 4 or every 6 h for dystonic reactions. If allergic to diphenhydramine use benztropine at 1-2 mg IV or IM x 1 dose, followed by oral dose of 1-2 mg daily or BID if needed to control the reaction.
[r] See Principles of Managing Breakthrough Treatment (AE-B).
[s] Navari RM, Nagy CK, Gray SE. The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Support Care Cancer 2013;21:1655-1663.

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.

AE-6

16.7 Appendix 7 NCCN Clinical Practice Guidelines in Oncology: Anorexia/Cachexia



16.8 Appendix 8 Glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing Products (Representative List)

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

16.9 Appendix 9 Summary of Changes and Rationales for Changes to Protocol KCP-330-004

16.9.1 Summary and Rationale for Changes to Version 5.0 Protocol KCP-330-004 Karyopharm Therapeutics Inc

A Phase 2 Study Evaluating the Efficacy and Safety of Selinexor (KPT-330) in Patients with Recurrent Gliomas

Clinical Trial Protocol No	**Sponsor Protocol No. KCP-330-004**
Development Phase:	Phase 2
Investigational Product:	Selinexor
Indication:	Glioblastoma
Sponsor:	Karyopharm Therapeutics Inc.
Drug Discoverer:	Karyopharm Therapeutics Inc.
Sponsor Address:	85 Wells Avenue Newton, MA 02459 USA

***From**: Version 5.0 dated 01 July 2015*
***To**: Version 6.0 dated 13 November 2015*

Summary and Rationale for Changes

The clinical study protocol KCP-330-004, A Phase 2 Study Evaluating the Efficacy and Safety of Selinexor (KPT-330) in Patients with Recurrent Gliomas, has been amended by the Sponsor for the following reasons:

- To eliminate Arms E and F (which were introduced in the last protocol amendment, but did not yet contain enrolled patients) as these arms are not going forward due to budgetary limitations.
- To add an exclusion criterion requiring patients not to have undergone major surgery within four weeks prior to Cycle 1 Day 1.

The revised protocol Version 6.0 dated 13 November 2015 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

Descriptions of the key changes that have been made to protocol KCP-330-004 Version 6.0 from the previous Version 5.0, including rationales for the changes, are listed below.

Administrative

- Updated the version number and date of the protocol from Version 5.0 dated 01 July 2015 to Version 6.0 dated 13 November 2015. (**Modified sections**: Global)
- Removed Ozmosis and GSO mbH as contacts for reporting of SAEs and pregnancies by the sites. Ozmosis was incorrectly added as the contact for reports for North America in Version 4.0 of the protocol. The Pharmacovigilance Department at Karyopharm Therapeutics Inc. will now receive reports for both the EU and North America. (**Modified sections**: Information to be provided regarding SAEs, and Sections 7.2 and 7.6)
- Removed GSO mbH as a contract research organization and replaced with Karyopharm Therapeutics Inc. (**Modified sections**: Title Page, Contact Addresses, Glossary of Abbreviations, and Sections 3.2, 7.8, 9 and 15)
- CCI [redacted]

Study Design

- Eliminated Arms E and F (which had been introduced in the last protocol amendment, but did not yet contain enrolled patients) because these arms are being removed from the study, due to budgetary limitations. (**Modified sections**: Global)
- Revised the end of study definition to clarify that the study will continue until the last patient in the study has died, has been off study treatment for 12 months, has been lost to follow-up, or has withdrawn consent, whichever occurs first. (**Modified sections:** Synopsis and Section 5.2.6)

Inclusion/Exclusion Criteria

- Added an exclusion criterion requiring patients not to have undergone major surgery within four weeks prior to Cycle 1 Day 1. (**Modified sections**: Synopsis and Section 4.3)

Background

- Updated the number of patients (from 900 to > 1,100) exposed to selinexor in order to be consistent with the most recent version of the Investigatgor's Brochure (as of 31 May 2015). (**Modified section**: Section 1.1.2.2).
- Updated the number of patients (from 650 to 730) whose safety results have been analyzed to be consistent with the most recent version of the Investigatgor's Brochure (as of 31 May 2015). (**Modified sections**: Sections 1.1.2. and 6.5.2).
- Updated the reported frequencies of the most common AEs to be consistent with the most recent version of the Investigatgor's Brochure (as of 31 May 2015). (**Modified section:** Section 1.1.2.2).
- Replaced "Figure 2: Overview of Study Design" to reflect the elimination of Arms E and F. (**Modified section**: Section 3.1.1)

Classification of Adverse Events by Causality

- Revised the definitions in the Classification of Adverse Events by Causality table for clarity. (**Modified section:** Table 7)

Declaration of Helsinki

- Deleted statement concerning the Declaration of Helsinki because it is not applicable to this study. However wording was retained that requires Investigators to comply with international standards for GCPs. (**Modified section:** Section 10.1)

Study Reporting

- Added text to explain that one or more interim CSRs may be submitted to regulatory authorities, in addition to the final CSR. (**Modified section:** Section 15)

16.9.2 Summary and Rationale for Changes to Version 4.0 Protocol KCP-330-004 Karyopharm Therapeutics Inc.

A Phase 2 Study Evaluating the Efficacy and Safety of Selinexor (KPT-330) in Patients with Recurrent Gliomas

Clinical Trial Protocol No	**Sponsor Protocol No. KCP-330-004**
Development Phase:	Phase 2
Investigational Product:	Selinexor
Indication:	Glioblastoma
Sponsor:	Karyopharm Therapeutics Inc.
Drug Discoverer:	Karyopharm Therapeutics Inc.
Sponsor Address:	85 Wells Avenue Newton, MA 02459 USA

***From**: Version 4.0 dated 23 March 2015*
***To**: Version 5.0 dated 01 July 2015*

Summary and Rationale for Changes

The clinical study protocol KCP-330-004, A Phase 2 Study Evaluating the Efficacy and Safety of Selinexor (KPT-330) in Patients with Recurrent Gliomas, has been amended by the Sponsor to incorporate changes suggested by the Investigators and internally, to provide clarity to eliminate inconsistencies between sections, and to correct prior errors.

The revised protocol Version 5.0 dated 01 July 2015 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

Descriptions of the key changes that have been made to protocol KCP-330-004 Version 5.0 from the previous Version 4.0, including rationale for the changes, are listed below.

Administrative

- Updated the version number and date of protocol from Version 4.0 dated 23 March 2015 to Version 5.0 dated 01 July 2015. (**Modified sections**: Global)
- Updated start date to January 2014 because sites did not start the study until Protocol Version 2.0 was approved. (**Modified section:** Synopsis [Start date])
- Updated time for enrollment to approximately 36 months. (**Modified sections:** Synopsis [Duration of treatment] and Section 3.2)
- Changed "and other brain cancers" to "gliomas" to avoid confusion with metastases. (**Modified sections:** Global)
- Clarified that randomization will be performed via the EDC system (**Modified section:** Section 3.2)

Background

- Updated side effects, selinexor background information, preclinical data, CCI [redacted] and number of patients treated with selinexor based on information in the Selinexor/KPT-330 IB v 4.0 (April, 2015). (**Modified sections:** Sections 1.1.2, 1.1.2.1, 1.1.2.2.1, 1.1.2.2.2, and 6.5.2)

Study Design

- CCI [redacted]
- CCI [redacted]
- Revised the end of study definition to clarify that the study will continue after collection of data for the primary analysis (6mPFS). (**Modified sections:** Synopsis [Duration of study] and Section 5.2.6.
- Revised the mITT population to include patients who discontinued treatment prior to the first post-baseline assessment due to death, toxicity, or disease progression. The change

was made to take a more conservative approach by including patients who do not have at least one post-dosing efficacy evaluation due to death, toxicity, or disease progression in the population that will be used for primary analyses of efficacy. (**Modified section:** Section 8.3.1)

- CCI
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Treatments

- Changed dosing frequency of selinexor from twice weekly during Weeks 1-3 of each 4-week cycle to twice weekly during Weeks 1-4 of each cycle for arms with twice weekly dosing. During discussions with Karyopharm medical monitors, Investigators indicated that they believed that some patients could benefit from dosing during Week 4, especially if they were tolerating the drug well and did not require a dosing break to mitigate side effects. The protocol (Section 6.3) includes provisions for doses to be skipped intermittently to address side effects, providing flexibility to the Investigators to modify dosing frequency as necessary. Patients who are currently being treated twice weekly for Weeks 1-3 under a previous version of the protocol may, at the discretion of the investigator, have the frequency of selinexor dosing increased to twice weekly for Weeks 1-4. (**Modified sections:** Synopsis [Planned sample size, Treatment plan], Table 1, Figure 2, Sections 1.2, 2.3, 3.1, 3.1.1, 3.1.2, 6.2.1.2, 6.3 and 6.5.2.

