CLINICAL STUDY PROTOCOL

XPORT-GBM-029

Study Title:	**A Phase 1/2 Study of Selinexor in Combination with Standard of Care (SoC) Therapy for Newly Diagnosed or Recurrent Glioblastoma**
Study Number:	XPORT-GBM-029
Study Phase:	Phase 1/2
Product Name:	Selinexor (KPT-330)
IND Number:	CCI
EudraCT Number:	2021-000080-67
Indication:	Newly Diagnosed or Recurrent Glioblastoma (GBM)
Investigators:	Multicenter
Sponsor:	Karyopharm Therapeutics Inc. 85 Wells Avenue Newton, MA 02459 USA Tel. +1 (617) 658-0600
Protocol Date and Version:	23 February 2020, Version 2.0 15 September 2020, Version 3.0 06 January 2021, Version 4.0 21 April 2021, Version 5.0 11 May 2021, Version 6.0

CONDUCT

In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

CCI

PROTOCOL APPROVAL SIGNATURE PAGE

SPONSOR: KARYOPHARM THERAPEUTICS INC.

I have read and understand the contents of this clinical protocol for Study No. XPORT-GBM-029 dated 11 May 2021 and agree to meet all obligations of Karyopharm Therapeutics Inc., as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other investigators of all relevant information that becomes available during the conduct of this Study.

Approved by:

PPD

PPD , MD
PPD
Karyopharm Therapeutics Inc.

Date

PPD

PPD , PhD
PPD
Karyopharm Therapeutics Inc.

Date

INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study No. XPORT-GBM-029 dated 11 May 2021 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the Study in accordance with current ICH, GCP E6, and applicable FDA regulatory requirements.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Institution

_____

Date

PROTOCOL SYNOPSIS

Sponsor: Karyopharm Therapeutics Inc.	**Investigational Product:** Selinexor (KPT-330)	**Developmental Phase:** Phase 1/2
Title of Study: A Phase 1/2 Study of Selinexor in Combination with Standard of Care (SoC) Therapy for Newly Diagnosed or Recurrent Glioblastoma		
Protocol Number: XPORT-GBM-029		
Indication: Newly Diagnosed or Recurrent Glioblastoma (GBM)		
Study Type: Interventional		

Study Rationale:

Glioblastoma Multiforme (GBM) is one of the most common and particularly aggressive forms of brain tumors of primarily glial cell origin. GBM is often referred to as a grade IV astrocytoma. The average age-adjusted incidence rate is 3.2 per 100,000 population (Ostrom 2015; Ostrom 2014). GBMs present at a median age of 64 years (Thakkar 2014) but can occur at any age, including childhood. Incidence is slightly higher in men than women (1.58:1) and in Whites relative to other ethnicities (Ellor 2014).

GBM is an incurable disease with few treatment advances for many years. The prognosis of GBM is poor due in part to its aggressive and extensive infiltration of surrounding central nervous system (CNS) tissue. It is frequently inaccessible for surgical resection due to the infiltrating nature of GBM within the brain. The blood-brain barrier presents an obstacle for many chemotherapeutic agents, with only small, lipophilic molecules able to reach the tumor (Upadhyay 2014). Median survival of patients with newly diagnosed GBM (nGBM) is 15 months (Thakkar 2014). Recurrence of disease is common, and median survival of recurrent disease is approximately 5 to 7 months (Lombardi 2019).

The current initial standard treatment in nGBM is surgery followed by radiation therapy (RT). Despite improvement in surgical and radiation modalities and with the addition of alkylating therapy, temozolomide (TMZ), to RT, the median survival remains poor. Little progress in therapeutic advances have been made in over a decade.

Patients with O6-methylguanine-DNA-methyltransferase (MGMT) promotor methylated (mMGMT) disease or MGMT unmethylated (uMGMT) disease may be treated with or without TMZ, respectively (Sadones 2009). The methylation status of the MGMT promoter has been identified as an independent prognostic factor of survival in GBM patients undergoing treatment with TMZ, with significant survival benefit for patients with a mMGMT promoter (~45% of GBM patients) (Stupp 2005; Stupp 2009).

Despite first line treatment with maximal safe resection, chemoradiation and TMZ, glioblastomas eventually recur. The TMZ/RT regimen is not curative and patients with nGBM have a high risk for relapse within 6 months to 1 year after the primary treatment (Stupp 2005). Although the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab was approved for recurrent GBM (rGBM) in 2009, there is still no established standard treatment for rGBM (Gallego 2015). Options at recurrence include surgical resection, bevacizumab, tumor treating fields (TTField), cytotoxic chemotherapy (e.g., lomustine; procarbazine, lomustine, and vincristine [PCV]; TMZ), regorafenib and clinical trials per NCCN guidelines. Unfortunately, most studies have demonstrated only modest progression-free survival (PFS) and overall survival (OS)

improvements. There remains a high unmet medical need for new therapies to address the poor prognosis of patients with rGBM.