Study Assessments

- Provided additional detail for the neurological examinations to improve consistency across sites and patients. A complete neurological examination is to be performed at screening and the End of Treatment visit. Neurological examinations during the study should be symptom directed. Any neurological deficits noted during the baseline exam must be followed at

subsequent visits. Any new neurological complaints reported by the patient and any deficits observed by the investigator should be assessed and followed at subsequent visits. (**Modified sections:** Table 1 and Sections 5.2.1, 5.2.2, and 5.2.3)

- CCI [redacted]
- Modified the description of the Ophthalmic Examination in Appendix 5 to include more information on ophthalmic examination, including replacement of the Lens Opacities Classification System III (LOCS III) cataract grading system with a 1-4 grading system for newly enrolling patients and enrolled patients for whom no cataracts have been detected to date. (**Modified sections:** Synopsis [Safety assessments], Table 1 and Sections 5.2.1 and 16.6)
- Added urine pregnancy testing as clinically indicated during the study as a safety measure to provide additional monitoring for pregnancies. (**Modified section:** Table 1)

Inclusion/Exclusion Criteria

- Revised inclusion criterion #1a to clarify that the patient's brain tumor must be diagnosed as GBM at first diagnosis. This change was made to avoid the inclusion of patients with lower grade tumors that at are histologically GBM at the time of the patient's second surgery. (**Modified sections**: Synopsis [Study populations, Inclusion criteria], Section 4.2)
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Revised inclusion criterion #8 to increase the threshold levels for inclusion for bilirubin (≤ 2 x ULN), AST (≤ 2.5 x ULN), and ALT (≤ 2.5 x ULN). The changes were made to broaden the inclusion requirements for bilirubin, AST, and ALT and align them with other Karyopharm clinical studies.
- CCI [redacted]

CCI [redacted]

Statistical Analysis

- CCI [redacted]
- Added timing for primary analysis (6mPFS) and the secondary analysis for OS for clarity and updated the timing for 6mPFS censoring for survival accordingly. **Modified sections**: Table 1 and Sections 3.1.5, 5.2.5, and 8.4.3).

Prophylactic/Supportive Care

- Updated the supportive care and dose adjustment guidelines for selinexor-related toxicities based on recent safety data. (**Modified section:** Table 6)
- Added subsection for dose reduction for decreased GFR as a safety measure. (**Modified section:** New Section 6.3.1)

Adverse Events

- Removed Appendix 1, "Adverse Event Categories for Determining Relationship to Test Drug" to remove inconsistencies in adverse event reporting information. (**Modified sections:** Section 7.1.1 and Appendix 1)
- Added text to clarify that pregnancy *per se* is not considered an AE but that a medical occurrence observed in the mother or fetus/newborn would be an AE. (**Modified section:** Section 7.6)

16.9.3 Summary and Rationale for Changes to Version 3.0 Protocol KCP-330-004 Karyopharm Therapeutics Inc.

A Phase 2 Study Evaluating the Efficacy and Safety of Selinexor (KPT-330) in Patients with Recurrent Glioblastoma or Other Brain Cancers after Failure of Radiation Therapy and Temozolomide

Clinical Trial Protocol No	**Sponsor Protocol No. KCP-330-004**
Development Phase:	Phase 2
Investigational Product:	Selinexor
Indication:	Glioblastoma
Sponsor:	Karyopharm Therapeutics Inc.
Drug Discoverer:	Karyopharm Therapeutics Inc.
Sponsor Address:	85 Wells Avenue Newton, MA 02459 USA

***From**: Version 3.0 dated July 16, 2014*
***To**: Version 4.0 dated March 23, 2015*

Summary and Rationale for Changes

The clinical study protocol KCP-330-004, A Phase 2 Study Evaluating the Efficacy and Safety of Selinexor (KPT-330) in Patients with Recurrent Glioblastoma or Other Brain Cancers after Failure of Radiation Therapy and Temozolomide, has been amended by the Sponsor to incorporate changes suggested by the Investigators and internally, to revise reporting for cerebellar toxicities of Grade 3 or higher as requested by the FDA, to provide clarity to eliminate inconsistencies between sections, and to correct prior errors.

The revised protocol Version 4.0 dated March 23, 2015 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

Descriptions of the key changes that have been made to protocol KCP-330-004 Version 4.0 from the previous Version 3.0, including rationale for the changes, are listed below.

Administrative

- Internal changes suggested by the Sponsor to provide clarity and to eliminate inconsistencies between sections, and to correct prior errors. (**Modified sections**: Global)
- Updated the version number and date of protocol from Version 3.0 dated 16 Jul 2014 to Version 4.0 dated 23 Mar 2015. (**Modified sections**: Global)
- Minor corrections to grammar throughout. (**Modified sections**: Global)
- Updated Sponsor address from 2 Mercer Road, Natick, MA 01760 to 85 Wells Avenue, Newton, MA 02459. (**Modified sections:** Global)
- Corrected titles of protocol approvers. (**Modified section:** Approval of the Protocol)
- Moved Summary and Rationale for Changes for Version 2.0 to Version 3.0 (previous Section 1) to a new appendix (Appendix 16.10.2). Section numbering has changed, accordingly. Also, added the Rationale for Changes for Version 1.0 to Version 2.0 as a new appendix (Section 16.10.3) for consistency of presentation across protocols. (**Modified sections:** Sections 1 and 16, and global change to section numbering)
- Updated start date to July 2013. (**Modified section**: Synopsis [Start date])
- Added PPD at Ozmosis Research Inc. as the contact person for SAEs and pregnancies at North American sites and provided her phone and fax numbers. (**Modified sections**: Information to be provided regarding SAEs/pregnancy, Sections 7.2 and 7.6)
- Updated number of sites participating in the trial to "approximately 6." (**Modified sections**: Synopsis [Total number of sites] and Section 3.3)
- Minor editorial revisions for Appendix 2 (ICH Guidance on Clinical Data Management) to remove outdated wording related to reporting of SAEs that occur within three weeks of stopping treatment and to align the information to be included for SAEs in the eCRF with the requirements of the protocol. (**Modified section**: Section 16.3)

Synopsis

- Removed all references to the protocol body within the synopsis and replaced with relevant text as needed for clarity. The synopsis is considered a stand-alone document and should not contain references to sections in the protocol body. (**Modified section**: Synopsis)
- Replaced text related to study treatment with durations for enrollment, treatment periods, and the study. (**Modified sections**: Synopsis [Duration of study, Sections 3.1.3 and 3.2])
- Added details related to measurement of disease status for clarity. (**Modified section**: Synopsis [Study procedures])
- Added details related to safety assessments for clarity. (**Modified section**: Synopsis [Safety assessment)])

Background and Rationale

- Condensed and rearranged background sections to align with current information on selinexor, based on recent Phase 1 and Phase 2 clinical trial data. Section 2.1.2, Nuclear Export from Version 3.0 was replaced with Section 1.1.2, Selinexor. Section 2.1.3, Selinexor Mechanism of Action and Preclinical Summary from Version 3.0 was replaced with Section 1.1.2.1, Preclinical Data. Section 2.1.4, Selinexor Clinical Summary from Version 3.0 was replaced with Section 1.1.2.2, Clinical Data that includes a subsection on reproductive risks. Figure 3 and text related to preclinical response curves were removed from Section 2.1.5, XPO1 and Selinexor in HGG from Version 3.0. Also, deleted outdated statements on CYP inhibition/substrates in Section 6.4. (**Modified sections:** Sections 1.1.2, 1.1.3, and 6.4)

Selinexor Dosing

- Changed to flat dosing: 60 mg twice weekly during Weeks 1-3 of each 4-week cycle (Arms CCI B, C, CCI) and 80 mg once weekly (Arm D). The revised doses are based on the analysis of prolonged dosing results in KCP-330-002: a dose of 35 mg/m^2 (~60 mg) twice weekly had acceptable efficacy and improved long-term tolerability and a dose of 50 mg/m^2 (~85 mg) twice weekly was tolerated and cleared DLT evaluation. CCI [redacted]
- CCI [redacted]
- Added description and storage information for the new tablet formulation (20 mg tablets in blister packs) that the initial drug product for the study (10 and 25 mg tablets in bottles) will transition to when supplies become available. (**Modified section:** Section 6.2.1.1)
- Revised pre-specified dose/schedule modifications for adverse events related to study drug. (**Modified sections:** Section 6.3, Table 6)
- Updated therapeutic range for selinexor from "12 mg/m^2 to 50 mg/m^2 orally twice weekly" to "6 mg/m^2 to ≥ 60 mg/m^2 (approximately 10 mg to 120 mg) orally" based on recent Phase 1 and Phase 2 clinical trial data. (**Modified section:** Section 6.3)

- Revised dose adjustments with changes in BSA to reflect flat dosing and removed rounding dosing guidelines based on BSA. Patient BSA will be still be assessed to ensure that the 60 mg or 80 mg dose does not result in a dose >70 mg/m^2. If a patient's dose will exceed this limit, the Investigator should contact the medical monitor prior to administration to discuss appropriate dosing. (**Modified section:** Section 6.3.2; Deleted section: Appendix 7 from Version 3.0)
- CCI [redacted]
- CCI [redacted]
- Clarified wording for missed doses. (**Modified section:** Section 6.3.3)