Exportin-1 (XPO1) may be a new, novel target in GBM. It is overexpressed in GBM and high-grade gliomas, and the degree of XPO1 overexpression correlates with higher tumor grade and poor survival (Liu 2016, Shen 2009).

Selinexor is a first-in-class, orally administered, small molecule, selective inhibitor of nuclear export (SINE) compound. Its mechanism of action consists of forming slowly reversible covalent bonds to the cysteine 528 cargo pocket of XPO1, thus shutting down XPO1 nuclear export activity. This results in nuclear retention of tumor suppressor proteins (TSPs) and their functional activation of p53, p21, Rb, Ikb, FOXO1A, etc. (Crochiere 2016, Kashyap 2016, Turner 2016) as well as reduced translation of proto-oncogene proteins (c-myc, bcl-2, mdm2, etc.; Golomb 2012, Culjkovic-Kraljacic 2012). Activation of TSPs and downregulation of proto-oncogenes block the cell division cycle and induce apoptosis in both solid and hematologic malignancies, while sparing normal cells. Selinexor demonstrates potent in vitro and in vivo efficacy in a variety of glioma tumor models as a single agent or in combination with radiation (Wahba 2018) and in combination with TMZ or lomustine (unpublished data).

Selinexor has been administered to over 3400 patients worldwide in various cancers such as multiple myeloma (MM), lymphomas, gynecological cancers, sarcomas, glioblastoma, etc. Selinexor is approved in the US and in EU for patients with previously treated Multiple Myeloma and relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

In a Phase 2 study (KCP-330-004, KING) selinexor was studied in patients with recurrent WHO Grade 4 gliomas. This study demonstrated that selinexor crosses the blood-brain barrier with adequate intra-tumoral penetration (Lassman 2020). Selinexor demonstrated single-agent activity in patients with rGBM with ORR of 10%, PFS rate at 6 months (PFS6) of 17% and OS of 10.2 months at 80 mg weekly (QW). Durable responses were achieved in some patients. A partial response (PR) was observed in a patient with uMGMT GBM who had received 2 prior systemic therapies. This patient has remained on treatment for >3 years. A complete response (CR) in a mMGMT patient who had received 2 prior systemic therapies and has remained on treatment for >1 year. Treatment-related hematological adverse events (AEs) included thrombocytopenia with Grade 1/2 in 6 (20.0%) patients and Grade 3 in 1 (3.3%) patient at the 80 mg QW dose. Other AEs included gastrointestinal and constitutional events, primarily nausea and anorexia; both were manageable with dose modification and appropriate supportive care (Lassman 2020). Based on the efficacy and favorable toxicity profile of selinexor in this study, the 80 mg QW dose is recommended for further development in GBM.

The results in rGBM (from the Phase 2 KING study) provided guidance for use of selinexor in earlier stages of GBM and to evaluate the use of combination therapies with selinexor. Preclinical data shows that selinexor sensitizes GBM stem-like cells in vitro and in vivo, and colorectal cells in vitro to radiation (Wahba 2018; Ferreiro-Neira 2016). Wahba, et al, demonstrated with polysome profiling that selinexor enhances radiosensitivity in vitro and in vivo by decreasing gene translational efficiency and that translational efficiency recovers to baseline at about 48 hours (Wahba 2018). This suggests that selinexor may be a more effective radiosensitizer when given twice weekly. The rationale for this study is based on the preclinical activity of selinexor in combination with RT (Wahba 2018) and with either TMZ or lomustine (unpublished data), good

penetration through the blood-brain barrier (as demonstrated in KING study as well as preclinical models averaging 0.72 in rats and 0.61 in cynomolgus monkeys [Green 2015]), as well as the clinical efficacy, and favorable side-effect profile of monotherapy selinexor in patients with rGBM.

This study will evaluate the effects of selinexor added to the standard RT therapy (S-RT) in patients with uMGMT nGBM (S-RT versus TMZ/RT) and added to the TMZ/RT therapy (S-TRT) in patients with mMGMT nGBM (S-TRT versus TMZ/RT). This study will also evaluate the effects of selinexor added to the most commonly used systemic therapy, lomustine (or carmustine), bevacizumab, and alternating TTField in patients with rGBM upon first relapse.

Bevacizumab, an antiangiogenic agent, received accelerated approval for recurrent glioblastoma in 2009 based on two studies (Friedman 2009; Kreisl 2009) and full approval in 2017 in the US based on durable objective response rather than survival benefit (Wick 2017). Selinexor showed significant tumor growth inhibition in combination with bevacizumab in a preclinical ovarian cancer model (Miyake 2013).