Study Design

- As approximately half of the patients in Arm B had a 1-level dose reduction, enrollment in Arm B was stopped to explore alternative dosing in Protocol Version 4.0 to potentially improve tolerability. An assessment of the efficacy data prior to the formal PFS analysis for the first 12 patients in Arm B revealed clinically meaningful efficacy in this challenging patient population. Two patients in Arm B have had PRs with PFS >160 days. CCI [redacted] Based on the data to date, the study team has concluded that patient enrollment should continue notwithstanding the results of formal PFS analysis, but at a reduced starting dose. Although enrollment in Arm B has been stopped, the study will continue with two new arms (Arms C and D, both using Simon's two-stage design) with flat dosing. (**Modified sections:** Synopsis [Study population, CCI [redacted] Planned sample size, Treatment plan, Statistical considerations, CCI [redacted]], Sections 1.2, 3.1, 3.2, 4.1, 6.3, 8.2.1, and 8.5, Table 1, Figure 2)
- Added Arms C and D to compare the efficacy, tolerability and safety of selinexor (60 mg) administered twice weekly during Weeks 1-3 of each 4-week cycle (Arm C) with selinexor (80 mg) administered once weekly (Arm D). (**Modified sections:** Synopsis [Study design, CCI [redacted] Planned sample size, Inclusion criteria, Exclusion criteria, Treatment plan, Statistical considerations, Randomization procedure (new section), and CCI [redacted] Sections 1.2, 2.3, 3.1, 3.1.2, 3.2, 3.3, 4.1, 4.2, 4.3, 5, 5.1.1, 5.1.2, 6.2.1.2, 8.2.1, 8.2.2, 8.3.1, 8.3.2, and 8.5, Tables 1 and 5, Figure 2)
- Added 1:1 randomization for new Arms C and D. (**Modified sections:** Synopsis [Study design, Treatment plan, and Randomization procedure (new section)], Sections 3.1, 3.2, 5, and 8.1, Tables 1 and 5, Figure 2)

- CCI [redacted]
- Updated the planned number of patients from 50 to 115. (**Modified sections:** Synopsis [Planned sample size], Section 3.3)
- CCI [redacted]

Study Assessments

- Clarified timing and purpose of elective PET scans. (**Modified sections:** Table 1, Sections 5.2.1 and 5.2.2)
- Reduced the frequency of ECGs during the treatment phase to "as clinically indicated." Cardiac abnormalities are not considered to be a safety concern. More than 550 patients have received selinexor as of December 15, 2014 and no significant cardiac significant abnormalities have been reported. The frequency of ECGs has been reduced to align with the schedule used in more recent trials and to avoid unnecessary testing. (**Modified sections:** Table 1, Sections 5.2.2)
- CCI [redacted]
- Clarified that the markers listed for immunohistochemistry and PCR testing for fixed biopsy samples from patients in the Surgical Arm are potential markers that may be tested. (**Modified section:** Section 5.1.2)
- Deleted functional proteomics evaluation by reverse phase protein array because the evaluation is no longer planned for fixed biopsy samples from patients in the Surgical Arm. (**Modified section:** Section 5.1.2)
- CCI [redacted]

- Deleted CCI blood draws for Arm B because enrollment in Arm B has been stopped and additional CCI data are not needed. CCI [redacted]
- CCI [redacted]
- Specified that the ophthalmologic exam is to be performed by an ophthalmologist, specified ETDRS and Snellen's as methods for determining best corrected visual acuity, and added the LOCS III as Appendix 6. (**Modified sections:** Sections 5.2.1 and 16.6, Table 1)
- Revised the timing of the lab assessments to include a window of 3 days prior to the scheduled visit. (**Modified section:** Table 1)
- Added that all cases of cerebellar toxicities of Grade 3 or higher must be captured as an SAE and reported to the regulatory authorities, IRBs, ECs, and Investigators in an expedited Safety Report within 7 days of awareness of the event. The FDA requires these events to be reported within 7 days of the site and Sponsor notification of the event. (**Modified section:** Section 7.1.3)
- Aligned Schedule of Assessments with study procedures and added windows for end of treatment, follow-up before progression of disease, and survival follow-up. (**Modified sections:** Sections 3.1.5, 5.2.1, 5.2.2, 5.2.3, 5.2.4, and 5.2.5, Table 1)

Inclusion/Exclusion Criteria

- CCI [redacted]
- Revised inclusion criterion #6 to specify that the CT/MRI for measurable disease assessment must take place within 14 days of starting treatment instead of within 21 days of starting treatment. For non-surgical patients the CT/MRI should be no more than 2 weeks old at treatment start to ensure an accurate baseline. (**Modified sections:** Synopsis [Inclusion criteria], Sections 4.1, 4.2, 5.1.1, and 5.2.2, Table 1)
- Revised inclusion criteria #9 and #10 to align with updated standard text for prevention of pregnancy for consistency across protocols (**Modified sections:** Synopsis [Inclusion criteria], Sections 4.2)

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Added exclusion criterion #18 to exclude patients with BSA < 1.2 m^2 from being randomized into Arms C and D to prevent patients randomized to Arm D (80 mg once weekly) from exceeding the maximum allowable selinexor dose of 70 mg/m^2. (**Modified sections:** Synopsis [Exclusion criteria] and Section 4.3)

Statistical Analysis

- Added a window of ± 14 days around the 6-month visit for the primary analysis of rate of PFS to account for potential differences between the window for evaluations and the actual visits for the patients and provide for the inclusion of all clinically meaningful patient data in the analysis. This window will be applied to the calculation of the point estimate of 6mPFS. Actual times of events (progression or death) will be used for the Kaplan-Meier statistical summary of PFS. (**Modified sections**: Synopsis [Primary analysis parameter] and Section 8.4.3)
- Revised analyses for addition of Arms C, D, E, and F. (**Modified sections:** Synopsis [Planned sample size, Statistical considerations, and Sample size calculation] and Sections 8.1, 8.2, 8.3, 8.4, and 8.5)

Prophylactic/Supportive Care

- Revised the dose adjustment guidelines for selinexor-related toxicities to include supportive treatment based on the event and the severity of the event. These changes were made to consolidate the recommendations for AE management in a single table. Added dose modification guidelines for anemia as a separate row. (**Modified sections:** Section 6.3, Table 6)
- Revised text allowing dose re-escalation to align with Version 2.0. The text was revised in Version 3.0 to align with the requirement for prophylactic therapy added in Amendment 2. However, in the current amendment prophylactic therapy has been replaced with supportive care guidelines. (**Modified section:** Section 6.3)

- Revised selinexor dose reduction in the setting of infection to recommend that dexamethasone should be adjusted per institutional guidelines and that adrenal suppression should be considered. (**Modified section:** Section 6.3.1)
- Replaced prophylactic therapy (Section 6.2.1 in Version 3.0) with required and recommended supportive care guidelines (Section 6.5). Required supportive care includes administration of a 5-HT3 antagonist and recommended supportive care includes glucocorticoids, appetite stimulants, and centrally acting agents. These changes were made based on clinical experience in ongoing Phase 1 and Phase 2 clinical studies. Dexamethasone is no longer required supportive care but rather a supportive care option. Section 7.5 Supportive Care from Version 3.0 (now Section 6.5 Supportive Care Guidelines) was re-ordered for clarity, to reflect that much of the information in the text in Version 3.0 is now in Table 6. (**Modified sections**: Sections 1.1.2, 5.2.1, 5.2.2, 6.3, 6.3.1, and 6.5, Table 6)
- Replaced "Liver enzyme increase" (Section 7.5.7 in Version 3.0) with "Liver Function Test Abnormalities" (Section 6.5.3) to update supportive measures to be taken in the event of GSH depletion. (**New section:** Section 6.5.3)
- Replaced the use of olanzapine and mirtazapine (Sections 2.1.4, 6.2.1, 7.5.1, and 7.5.3 and Table 6 in Version 3.0) with references to the NCCN clinical practice guidelines in oncology for antiemesis and anorexia/cachexia based on feedback from the FDA. Added NCCN Guidelines for antiemesis as Appendix 7 and anorexia/cachexia as Appendix 8. (**Modified sections:** Section 6.5.2 and Table 6; **New sections:** Sections 16.7 and 16.8)
- Clarified that the use of supportive care is in accordance with institutional guidelines or as recommended in the supportive care and dose adjustment guidelines (Table 6). (**Modified section**: Section 6.4.1.2)