Alternating TTField were approved for recurrent glioblastoma based upon the results of the EF-11 trial (Stupp 2012). Patients were randomized to TTField versus Investigator's choice active chemotherapy. The primary endpoint was OS. The study failed to show improved survival with TTField, but endpoints with TTField were shown to be equivalent to chemotherapy: OS 6.6 and 6.0 months, 1-year survival 20% and 20% and PFS6 21.4% and 15.1%, respectively. Preclinical data shows that combined treatment with selinexor and TTField is favorable. In-vitro, the combined treatment of TTField and selinexor demonstrate enhanced efficacy as compared to each treatment alone in LN229, A172 and F98 glioma cell line. In vivo, in F98 intracranial rat glioma model, the combined treatment of TTField (200 kHz, 7 days) and 10 mg/kg BIW selinexor (3 doses overall), led to highest reduction in tumor volume fold increases on the last day of TTField application (Day 14) as compared to the control ($p<0.05$) and to selinexor and TTField alone (the results did not reach statistical significance) (internal unpublished Novocure data).

Arms D (selinexor plus bevacizumab) and E (selinexor plus TTField) were added to the protocol based on the preclinical activity observed with selinexor in combination with bevacizumab and in combination with TTField, the lack of significant overlapping toxicities between selinexor and bevacizumab and TTField, and the poor prognosis and unmet need of patients with recurrent glioblastomas. Arms D and E will be evaluated in Phase 1a and 1b of the study and could be evaluated further in Phase 2 of the study based on the data from Phase 1.

Rationale for revised dose levels in Arm B (selinexor with RT and TMZ [S-TRT]) in nGBM patients with mMGMT:

After review of the data from the protocol Version 4.0, dose level 2 in the dosing schedule of Arm B (selinexor 80 mg QW at Weeks 1, 2, 4, and 5 with concomitant RT and TMZ), was revised with protocol Version 5.0 due to occurrence of 2 dose-limiting toxicities (DLTs) among the 3 patients enrolled at this dose level. The DLT included 1 patient who missed 2 of 4 doses of selinexor due to Grade 2 to 4 thrombocytopenia, and another patient who developed Grade 4 neutropenia for >7 days. Details of revised dosing are provided in the relevant sections.

Objectives and Endpoints

Objectives	Endpoints
Primary Objectives **Phase 1a (for all arms)** • To assess the maximum tolerated dose (MTD) per arm • To evaluate the RP2D per arm	**Primary Endpoints** **Phase 1a (for all arms)** • MTD/RP2D per arm • The occurrence of Grade ≥3 AE, all serious adverse events (SAEs), and all AEs leading to treatment discontinuation
Phase 1b (for all arms) • To determine the efficacy of selinexor in all patients as determined by the 3-month PFS (PFS3) rate with PFS assessment as per RANO/modified RANO per Investigator assessment • To determine the efficacy of selinexor in all patients as determined by the OS	**Phase 1b (for all arms)** • All Arms: PFS3 (survival probability of having PFS ≥3 months as estimated by Kaplan-Meier method per Investigator assessment) • OS, defined as the time from initiation of treatment until death due to any cause
Phase 2 • Arms A and B: to determine the efficacy of selinexor in all nGBM patients as determined by PFS per modified RANO per independent review committee (IRC) in patients randomized to the experimental arm (S-RT in Arm A and S-TRT in Arm B) vs the control arm treated with SoC regimen (TRT) in the targeted population • Arm C: to compare OS in all rGBM patients randomized to the experimental arm (selinexor + lomustine [or carmustine]) vs the control arm treated with SoC regimen (lomustine/carmustine) in the targeted population	**Phase 2** • Arms A and B: PFS, defined as the time from date of randomization until the first date of progressive disease (PD) or death due to any cause per IRC assessment • Arm C: OS, defined as the time from randomization until death due to any cause
Secondary Objectives **Phase 1a** • To assess OS for each arm independently	**Secondary Endpoints** **Phase 1a** • OS

Phase 1a/b • To assess time-to-progression (TTP) and PFS for each arm independently • For Arm C, D, and E only: To evaluate the overall response rate (ORR) and disease control rate (DCR) based on RANO/modified RANO criteria • For Arm C, D, and E only: To assess duration of response (DOR) • To assess selinexor pharmacokinetics (PK) in plasma when administered with radiation therapy, temozolomide, and/or lomustine or carmustine, bevacizumab, and TTField	**Phase 1a/b** • TTP, defined as time from date of first study treatment until progression or death due to progression • PFS • For Arm C, D, and E only: ORR, defined as the proportion of patients who have a response of partial response (PR) or complete response (CR) • For Arm C, D, and E only: DCR, defined as the proportion of patients in whom the best overall response is determined as CR, PR or stable disease (SD) • For Arm C, D, and E only: DOR, defined as time from date of first occurrence of objective response (PR or CR) until progression • Selinexor PK parameters (e.g., clearance [CL], area under the concentration curve [AUC], maximum concentration [C_{max}])
Phase 1b • To obtain additional safety, tolerability data	**Phase 1b** • To further characterize the occurrence of Grade ≥3 AE, all serious adverse events (SAEs), and all AEs leading to treatment discontinuation and confirm tolerability at the MTD/RP2D
Phase 2 • Arms A and B: to determine the efficacy of selinexor in all nGBM patients as determined by PFS per modified RANO criteria per Investigator assessment in patients randomized to the experimental arm vs the control arm treated with SoC regimen in the targeted population • Arms A and B: to compare OS in all nGBM patients randomized to the experimental arm vs the control arm treated with SoC regimen in the targeted population	**Phase 2** • Arms A and B: PFS per Investigator assessment • Arms A and B: OS for patients with nGBM

• Arm C: to determine PFS per RANO criteria per IRC and investigator assessment in all rGBM patients randomized to the experimental arm vs the control arm treated with SoC regimen in the targeted population	• Arm C: PFS per IRC assessment • Arm C: PFS per Investigator assessment
• Arm C only: to compare the ORR and DCR based on the response per RANO per Investigator assessment and per IRC in patients randomized to the experimental arm vs the control arm treated with SoC regimen in the targeted population	• Arm C only: ORR per IRC and Investigator assessment • Arm C only: DCR per IRC and Investigator assessment
• Arm C only: to compare the DOR per RANO per Investigator assessment and per IRC in patients randomized to the experimental arm vs the control arm	• Arm C only: DOR per IRC and Investigator assessment
• All Arms: to determine the efficacy of selinexor in all patients as determined by the 6-month PFS (PFS6) rate where PFS assessment as per RANO/modified RANO per investigator assessment and per IRC	• All Arms: PFS6 (survival probability of having PFS ≥ 6 months as estimated by Kaplan-Meier method per IRC and Investigator assessment)
• All Arms: to assess the 1 and 2-year OS rate of patients in experimental and control arm	• All Arms: 1-year OS (OS1) and 2-year OS (OS2) rate as estimated by Kaplan-Meier method
• All Arms: to assess the safety and tolerability of treatment in patients randomized to the experimental arm vs the control arm treated with SoC regimen in the targeted population	• All Arms: Safety • All Arms: Incidence of selected Grade ≥3 AEs, including hematological abnormalities, gastrointestinal disorders (nausea, vomiting, and diarrhea), and fatigue • All Arms: Incidence of all SAEs • All Arms: Incidence of AEs leading to treatment discontinuation
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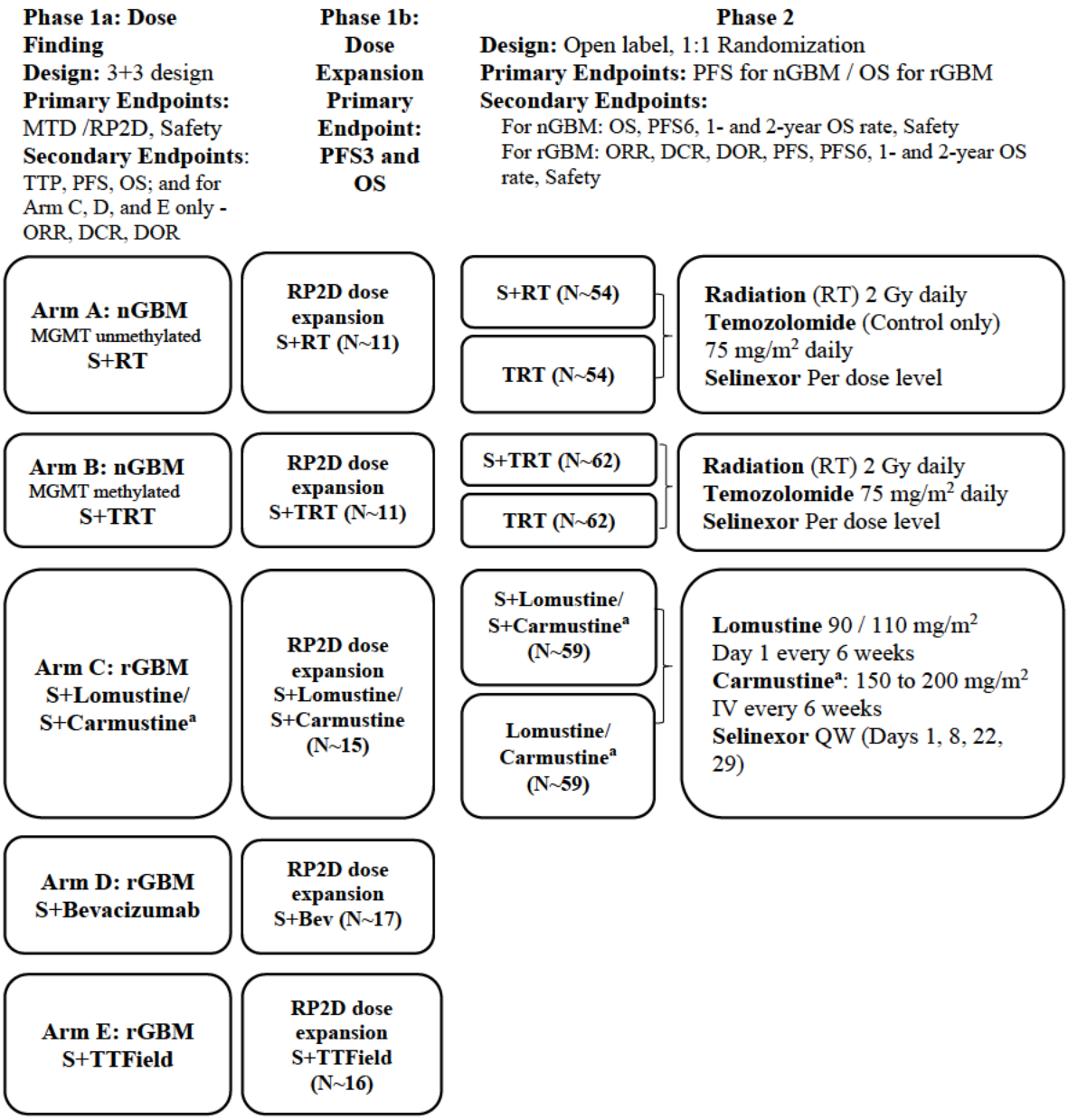
Note: The modified RANO criteria are applicable for Arms A, B, and D; and RANO criteria are applicable for Arms C and E. For Arm C, carmustine can be substituted if lomustine is not available.
Overall Study Design: This is a Phase 1/2 study of selinexor in combination with SoC therapy for nGBM or rGBM. This study will be conducted in 2 phases: a Phase 1a dose finding study followed by Phase 1b (dose expansion) and a Phase 2 randomized efficacy exploration study and will independently evaluate 3 different combination regimens in 3 treatment arms in patients with nGBM (Arms A and B) or with rGBM (Arm C). • Arm A: evaluating the combination of selinexor with RT (S-RT) in nGBM patients with uMGMT • Arm B: evaluating the combination of selinexor with RT and TMZ (S-TRT) in nGBM patients with mMGMT • Arm C: evaluating the combination of selinexor with lomustine (or carmustine, if lomustine is not available) (S-L/C) in rGBM patients regardless of MGMT status • Arm D: evaluating the combination of selinexor with bevacizumab in rGBM patients regardless of MGMT status • Arm E: evaluating the combination of selinexor with TTField in rGBM patients regardless of MGMT status