Concomitant Medications

- Revised the text for prevention of pregnancy and related inclusion criteria with updated standard text for consistency across protocols (**Modified sections:** Synopsis [Inclusion criteria], Sections 4.2 and 6.4.1.1)
- Deleted statement allowing warfarin. Concurrent warfarin or other Coumadin-derived anticoagulants are prohibited, as anticoagulants could increase the chance of bleeding in those patients with decreased platelets associated with selinexor. (**Modified section**: Section 6.4.2)
- Concomitant medication guidelines were updated based on recent Phase 1 and Phase 2 clinical trial results and Investigator input. (**Modified section:** Section 6.4.2)
- Removed the acetaminophen (paracetamol) restriction as ongoing clinical safety evaluations on the use of selinexor in combination with acetaminophen (paracetamol) have not shown any significant clinical or laboratory abnormalities with doses of acetaminophen (paracetamol) up to 1 gram and selinexor up to 55 mg/m^2 (approximately 80-100 mg). (**Modified sections:** Sections 6.4 and 6.4.2)

- New guidance regarding GSH-, SAM-, or NAC-containing products was added, along with a new Appendix 9 listing representative products. These changes were based on FDA recommendations. (**Modified sections:** Sections 6.4.2 and 16.9)

16.9.4 Summary and Rationale for Changes to Version 2.0 Protocol KCP-330-004 Karyopharm Therapeutics Inc.

A Phase II, Two-Tier Study Evaluating the Efficacy and Safety of Selinexor (KPT-330) in Patients with Recurrent Glioblastoma after Failure of Radiation Therapy and Temozolomide

Clinical Trial Protocol No	**Sponsor Protocol No. KCP-330-004**
Development Phase:	Phase 2
Investigational Product:	Selinexor
Indication:	Glioblastoma
Sponsor:	Karyopharm Therapeutics Inc.
Drug Discoverer:	Karyopharm Therapeutics Inc.
Sponsor Address:	85 Wells Avenue Newton, MA 02459 USA

***From**: Version 2.0 dated November 15, 2013*
***To**: Version 3.0 dated July 16, 2014*

The clinical study protocol KCP-330-004, A Phase 2, Two-Tier Study Evaluating the Efficacy and Safety of Selinexor (KPT-330) in Patients with Recurrent Glioblastoma after Failure of Radiation Therapy and Temozolomide, has been amended by the Sponsor to incorporate changes suggested internally and to provide clarity to eliminate inconsistencies between sections, and to correct prior errors.

The revised protocol Version 3.0 dated July 16, 2014 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A description of the key changes that have been made to protocol KCP-330-004 Version 3.0 from the previous Version 2.0, including rationale for the changes, are listed below.

Administrative

- Internal changes suggested by the Sponsor to provide clarity and to eliminate inconsistencies between sections, and to correct prior errors (**Modified sections**: Global)
- Updated the version number and date of protocol from Version 2.0 dated 15 Nov 2014 to Version 3.0 dated 16 July 2014 (**Modified sections**: Global)
- Updated Sponsor name. Name changed from NPM to Karyopharm. (**Modified section:** Global)
- Minor corrections to grammar throughout (**Modified sections**: Global)
- Updated the electronic mail address to which the patient registration form will be sent from PPD to PPD (**Modified section:** Section 4.2)

Inclusion/Exclusion Criteria

- Revised inclusion criterion # 8 to specify that for bilirubin elevation related to Gilbert's Syndrome bilirubin levels must be < 4 times ULN based on input from study Investigators. (**Modified sections:** Synopsis [inclusion criteria], Section 5.2)
- Revised inclusion criterion # 6 to reflect Measurable disease (according to Response Assessment in Neuro-Oncology [RANO] guidelines, within 21 days of starting treatment instead of within 14 days of starting treatment. (**Modified sections:** Synopsis [inclusion criteria], Section 5.2)
- Revised inclusion criterion #11 to decrease the number of required slides of archived paraffin-embedded tissue that must be available from 20 unstained slides to 10 unstained slides, but if less than 10 the Sponsor must be contacted. This is based on Investigator feedback regarding limited availability of archival tissue. (**Modified sections:** Synopsis [inclusion criteria], Section 5.2)
- Removed inclusion criterion # 12 (the resection of enhancing tumor tissue amount (500 mg) and of non-enhancing tumor tissue amount (300 mg), based on input from study Investigators that specification of tumor quantity is irrelevant as patients undergoing cytoreductive surgery are expected to have sizable tumors and therefore the availability of tissue for analysis will not be an issue. (**Modified sections:** Synopsis [inclusion criteria], Section 4.1, Section 5.2)

- Revised exclusion criterion #2 to specify that the time period from the time of treatment with other chemotherapy or investigational agents must be at least 4 weeks prior to the start of treatment within the study; the option of the time period of 5 half-lives was removed due to the wide variability in half lives of different chemotherapies. (**Modified sections:** Synopsis [inclusion criteria], Section 5.3)
- Revised exclusion criterion #8 to specify that a prior history of DVT or PE is not exclusionary. Patients on the ongoing Phase 1 studies with selinexor have developed cancer related DVT or PE during the study and have continued treatment with selinexor while receiving appropriate DVT treatment with no apparent outward effects. (**Modified sections:** Synopsis [inclusion criteria], Section 5.3)
- Removed the exclusion criterion that specified that patients with body weight significantly below ideal body weight in the opinion of the Investigator are to be excluded. Based on Investigator input that this is irrelevant for patients with advance cancer, especially since the protocol includes required prophylaxis for anorexia. (**Modified sections:** Synopsis [inclusion criteria], Section 5.3)

Study Design

- CCI [redacted]
- CCI [redacted]
- Removed the required accrual of 6-10 patients per site; currently, there is not a requirement for the number of patients to be enrolled at each site. (**Modified Section:** Section 4.3)
- Revised the amount required to be taken with selinexor from 240 mL (8 ounces) to 120 mL (4 ounces). (**Modified sections:** Synopsis [treatment plan], Section 7.2.1.2)
- CCI [redacted]
- Added Wednesday/Friday as an option for dosing days. (**Modified sections:** Synopsis [treatment plan], Section 4.1, Section 4.1.1, Section 7.2.1.2)
- CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- Concurrent Warfarin or other Coumadin-derived anticoagulants are prohibited, as anticoagulants could increase the chance of bleeding in those patients with decreased platelets associated with selinexor. (**Modified section:** Section 7.4.2)

Study Assessments

- Revised the Baseline assessment of Disease Status by MRI imaging of the brain to take place within 21 days prior to start of treatment instead of 14 days prior to start of treatment. (**Modified section**: Section 5.1, Section 6.1.1, Section 6.2.2)
- Revised the time points for the collection of oxygen saturation and coagulation assessments to be collected at screening and at future visits if clinically indicated. (**Modified sections:** Schedule of Assessments, Section 6.2.3)
- Revised the time points for the assessment of urinalysis to be collected at screening and at future visits if clinically indicated. (**Modified sections:** Schedule of Assessments, Section 6.2.2, Section 6.2.3, Section 6.2.4)
- The ophthalmological examination assessment was revised to specify that if a cataract is seen during the examination, the cataract will be graded according to the Lens Opacities Classification System (LOCS III). This change was made to more accurately assess the status of any cataract. (**Modified sections:** Schedule of Assessments, Section 6.2.2)
- Revised the timing of the hematology assessment to include a window of 3 days prior to the scheduled visit. (**Modified sections:** Schedule of Assessments, Section 6.2.1, Section 6.2.3, Section 6.2.4)
- CCI [redacted]
- Revised the suggested timing of MRI scans for patients who discontinued for reasons other than progression of disease to every 8 weeks. (**Modified section:** Section 4.1.4, Section 6.2.5)
- Revised assessment of disease status by MRI to also allow for assessment of disease status by CT. (**Modified sections:** Schedule of Assessments, Section 6.1.1, Section 6.2.2, Section 6.2.3)
- Clarified that whole RNA in leukocytes will be isolated from blood samples for XPO1 inhibition; time points for sample collection was revised to 2 and 4 hours pre- and post-dosing. (**Modified sections:** Schedule of Assessments, Section 6.1.1)
- CCI [redacted]

- Revised the amount of blood that will be collected for blood draws CCI [redacted]. (**Modified sections:** Schedule of Assessments, Section 6.1.2)
- Revised the amount of blood that will be collected for blood draws CCI [redacted]. (**Modified sections:** Schedule of Assessments, Section 6.1.2)

Safety and Tolerability

- Supportive care and prophylactic guidelines were updated based on recent Phase 1 clinical trial results and Investigator input. (**Modified section**: Section 6.2.1)
- Added Classification of Adverse Events by Causality, Table 8 to adverse event section for clarification of AEs related or not related to study drug. (**Modified section:** Section 8.1.1)
- Removed the required collection of medical terms according to NCI-CTC Version 4.03, not as reported by the patient for SAEs. (**Modified section:** Section 8.1.5)
- Updated the safety teleconferences from monthly to regular teleconferences. (**Section modified:** Section 8.8)
- Removed the requirement of grading the toxicity of AEs every 2 weeks for the first 2 cycles and every 4 weeks thereafter (**Modified section:** Synopsis [safety assessment])
- Updated information related to the MTD to specify that escalating beyond 70 mg/m^2 twice weekly is prohibited in any study. Details of these updates to KPT-330 dosing information were documented in a May 20, 2014 addendum to the Investigators Brochure and provided to all Investigators. (**Modified sections:** Section 2.1.4)
- CCI [redacted]
- The dose adjustment guidelines have been updated based on recent results of the Phase 1 clinical trials. (**Modified sections:** Section 7.3.1)
- Updated the electronic mail address to which the SAE forms will be sent from PPD to PPD (**Modified section:** Section 8.2)