The study overview is presented below and is further summarized in Table 1.



Bev: bevacizumab; DOR: duration of response; DCR: disease control rate; QW: once a week; nGBM: newly diagnosed GBM; ORR: objective response rate; OS: overall survival; MGMT: O6-methylguanine-DNA-methyltransferase; MTD: maximum tolerated dose; PFS: progression-free survival; PFS3: progression-free survival rate at 3 months; PFS6: progression-free survival rate at 6 months; RP2D: recommended Phase 2 dose S: selinexor; rGBM: recurrent GBM; RT: radiotherapy; S: selinexor; TRT: temozolomide + radiotherapy; TTP: time to progression; TTField: tumor treating fields.
[a] Carmustine may be substituted for lomustine if lomustine is not available.

Phase 1a: Multi-center, open-label dose escalation study to assess the maximum tolerated dose (MTD), recommended Phase 2 dose (RP2D), safety and preliminary efficacy in patients with nGBM or rGBM of different combination regimens of selinexor with SoC therapies.

Phase 1b (expansion): Open label study to confirm safety of the MTD/RP2D and explore preliminary signal of efficacy (PFS3) and OS in patients with nGBM and rGBM before proceeding to Phase 2.

Phase 2: Phase 2 open label, randomized study to evaluate a combination regimen with or without selinexor in patients with nGBM or rGBM.

Study Procedure for Primary and Key Secondary Endpoint Analysis

Efficacy:
Objective disease response assessment will be made according to modified RANO (Arms A, B, and D) or RANO (Arms C and E). The data used for Phase 2 primary statistical analysis will be provided by the independent review committee (IRC).

- Progression is defined as the first occurrence of PD per RANO/modified RANO including both radiological PD and clinical deterioration.
- Clinical disease progression should be radiographically confirmed whenever possible and must be comprehensively documented by the treating physician. Patients who have clinical disease progression in the absence of radiographical confirmation will be still counted as PD. Serial scans should utilize the same type of scanner and techniques as closely as possible as prior scans.
- PFS is defined as the duration of time from randomization (Phase 2)/first dose of study treatment (Phase 1a/b) until progression or death due to any cause.
- 3-month progression-free survival (PFS3) rate (progression of disease defined according to the RANO/modified RANO criteria).
- OS is defined as the duration of time from randomization (Phase 2)/first dose of study treatment (Phase 1a/b) until death due to any cause.
- TTP is defined as the duration of time from first dose of study treatment (Phase 1) until progression or death due to progression.