Selinexor Dosing

- CCI [redacted]

Table A: Pre-Surgery Dosing Table

Group	No. Of patients	1st dose	2nd dose	3rd dose	Surgery
1	5	Day 1	Day 3	2 hr prior to surgery (Day 8)	Day 8
2	5	Day 1	Day 3	12 hr prior to surgery (Day 7 or 8)	Day 8
3	5	Day 1	Day 3	24 hr prior to surgery (Day 8)	Day 9
4	5	Day 1	Day 3	48 hr prior to surgery (Day 8)	Day 10

- Updated the pre-specified dose/schedule modifications table for adverse events related to study drug from the dose of 50 mg/m^2 twice weekly to once weekly (D1) in order to optimize specific anti-tumor activity and patient's tolerability. (**Modified sections:** 7.3 Table 3)

16.9.5 Summary and Rationale for Changes to Version 1.0 Protocol KCP-330-004 Karyopharm Therapeutics Inc.

A Phase II, Two-Tier Study Evaluating the Efficacy and Safety of Selinexor (KPT-330) in Patients with Recurrent Glioblastoma after Failure of Radiation Therapy and Temozolomide

Clinical Trial Protocol No	**Sponsor Protocol No. KCP-330-004**
Development Phase:	Phase 2
Investigational Product:	Selinexor
Indication:	Glioblastoma
Sponsor:	Karyopharm Therapeutics Inc.
Drug Discoverer:	Karyopharm Therapeutics Inc.
Sponsor Address:	85 Wells Avenue Newton, MA 02459 USA

***From**: Version 1.0 dated September 17, 2013*
***To**: Version 2.0 dated November 15, 2013*

RATIONALE FOR AMENDMENT 1

This protocol has been amended to address comments received after review of the initial protocol by the FDA. The Danish Health and Medicines Agency also requested to clarify the 24-hour reporting requirement for serious adverse events, which is also included in this protocol amendment. This final protocol Version 2.0 supersedes draft Version 1.1 submitted to the Danish Health and Medicines Agency to address their comment. In addition, this amendment also incorporated changes suggested internally by the Sponsor to provide clarity, to eliminate inconsistencies between sections, and to correct prior errors.

These changes include:

- Describing the use of new dosing and the tablet formulation planned for use in this study. Identifies the initial starting dose for all patients at 50mg/m^2.
- Removing the initial protocol provision to allow dose escalation in some patients to 40 mg/m^2 or higher based on 'Investigator's opinion and tolerability'.
- Revising the dose modification criteria in the protocol (Section 6.3) with specific dose levels and schedules in place of 'flexible dose reductions or schedule modifications'.
- Clarifying the dose adjustment guidelines in Table 4 to clearly specify when the study drug should be discontinued in the event of occurrence or recurrence of each toxicity, either at initial occurrence or following dose reduction.
- Clarifying the dose reduction or discontinuation criteria in Table 4 for each toxicity grade.
- Removing the provisions of re-escalating the previously toxic dose after dose reduction for any toxicity.
- Revising the dose modification criteria for thrombocytopenia (to hold the drug for ≥ Grade 3 thrombocytopenia until resolved to ≤ Grade 1 and then resume at a lower dose; specify when to further dose reduce and when to discontinue for recurrent toxicity) and for renal toxicity based on NCI-CTCAE (Version 4.03) criteria for serum creatinine levels.
- Expanding the inclusion criteria to allow enrollment of patients with aspartate aminotransferase (AST) levels less than twice the upper limit of normal (< 2X ULN).
- CCI [redacted]
- CCI [redacted]
- Providing data on the timing of occurrence of thrombocytopenia in relation to study drug administration in Phase I studies.
- Adding ophthalmology examination during the study as clinically indicated in addition to the protocol specified screening ophthalmology examination, based on the adverse event of blurred vision observed in the Phase I studies.

- Clarifying that Investigators are to report SAEs within 24 hours to the Sponsor, or designee, upon notification.

Specific changes, by section, are displayed in the table in **Boldface**. [Note for changes not easily shown in a table, such as changes in the Schedule of Study Events, the original and revised table may be proved in separate pages as attachments that are referenced in the appropriate sections of the table.]

Minor changes to correct typographical and other errors are not shown. A redline version of this document is available upon request.

List of Changes from the initial protocol incorporated into this Amendment 1

Section	Previous Wording	New Wording	Reason for Change
Title Page	Data Management: Ozmosis Inc. Statistics: Ozmosis Inc.	None	A different vendor was chosen.
Protocol version (Date)	Version 1.0, 2013.09.17	Version 2.0, 15 Nov 2013	
Synopsis/ Study Design	• Open label, non-randomized, multicentre, Phase II study • CCI [redacted]	• Open label, non-randomized, multicentre, Phase II study • CCI [redacted]	CCI [redacted] Text also updates the end of treatment for Medical Arm B patients to not limit discontinuation to disease progression alone. This was changed to be consistent with Section 5.4 that provides multiple reasons for possible drug delay or discontinuation.
Synopsis/ Duration of Study	With an expected accrual rate of 2 patients per month, and a total number of 30 patients planned, the anticipated enrollment period is 15 months.	**Selinexor (taken orally) will be given twice weekly for a total of 8 doses per cycle. One cycle is defined as 28 days or 8 doses. For Surgical Arm patients' treatment cycles are defined as beginning with post-operative resumption of therapy. Patients may continue to receive treatment with Selinexor in repeated cycles until they leave the study, as described in Section 5.4. Study drug administration may be delayed for toxicity according to protocol Section 6.3.**	Clarification of patient's experience of duration on study.
Synopsis/ Study Population	Patients with WHO grade IV gliomas (glioblastoma, GBM and subvariants) with recurrent disease, who have failed prior treatment with radiation therapy and temozolomide.	Patients with WHO **Grade 4** gliomas (glioblastoma, GBM and subvariants) with recurrent disease, who have failed prior treatment with radiation therapy and temozolomide **and who meet the inclusion and none of the exclusion criteria are eligible for enrollment.**	Updates the Grade designation to current format and clarifies that inclusion and exclusion criteria must also be met by patients for enrollment in both study Arms.

Section	Previous Wording	New Wording	Reason for Change
CCI			
Synopsis/ Planned Sample Size	*A total of* 30 patients are planned to be enrolled. CCI the remainder will be enrolled in Arm B (medical arm). CCI	Approximately **37** patients are planned to be enrolled. CCI **approximately 30** will be enrolled in Arm B (Medical Arm). **The primary patient populations (ITT and PP) are comprised of Arm B (Medical Arm) patients only.**	CCI
Synopsis/ Inclusion Criteria	[NEW TEXT]	Hepatic function: bilirubin < 1.5 times the upper limit of normal (ULN), ALT < 2.0 times ULN; **AST < 2.0** times ULN	Allows for enrollment of patents with AST levels below 2.0 X the ULN.
Synopsis/Treatment Plan	Patients will receive Selinexor twice weekly (Monday/Wednesday or Tuesday/Thursday) orally at a starting dose of 35 mg/m². *The dose may be titrated as tolerated with a maximum dose of 40 mg/m² and the minimum dose of 5 mg/m² according to dose modification guidelines in the protocol.* One cycle is 28 days or 8 doses. CCI	Patients will receive Selinexor twice weekly (Monday/Wednesday or Tuesday/Thursday) orally at a starting dose of 50 mg/m². One cycle is 28 days or 8 doses. CCI	Dosing information has been revised to better reflect the current protocol amendment and the use of drug tablets in this study.

Section	Previous Wording	New Wording	Reason for Change
	CCI Arm B: Medical cohort [new text] *Up to 23* patients who do not require surgery will be treated with Selinexor twice weekly. Treatment in both arms of the study will continue until disease progression or the development of unacceptable toxicities. *If arm B is fully accrued,* CCI	Arm B: Medical cohort **(ITT and PP populations) Approximately 30 patients** who do not require surgery will be treated with Selinexor twice weekly. Treatment in both arms of the study will continue until disease progression or the development of unacceptable toxicities.	
Schedule of Study Events Notes	8. Full ophthalmologic exam: required at screening and if clinically indicated. The exam can be omitted if the patient cannot cooperate due to factors related to GBM. Prior to dilation: best corrected visual acuity, visual field examination via automated perimetry, tonometry, color vision test. Dilated fundoscopy and slit lamp exam.	8. Full ophthalmologic exam: required at screening and if clinically indicated. The exam can be omitted if the patient cannot cooperate due to factors related to GBM. Prior to dilation: best corrected visual acuity, visual field examination via automated perimetry, tonometry, color vision test. Dilated fundoscopy and slit lamp exam. **This exam may be repeated as clinical indicated throughout the study.** **[The following is New Text]** **10. ECGs to be performed in a supine position as follows: at screening, Cycle 1 Day 1 (pre-dose and 2±0.5hrs post-dose) and Cycle 2 Day 1 (pre-dose and 2±0.5 hrs post-dose). For Cycles 3 and beyond: pre-dose on specified days and at the final visit.** **17. Elective PET-FET will be performed at baseline; pre-treatment; post-**	Changes made to notes to ensure consistency with assessment changes and specific timing provided in this Amendment.