For Arm C (Phase 1a/b and 2); Arms D and E (Phase 1a/b only)

- ORR is defined as PR+CR
- DOR is defined as the duration of time from first occurrence of CR or PR until the first date that disease progression is objectively documented
- DCR is defined as the proportion of patients who achieve CR, PR, or SD, following randomization/first dose of study treatment (i.e., ORR+SD)

Imaging Procedure

Disease status will be measured by contrast-enhanced magnetic resonance imaging (MRI), including pre-contrast T1/T2/FLAIR, and post-contrast T1, and assessed using the modified RANO (Arms A, B, and D) or RANO (Arms C and E) criteria. In Arms A and Arm B, imaging will be performed at Screening, 4 weeks from the end of Cycle 1, end of Cycle 3, end of Cycle 4, and then approximately every 2 cycles (Day 22 to Day 28 of the cycle) thereafter. MRI evaluation at the end of Cycle 3 is only applicable for Phase 1 of the study.

In Arm C, imaging will be performed at Screening, at the end of Cycle 1, at the end of every cycle thereafter.

In Arms D and E, imaging will be performed at Screening, the end of Cycle 2, end of Cycle 3, end of Cycle 4, and at the end of every 2 cycles at least thereafter for 1 year, and 3 cycles after 1 year.

Safety

Safety will be monitored by assessing vital signs and weight, performance status, neurological examinations per NANO criteria, 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 NCI-CTCAE v5.0.

Safety blood samples will include blood count, clinical chemistry (including liver function tests).

Pharmacokinetics Analysis

Blood samples of approximately 2 mL will be collected for the measurement of plasma concentrations of selinexor at 2, 4, and 6 hours post selinexor dose on C1D1 and C3D1 in Arms A and B, and C1D1 and C2D1 in Arms C, D, and E. In Phase 2, only those patients on the experimental arms (selinexor containing) will have blood drawn for PK. If a patient experiences emesis within 6 hours postdose on a PK sampling day, no further PK samples will be collected on that day. Plasma samples will be analyzed via a validated high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS) method for plasma selinexor. Selinexor PK might be assessed using population PK modeling approach and subsequent exposure-response analyses would be performed if deemed necessary.

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Number of Patients (planned):

Phase 1a:

For nGBM Arm A, B and rGBM Arm C, Arm D, and Arm E, approximately 9 to 18 evaluable patients will be enrolled for each arm for a total of 45 to 90 patients. With emerging data and upon Safety Review Committee (SRC) agreement, selected dose level can be expanded with additional patients to better understand the safety, anti-tumor activity and PK/PDn of that dose.

Phase 1b:

Arm A: nGBM uMGMT, approximately 11 patients are required with a 1-sided 95% confidence interval

Arm B: nGBM mMGMT, approximately 11 patients are required with a 1-sided 95% confidence interval

Arm C: rGBM regardless of MGMT status, approximately 15 patients are required with a 1-sided 95% confidence interval

Arm D: rGBM regardless of MGMT status, approximately 17 patients are required with a 1-sided 95% confidence interval

Arm E: rGBM regardless of MGMT status, approximately 16 patients are required with a 1-sided 95% confidence interval

Phase 2:

Arm A: nGBM uMGMT, approximately 108 patients (54 patients in S+RT experimental arm and 54 patients in TRT control arm)

Arm B: nGBM mMGMT, approximately 124 patients (62 patients in S+TRT experimental arm and 62 patients in TRT control arm)

Arm C: rGBM regardless of MGMT status, approximately 118 patients (59 patients in S+L/C experimental arm and 59 patients in L/C control arm). Patients will be stratified by number of prior lines of anti-GBM regimens (1 versus >1) in Arm C.

The number of patients for each Arm in the Phase 2 portion will be evaluated again at the end of the Phase 1 portion. It is planned to randomize patients in a 1:1 allocation to treatment and control arm.

Study Population:

Inclusion Criteria

1. Written informed consent in accordance with federal, local, and institutional guidelines.
2. Age ≥18 years at the time of informed consent and ≥22 years for Arm E.
3. Pathologically confirmed glioblastoma (including all histological variants; documentation to be provided) that are newly diagnosed (for Arms A and B) or relapsed disease (for Arms C, D and E) after 1 to 2 lines of systemic therapy (RT ± TMZ or RT ± TMZ in combination with other drug) (surgical resection of recurrent disease allowed). For Arms A and B, MGMT status should be available.
4. Prior therapy:
   a. Arms A and B: patients who have not received RT or any systemic therapy for brain tumor and must be eligible for definitive external beam RT and TMZ.
   b. Arms C, D and E: patients must have received prior treatment with RT with or without TMZ (RT ± TMZ in combination with other drug is allowed) and may have received one additional line of therapy for recurrence.
5. Measurable disease according to RANO/modified RANO guidelines is required only for Arms C, D and E; it is not required for Arms A or B.
6. Patients enrolling into Arms C, D and E must be on a stable or decreasing dose of corticosteroids (or none) for at least 5 days prior to the baseline MRI.
7. KPS greater than or equal to 70 (for Arms A and B) and 60 (for Arms C, D and E).
8. Patients must have adequate organ function ≤2 weeks of study treatment as defined by the following laboratory criteria:
   c. Hematological function ≤7 days prior to Cycle 1 Day 1: Absolute neutrophil count (ANC) ≥1.5 x 10^9/L; platelet count ≥150 x 10^9/L; and hemoglobin (Hb) ≥10.0 g/dL. Transfusion is not allowed within 7 days prior to C1D1.
   d. Hepatic function: bilirubin ≤2 x the upper limit of normal (ULN), ALT ≤2.5 x ULN, AST ≤2.5 x ULN; unless bilirubin elevation is related to Gilbert's Syndrome for which bilirubin must be <4 x ULN.
   e. Renal function: calculated (Cockcroft-Gault) or measured creatinine clearance ≥30 mL/min.
9. Female patients of childbearing potential must have a negative serum pregnancy test at Screening and agree to use highly effective methods of contraception throughout the study and for 6 months following the last dose of study treatment.

10. Fertile male patients who are sexually active with a female of childbearing potential must use highly effective methods of contraception throughout the study and for 6 months following the last dose of study treatment.
11. For Arms A and B: patients must have had surgery and/or biopsy not greater than 8 weeks prior to initial screening.
12. Patients must consent to provide tumor tissue and blood samples to be used for future molecular testing for correlative studies.
13. Limited to supratentorial disease for Arm E only.

Exclusion Criteria

1. Patients who are receiving any other investigational agents and /or have had prior therapy including:

   For Arms A and B only:

   a. Patients who have previously received RT to the brain.
   b. Patients who received chemotherapy for the treatment of their glioma.
   c. Patients who are being treated with implanted Gliadel wafers.

   For Arm C:

   d. Prior nitrosoureas.

   For Arms C, D and E:

   e. <4 weeks from prior TMZ or other chemotherapy, or <4 weeks or 5 half-lives (whichever is shorter) for investigational agents prior to start of study treatment.
   f. Prior treatment bevacizumab or other direct VEGF/VEGFR inhibitors. For any questions of the definition of a direct VEGF/VEGFR inhibitor, consult the study Medical Monitor.
   g. Any AE which has not recovered to Grade ≤1, or returned to baseline, related to the previous GBM therapy, except alopecia, and some other grade 2 AEs that have been stabilized (upon Medical Monitor approval).

2. Patients who are being treated or plan to be treated during this study with TTField for patients in Arms A to D.
3. Major surgery <2 weeks prior to the start of study treatment for Arms A to C and E, <4 weeks for Arm D.
4. History of allergic reactions attributed to compounds of similar chemical or biological composition to selinexor or other study treatment.
5. Patients must not have significantly diseased or obstructed gastrointestinal tract malabsorption, uncontrolled vomiting or diarrhea, or inability to swallow oral medication.
6. Patients with coagulation problems and medically significant bleeding in the month prior to start of treatment (peptic ulcers, epistaxis, intracranial hemorrhage, spontaneous bleeding). Prior history of DVT or PE is not exclusionary.
7. Currently pregnant or breastfeeding.
8. For Arms A and B: patients with pre-existing known or suspected radiation sensitivity syndromes will be excluded due to potential confounding effect on outcome.
9. Any life-threatening illness, active medical condition, organ system dysfunction, or serious active psychiatric issue which, in the Investigator's opinion, could compromise the patient’s safety or the patient’s ability to remain compliant with study procedures.

10. Uncontrolled (i.e., clinically unstable) infection requiring parenteral antibiotics, antivirals, or antifungals within 7 days prior to first dose of study treatment; however, prophylactic use of these agents is acceptable even if parenteral.
11. Patients with mutated Isocitrate Dehydrogenase (IDH) should be excluded for Phase 2.
12. For patients in Arm C, Forced Vital Capacity (FVC) or Carbon Monoxide Diffusing Capacity (DLCO) below 70% of predicted.
13. For Arm E: implanted active electronic medical devices such as programmable intraventricular shunts, spinal cord, vagus nerve or deep brain stimulators, pacemakers or implantable automatic defibrillators, skull defect (i.e. missing bone with no replacement), sensitivity to conductive hydrogels as used in ECGs, an underlying serious scalp condition that may interfere with placement of arrays, or bullet fragments, or documented clinically significant arrythmias.

Study Treatment/Treatment Arms, Dose, and Mode of Administration

Phase 1a - Dose Escalation

Primary endpoints: MTD/RP2D, occurrence of Grade ≥3 adverse events (AEs), all serious adverse events (SAEs), and all AEs leading to treatment discontinuation.