Section	Previous Wording	New Wording	Reason for Change
		treatment, pre-operative and post-operative.	
1.2 Study Rationale	*In the Phase I study KCP-330-002 including patients with advanced solid tumor malignancies, the dose of 35 mg/m² administered twice weekly was chosen for the expansion phase of the study based on the occurrence of DLTs. Evidence for antitumor activity was existent at this dose.* CCI [New Text]	**In the ongoing dose escalation Phase 1 study (KCP-330-002/OZM-043) in patients with advanced solid tumors, a Selinexor dose of 50 mg/m² twice weekly was tolerated and cleared DLT evaluation**. CCI	CCI
2.3 Exploratory Objectives	[New Text]	CCI	CCI

Section	Previous Wording	New Wording	Reason for Change
		CCI [redacted]	
3.1 Overview of Study Design and Dosing Regimen	After screening and registration in the study, patients will receive Selinexor twice weekly (Monday/Wednesday or Tuesday/Thursday) orally at a starting dose of *35 mg/m². The dose may be titrated as tolerated with a maximum dose of 40 mg/m² and a minimum dose of 5 mg/m².*	After screening and registration in the study, patients will receive Selinexor twice weekly (Monday/Wednesday or Tuesday/Thursday) orally at a starting dose **of 50 mg/m². The dose may be reduced due to adverse events related to study drug to a minimum dose of 15 mg/m² once weekly (see Table 3).**	Identifies the increased starting dose based on recent clinical experience.
Same section	CCI [redacted]		
Same section	*A minimum* CC [redacted] *123 patients* will be enrolled in arm B. *If arm B is fully accrued,* CCI [redacted]	**Approximately** CCI [redacted] **30** patients will be enrolled in Arm B. **Formal statistical analyses for efficacy will pertain only to non-surgical (Arm B) patients.** CCI [redacted]	Clarifies enrollment changes and the statistical analysis planned for each Arm.
3.3 Sites	A total of 3-5 sites will participate in the study. Recruitment will be competitive with an expected accrual of 6-10 patients at each site until the *planned total number of 30 patients is reached.*	A total of 3-5 sites will participate in the study. Recruitment will be competitive with an expected accrual of 6-10 patients at each site until the planned total number **of approximately 37 patients is reached.**	Clarifies increased planned enrollment.
4.2 Inclusion Criteria	8. … Hepatic function: bilirubin < 1.5 times the upper limit of normal (ULN), ALT < 2.0 times ULN; [New Text]	8. ... Hepatic function: bilirubin < 1.5 times the upper limit of normal (ULN), ALT < 2.0 times ULN; **AST < 2.0 times ULN.**	Clarifies enrollment eligibility based on AST levels obtained at screening.
5.1.1 Tumor Assessment	CCI [redacted]	CCI [redacted]	Changes to identify response for both study Arms.
5.2.1 Required Prophylactic Therapy for All Patients	[New Text]	**Patients will receive prophylactic treatment to prevent anorexia and nausea, which includes:**	Provides detailed information for investigators for prophylactic

Section	Previous Wording	New Wording	Reason for Change
		• Megesterol acetate 160-400 mg daily, 0-3 days before the first dosing day of KPT-330 **OR** **• Dexamethasone 2-4 mg (or equivalent steroid) on days of dosing and the following day. Dexamethasone may be given prior to initiation of dosing or more frequently as needed** **AND** **• Olanzapine 5.0 mg qhs or 2.5 mg bid, 0-3 days before the first dosing day of KPT-330** **OR** **• Mirtazapine 15 mg qd (qpm/phs), 0-3 days before the first dosing day of KPT-330** **If the patient is on steroids coming on the study, megesterol acetate should be added prophylactically to prevent anorexia. If an increased risk of adverse effects due to olanzapine is anticipated, olanzapine can be omitted. However, it is recommended that mirtazapine or other appetite stimulating serotonergic agent be used. Additional standard supportive care agents may be used as needed (prn). Supportive care may be tapered or discontinued in Cycle 2 or later in patients who tolerate Selinexor well in Cycle 1.**	treatment now required in this study.
5.2.2 Screening Procedures (Ophthalmologic Exam)	Full ophthalmologic exam: required at screening and *of clinically indicated.*	Full ophthalmologic exam: required at screening and **if clinically indicated during the treatment phase.**	Clarifies the investigator's option to examine any patient as needed while the study is ongoing.
Same Section (Prophylactic therapy)	[New Text]	**Initiated 0-3 days prior to first Selinexor dose (see section 5.2.1)**	Identifies the new requirement that all patients undergo Prophylactic therapy and its timing.

Section	Previous Wording	New Wording	Reason for Change
6.2.1.1 Drug Name, Formulation and Storage	[New Text]	**Tablets: Selinexor (KPT-330) for oral administration will be supplied in two (2) tablet strengths: 10 and 25 mg. Bottles of 50 tablets per bottle will be supplied for each of the two strengths.**	Describes the tablets by strength dispensed.
6.3 Dose Modifications for Selinexor	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 3 weeks the patient is taken off protocol treatment. 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/m^2 to ≥35mg/m^2 orally twice weekly. At the present time, we cannot predict which patient's tumors will respond to lower doses, nor can tolerability be predicted. Therefore, in order to individualize and optimize therapeutic benefit with this oral SINE XPO1 antagonist, initiation of study therapy will be with a relatively high dose (*35mg/m^2* twice weekly by mouth) of Selinexor. Although this is a high dose, it is below the MTD of oral Selinexor, and we believe will maximize early disease control with good tolerability in the majority of patients. *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. In addition, if a patient is experiencing one or more Grade ≤2 toxicities such as fatigue or anorexia, then 1-2*	Re-escalation of the study drug is **only** allowed as outlined in the sections that apply for the specific toxicity. If toxicity requires a treatment delay of more than 3 weeks the patient is taken off protocol treatment. At the present time, we cannot predict which patient's tumors will respond to lower doses, nor can tolerability be predicted. Therefore, in order to individualize and optimize therapeutic benefit with this oral SINE XPO1 antagonist, initiation of study therapy will be with a relatively high dose **(50mg/m^2 twice weekly by mouth) of Selinexor.** Although this is a high dose, it is below the MTD of oral Selinexor, and we believe will maximize early disease control with good tolerability in the majority of patients. Therefore, in order to optimize specific anti-tumor activity and the patient's tolerability, we will allow for dose and/or schedule modifications as described below (Table 5). **Patients should also be treated aggressively with supportive care to reduce toxicities.**	

Section	Previous Wording	New Wording	Reason for Change
	doses of Selinexor can be held, and then dosing resumed at the current dose. In this last iteration, dosing for e.g., 3 of every 4 weeks may be considered in some patients. In addition, given that 35mg/m^2 is not the MTD of Selinexor (twice weekly 40mg/m^2 and 50mg/m^2 are currently under investigation), we will allow patients with acceptable tolerability who, in the opinion of their treating oncologist, may benefit from a dose escalation in order to derive additional anti-tumor benefit, to increase their dose to 40mg/m^2 or, as ongoing cohorts allow, to higher doses, twice weekly. In conclusion, the wide therapeutic range, lack of significant acute toxicity, reversibility of common adverse effects (anorexia, nausea, fatigue), and the oral dosing regimen of Selinexor allows for flexibility in treating patients with cancer, and as such, individualization of each patient's regimen is easily accomplished.		
6.3.1 Dose Adjustment Guidelines for Selinexor Related Toxicities (Table 4)	[Formerly Table 3]	**[Significant New Text—See Table 4 (Version 2)]**	This table has been heavily revised to reflect more specific dose adjustments, assessments, and timing of adjustments by adverse event class and AE Grade. Too extensive to present here. A line-by-line tracked changes comparison of the table is available upon request.
Same section, last paragraph	*If the patient tolerates a reduced dose for at least four weeks, patients dose may be escalated to the dose they received prior to the reduction after authorization from the medical monitor and Principal Investigator.* [replaced by New Text]	**For patients whose dose has been reduced due to neutropenia, anorexia or fatigue, dose re-escalation is permitted if the institution of supportive care measures has reduced these toxicities to Grade ≤1 or to baseline for at least 2 weeks. Dose re-escalation is only permitted for these adverse events when**	This additional text was added in conjunction with the prophylactic therapy now required by this Amendment.

Section	Previous Wording	New Wording	Reason for Change
		supportive measures have been successful.	
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 clinically stabilized or resolved.* After the infection has stabilized clinically, 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 *in consultation with the Medical Monitor, but the infection must be clinically resolved prior to restarting Selinexor.* Prophylactic antibiotics are permitted concurrently with Selinexor treatment, but are not required.	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.**	Clarifies details of reinitiation of study drug and describes the Sponsor's current clinical experience with opportunistic infections.
6.4 Concomitant Medication and Treatment	*Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. Patients may continue their baseline medication(s). All concomitant medication(s) must be reported in the case report form (CRF). Any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s) and any clinical findings. 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.*	***In vitro* studies show that KPT-330 may have moderate CYP450 inhibition under some circumstances. Concomitant sensitive CYP3A4 substrates or CYP3A4 substrates with a narrow therapeutic index should be used with caution as Selinexor could increase exposure to these substrates. It should be noted, however, that in >200 adult patients with advanced, relapsed/refractory hematologic cancers in ongoing Phase 1 studies, no restrictions on concomitant medications with any CYP3A4 substrates are required. In addition, there are no reports of drug-drug interactions in any of the >200 adult**	This text reflected the latest information available on CPY substrates and caution about using these agents in this study.

Section	Previous Wording	New Wording	Reason for Change
	[Replaced with new text]	**patients with cancers dosed with KPT-330 as of 8 November 2013.**	
6.4.2 Prohibited Medications	Patients should minimize the use of products containing acetaminophen [new text]. 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. [new text] Concurrent therapy with an approved or investigative anticancer therapeutic, other than glucocorticoids as specified herein, is not allowed. 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 to begin in late 2013 and therefore that these recommendations are empirical.*	Patients should minimize the use of products containing acetaminophen **on the days of Selinexor dosing. Acetaminophen should not be taken within 4 hours before or after Selinexor dosing.** 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 **within 4 hours before or after Selinexor dosing.** **Concomitant sensitive CYP3A4 substrates or CYP3A4 substrates with a narrow therapeutic index should be used with caution as Selinexor could increase exposure to these substrates. It should be noted, however, that in >200 adult patients with advanced, relapsed/refractory hematologic cancers in ongoing Phase 1 studies, no restrictions on concomitant medications with any CYP3A4 substrates are required. In addition, there are no reports of drug-drug interactions in any of the >200 adult patients with cancers dosed with KPT-330 as of 8 November 2013.** **Concurrent therapy with an approved or investigative anticancer therapeutic, other than glucocorticoids as specified herein, is not allowed.** **Inactivation of Selinexor by glucuoronidation is the most common**	This information is provided based on the most current clinical experience and to provide better guidance on dose timing if required.

Section	Previous Wording	New Wording	Reason for Change
		metabolic pathway; glutathione conjugation is also significant metabolic pathway in vitro and in vivo, including in humans. 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 preliminary studies of Selinexor in combination with acetaminophen **have shown no significant changes in adverse events relative to Selinexor alone, nor have there been any significant increases in liver function tests in these adult cancer patients pre-dosed with 500-1000mg acetaminophen prior to dosing of Selinexor as of 8 November 2013.**	
6.5.2 Fatigue	Patients with Selinexor associated fatigue should receive Selinexor no more than twice weekly unless the treating physician determines that the benefits outweigh the risks. *If this does not reduce fatigue to an acceptable level, then a dose reduction of 30% should be instituted. Once-weekly dosing (at the higher dose) can also be considered in patients whose disease is highly responsive to Selinexor.[Text deleted]*	Patients with Selinexor associated fatigue should receive Selinexor no more than twice weekly unless the treating physician determines that the benefits outweigh the risks. **If this does not reduce fatigue to an acceptable level, then a dose reduction of one level (see Table 3) should be instituted.**	This section was changed to be consistent with the dose reduction schedule outlined in Table 3 of this Amendment.
6.5.5 Thrombocytopenia	Physicians should consider the use of Intravenous immune globulin in patients with enlarged spleens and thrombocytopenia.	Physicians should consider the use of Intravenous immune globulin in patients with enlarged spleens and thrombocytopenia.	This section was changed to be consistent with the dose reduction in response to specific adverse events displayed in Table 4. These

Section	Previous Wording	New Wording	Reason for Change
	Patients with Selinexor associated Grade ≥3 thrombocytopenia should receive Selinexor no more than twice weekly prior to any dose reduction. Dose reduction of 30% should then be considered. Once-weekly dosing can also be considered in patients whose disease is highly responsive to Selinexor. [Text deleted]		recommendations are based on the latest clinical data available from the Phase 1 trials.
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 *within one working day of knowledge* (expedited reporting).	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 **within 24 hours** (expedited reporting).	This change clarifies the 24-hour reporting deadline. The prior text may have caused some sites to delay reporting beyond the required time window.
7.6 Pregnancy	Pregnancies occurring up to 6 months after the completion of the last treatment cycle must also be reported to the investigator. The investigator must report all pregnancies ***within one working day to GSO mbH.*** GSO mbH will forward all pregnancy reports to the sponsor *within one working day.* The patient should be monitored until the conclusion of the pregnancy.	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**. GSO mbH will forward all pregnancy reports to the sponsor **within 24 hours**.	This text has been changed to reflect to more specific language for SAE reporting and other important required notifications described in this Amendment.
8.1 Trial Design and Hypotheses	This trial has been designed as an open label, non-randomized, 2 arm, multicentre, Phase II study. CCI [redacted] *and patients who do not require surgery will be treated with Selinexor alone (Arm B) until disease progression.* *This hypothesis will be tested using the data from* CCI [redacted] *Arm B* CCI [redacted]	This trial has been designed as an open label, non-randomized, 2 arm, multicentre, Phase II study. CCI [redacted] **Patients in Medical Arm (Arm B) will be treated with Selinexor alone (2 x week)**.	CCI [redacted]
Same section/Secondary objectives	[New text]	CCI [redacted]	

Section	Previous Wording	New Wording	Reason for Change
		CCI	

CCI

Section	Previous Wording	New Wording	Reason for Change
8.3.1 Intent-to-Treat Population	The treated population (ITT) will consist of *all patients who receive at least one dose of study medication and have post-baseline efficacy follow-up information.* This population will include patients with at least one dose of study drug who have discontinued therapy due to toxicity or disease progression and patients who have taken at least one dose of study drug and have died from any cause related to study drug or disease. Patients who die due to causes clearly unrelated to study drug or disease will be censored at the time of death. *Similarly, patients who die during surgery* CCI [redacted] This population will be used for supportive analyses of efficacy; additional sensitivity analyses will be performed on this population, as described in Section 8.4.3.	The treated population (ITT) **will consist of all Arm B patients who receive at least one dose of study medication and have post-baseline efficacy follow-up information.** [redacted] This population will include patients with at least one dose of study drug who have discontinued therapy due to toxicity or disease progression and patients who have taken at least one dose of study drug and have died from any cause related to study drug or disease. This population will be used for primary analyses of efficacy; additional sensitivity analyses will be performed on this population, as described in Section 8.4.3.	This text has been changed to be consistent with the designation of the Medical Arm (Arm B) as the ITT population for this study.

Section	Previous Wording	New Wording	Reason for Change
8.3.2 Per Protocol Population	The per-protocol population will consist *of all patients* who have been administered at least 2 months of study drug treatment, who are compliant with study assessments and have received at least 80% of their prescribed study medication, and who have no major protocol violations that would compromise the assessment of efficacy. Major violations will be determined independently of knowledge of response to therapy. CCI [redacted] This population will be used for *primary* inferences concerning efficacy, however, if there are major differences between the results in this population and those obtained in the ITT population, this will be taken into consideration in the decision to continue to later phase studies, or in the design of further studies. *It is anticipated that the Per-protocol population will provide the basis for the Simon two-stage analysis. [Deleted text]*	The per-protocol population will consist of all **Arm B patients** who have been administered at least 2 months of study drug treatment, who are compliant with study assessments and have received at least 80% of their prescribed study medication, and who have no major protocol violations that would compromise the assessment of efficacy. CCI [redacted]	These changes have been made to confirm that Arm B will comprise the PP population CCI [redacted]
CCI [redacted]			

Section	Previous Wording	New Wording	Reason for Change
8.3.4 Safety Population	The safety population will consist of all patients who have received any amount of study medication. [New text]	The safety population will consist of all patients who have received any amount of study medication. **The safety population will include both the non-surgical and surgical patient groups; analyses of safety will be produced for both the pool of surgical and non-surgical patients, as well as each group separately.**	This text change clarifies the analysis of safety for both Arms, separately and together.
8.4.1 General Statistical Considerations	[New text]	**Formal statistical analyses for efficacy, as described in the following sections and consistent with the Simon two-stage design, will pertain only to the primary patient populations (ITT and PP) that include non-surgical patients. Descriptive statistics only will be presented for the surgical group.**	This new text provides the planned efficacy analysis as limited to the ITT and PP populations. CCI [redacted]
8.4.2 Demographics and Baseline Characteristics	Baseline characteristics include: Performance Status; duration from initial diagnosis; response to previous therapy (Y/N). [New text added]	Baseline characteristics include: Performance Status; duration from initial diagnosis; response to previous therapy (Y/N). **Demographics and baseline characteristics will be summarized separately for non-surgical and surgical patients.**	This text was added to identify the difference in the planned analysis of this parameter for the two study Arms.

Section	Previous Wording	New Wording	Reason for Change
8.4.3 Efficacy Evaluation	The analysis of 6-month PFS will be performed by calculating the point estimate of the percentage of *patients* who have neither progressed nor died at 6 months following the start of therapy, where progression will be determined by the RANO criteria. To be consistent with the Simon design, a lower one-sided 90% CI will be presented on rate of 6-month PFS; additionally, for descriptive purposes a two-sided 95% CI will also be calculated, using exact methods. The 6-month PFS results will be presented for the first stage of the study and for both stages combined, consistent with the Simon design; *an additional presentation of results from both stages combined will summarize the data from* CCI *Arm B separately, without statistical inference. [Deleted text]*	The analysis of 6-month PFS will be performed by calculating the point estimate of the percentage of **non-surgical** patients who have neither progressed nor died at 6 months following the start of therapy, where progression will be determined by the RANO criteria. To be consistent with the Simon design, a lower one-sided 90% CI will be presented on rate of 6-month PFS; additionally, for descriptive purposes a two-sided 95% CI will also be calculated, using exact methods. The 6-month PFS results will be presented for the first stage of the study and for both stages combined, consistent with the Simon design.	This Amendment includes only Medical Arm (Arm B) patients in this analysis.
Same section, Secondary Analyses:	*All secondary efficacy analyses will be performed on the respective complete analysis population, that is, no presentation of results on each of the two study stages is planned. However, results will be presented in a breakdown by* CCI *, Arm B and total. [Deleted text]*		The Amendment describes a changed analysis plan. This text has been deleted because it no longer reflects the planned analysis.

Section	Previous Wording	New Wording	Reason for Change
CCI CCI			
8.5 Interim and Final Analysis	*The final analysis will take place after there are 30 patients evaluable for analysis of 6-month PFS. Additional data summarization may take place after all available survival data are collected, or after Sponsor decision, as appropriate. [Text deleted]*		The deleted text no longer reflects the planned analysis outlined in this Amendment.

17 REFERENCES

1 Wen PY, Kesari S. Malignant gliomas in adults. *N Engl J Med* 2008;**359**:492-507.
2 Stupp R, Mason WP, van den Bent MJ et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. *N Engl J Med* 2005;**352**:987-96.
3 Mirimanoff RO, Gorlia T, Mason W et al. Radiotherapy and Temozolomide for Newly Diagnosed Glioblastoma: Recursive Partitioning Analysis of the EORTC 26981/22981 – NCIC CE3 Phase III Randomized Trial. *J Clin Oncol* 2006;**24**:1563-2569.
4 Hart MG, Garside R, Rogers G, Stein K, Grant R. Temozolomide for high grade glioma. *Cochrane Database Syst Rev* 2013;**4**:CD007415.
5 Eftimov TN, Ivanov ID, Petkov AP, Nakov E. Management of recurrent high-grade gliomas. *Cancer Therapy* 2007;**5**:243-252.
6 Happold C, Roth P, Wick W, Steinbach JP, Linnebank M, Weller M, Eisele G. ACNU-based chemotherapy for recurrent glioma in the temozolomide era. *J Neurooncol* 2009;**92(1)**:45-8.
7 Westphal M, Hilt DC, Bortey E, Delavault P et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro Oncology* 2002;**5**:79-88.
8 Brandes AA, Tosoni A, Basso U, Reni M et al. Second-Line Chemotherapy With Irinotecan Plus Carmustine in Glioblastoma Recurrent or Progressive After First-Line Temozolomide Chemotherapy: A Phase II Study of the Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO). *J Clin Oncol* 2004;**22**:4779-4786.
9 Kappelle AC, Postma TJ, Taphoorn MJB et al. PCV chemotherapy for recurrent glioblastoma multiforme. *Neurology* 2001;**56**:118-120.
10 Perry JR, Bélanger K, Mason WP, Fulton D et al. Phase II trial of Continuous Dose-Intense Temozolomide in Recurrent Malignant Glioma: RESCUE Study. *J Clin Oncol* 2010;**29**:2051-2057.
11 Omuro A, Chan TA, Abrey LE et al. Phase II trial of continuous low-dose temozolomide for patients with recurrent malignant glioma. *Neuro Oncol* 2013;**15(2)**: 242-50.
12 Gil-Gil MJ, Mesia C, Rey M, Bruna J. Bevacizumab for the Treatment of Glioblastoma. *Clin Med Insights Oncol* 2013;**7**:123-135.
13 Bokstein F, Shpigel S, Blumenthal ST. Treatment with bevacizumab and irinotecan for recurrent high-grade glial tumors. *Cancer* 2008;**112**:2267-2273.
14 Vredenburgh JJ, Desjardins A, Herndon JE et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol* 2007;**25**:4722-4729.
15 Poulsen HS, Grunnet K, Sorensen M et al. Bevacizumab plus irinotecan in the treatment of patient with progressive recurrent malignant brain tumors. *Acta Oncol* 2009;**48**:52-58.
16 Batchelor TT, Sorensen AG, di Tomaso E et al. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. *Cancer Cell* 2007;**11**:83-95.
17 Kesselheim JC, Norden AD, Wen PY, Joffe S. Discontinuing bevacizumab in patients with glioblastoma: an ethical analysis. *Oncologist* 2011;**16(10)**:1435-9.
18 Chinot OL. Bevacizumab-based therapy in relapsed glioblastoma: rationale and clinical experience to date. *Expert Rev Anticancer Ther* 2012;**12(11)**:1413-27.
19 Wen PY, Lee EQ, Reardon DA, Ligon KL, Alfred Yung WK. Current clinical development of PI3K pathway inhibitors in glioblastoma. *Neuro Oncol* 2012;**14(7)**:819-29.
20 Lassen U, Sorensen M, Gaziel TB et al. Phase II study of bevacizumab and temsirolimus combination therapy for recurrent glioblastoma multiforme. *Anticancer Res* 2013;**33(4)**:1657-60.
21 Van den Bent MJ, Brandes AA, Rampling R et al. Randomized Phase II Trial of Erlotinib Versus Temozolomide or Carmustine in Recurrent Glioblastoma: EORTC Brain Tumor Group Study 26034. *J Clin Oncol* 2009;**27**:1268-1274.

22 Bode U, Massimino M, Bach F et al. Nimotuzumab treatment of malignant gliomas. *Expert Opin Biol Ther* 2012;**12(12)**:1649-59.
23 Muhic A, Poulsen HS, Sorensen M et al. Phase II open-label study of nintedanib in patients with recurrent glioblastoma multiforme. *J Neurooncol* 2013;**111(2)**:205-12.
24 Kreisl TN, McNeill KA, Sul J et al. A phase I/II trial of vandetanib for patients with recurrent malignant glioma. *Neuro Oncol* 2012;**14(12)**:1519-26.
25 Reardon DA, Dresemann G, Taillibert S et al. Multicentre phase II studies evaluating imatinib plus hydroxyurea in patients with progressive glioblastoma. *Br J Cancer* 2009;**101(12)**:1995-2004.
26 Hu J, Wen PY, Abrey LE et al. A phase II trial of oral gimatecan for recurrent glioblastoma. *J Neurooncol* 2013;**111(3)**:347-53.
27 Grossmann KF, Colman H, Akerley WA et al. Phase I trial of verubulin (MPC-6827) plus carboplatin in patients with relapsed glioblastoma multiforme. *J Neurooncol* 2012;**110(2)**:257-64.
28 Reardon DA, Groves MD, Wen PY et al. A phase I/II trial of pazopanib in combination with lapatinib in adult patients with relapsed malignant glioma. *Clin Cancer Res* 2013;**19(4)**:900-8.
29 Shen A, Wang Y, Zhao Y, Zou L, Sun L, Cheng C. Expression of CRM1 in human gliomas and its significance in p27 expression and clinical prognosis. *Neurosurgery* 2009;**65(1):** 153-9.
30 Wang D, He F, Zhang L et al. The role of p27 (Kip1) phosphorylation at serine 10 in the migration of malignant glioma cells in vitro. *Neoplasma* 2011;**58(1):**65-73.
31 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.
32 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.
33 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.
34 Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Onc 2004; **22**:2918.
35 Green AL, Ramkissoon SH, McCauley D, et al. Preclinical antitumor efficacy of selective exportin 1 inhibitors in glioblastoma. *Neuro-Oncology* 2014;**0**:1–11, doi:10.1093/neuonc/nou303.
36 Simon R. Optimal Two-Stage Designs for Phase II Clinical Trials. *Controlled Clinical Trials* 1989;**10**:1-10.
37 Wen PY, Macdonald DR, Reardon DA et al., Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology (RANO) Working Group. *J Clin Oncol* 2010:**28(11)**;1963-72. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3631110/.