Secondary endpoints: PFS, TTP, OS, Pharmacokinetics (PK) and For Arm C, D, and E only - ORR per RANO/modified RANO criteria, DCR, and DOR.

An independent 3+3 Dose escalation of selinexor will be performed in each arm (approximately 2~3 dose levels) until the MTD and/or RP2D for that Arm is reached. Safety Review Committee (SRC) meetings will occur between each dose level to review DLTs. Consensus among SRC to proceed to next dose level will be documented. The SRC is comprised of Investigators and sponsor medical monitors.

In each Arm, based on emerging data and upon SRC approval, selected dose level can be expanded to better understand safety, efficacy, and PK/PDn of that dose. The RP2D to be used in the Phase 2 portion for each arm will be determined by SRC, based on the MTD and the totality of efficacy and safety data seen in Phase 1 dose escalation study.

Dose Escalation Scheme

Arm A (S-RT): Selinexor in nGBM uMGMT:

Dose Levels	Selinexor, Day 1 of each treatment week during radiation period; Then once weekly at 80 mg after radiation stops[a]	Radiation Treatment Daily; continue until radiation stops (42-day treatment duration unless stopping early for toxicity)
-1	60 mg Weeks 1, 4	2 Gy
1	60 mg, Weeks 1, 2, 4, 5	2 Gy
2	80 mg, Weeks 1, 2, 4, 5	2 Gy
3	80 mg, Weeks 1, 2, 3, 4, 5, 6	2 Gy

[a]The dose regimen specified in the table is for radiation period (Cycle 1) only. After the radiation stops, selinexor 80 mg will be dosed on Day 1 and Day 15 in Cycle 2, and subsequently will continue at 80 mg once weekly adjuvant therapy until PD (see Concurrent Therapy table below).

Arm B (S-TRT): Selinexor in nGBM mMGMT:

After review of the data from the protocol Version 4.0, dose level 2 in the dosing schedule of Arm B (selinexor 80 mg QW at Weeks 1, 2, 4, and 5 with concomitant RT and TMZ), was revised with protocol Version 5.0 due to occurrence of 2 DLTs among the 3 patients enrolled at this dose level. The DLT included one patient who missed 2 of 4 doses of selinexor due to Grade 2 to 4 thrombocytopenia, and another patient developed Grade 4 neutropenia > 7 days.

Three new dosing levels were introduced in protocol Version 5.0: 2a, 2b, and 3a each of which will maintain the 3+3 design.

- Dose level 2a will evaluate 40 mg Days 1 and 3, Weeks 1, 3, 5
- Dose level 2b will evaluate 80 mg Day 1 of Weeks 1, 3, 5. This dose level reduces the number of doses during the 6 weeks of the concomitant phase of treatment with RT and TMZ from the current 4 to 3 while maintaining the 80 mg dose.
- Dose level 3a will evaluate 60 mg Days 1 and 3, Weeks 1, 3, 5

Dose levels 2a and 2b will enroll concurrently and patients will be randomly assigned to dose level 2a and 2b until either of these 2 dose levels stops enrollment.

- If Dose level 2a clears the DLT evaluation period per the SRC, the next dose level, 3a, will enroll at 60 mg, Days 1 and 3, Weeks 1, 3, 5. The dose of 60 mg twice weekly is the approved dose of XPOVIO for DLBCL and was evaluated in Arm C in KCP-330-004 (KING) in recurrent GBM.

If dose level 2b clears the DLT evaluation period, there will be no further dose escalation. This will be the MTD at this schedule.

Dose Levels	Selinexor Day 1 of each treatment week during radiation period; Then once weekly after radiation stops[a]	Temozolomide Once daily (QD) for 42 days; Then adjuvant therapy per label after radiation stops[a]	Radiation Treatment Daily Continue until radiation stops (42-day treatment duration unless stopping early for toxicity)
-1	60 mg, Weeks 1, 4	75 mg/m^2	2 Gy
1	60 mg, Weeks 1, 2, 4, 5	75 mg/m^2	2 Gy
2	80 mg, Weeks 1, 2, 4, 5	75 mg/m^2	2 Gy
2a	40 mg, Days 1 and 3, Weeks 1, 3, 5	75 mg/m^2	2 Gy
2b	80 mg, Day 1, Weeks 1, 3, 5	75 mg/m^2	2 Gy
3a	60 mg, Days 1 and 3, Weeks 1, 3, 5	75 mg/m^2	2 Gy

[a] The dose regimen specified in the table is for radiation period only. After the radiation stops, temozolomide will continue as adjuvant therapy per label for 6 cycles (Cycle 3-8). Selinexor will be dosed at 60 mg (dose level 2a) or 80 mg (dose level 2b and 3a) on Day 1 and Day 15 in Cycle 2, and subsequently continued at the same dose once weekly until PD.

Arm C (S-L/C): Selinexor with Lomustine/Carmustine in 1st rGBM (42 Day Cycle):

Dose Levels	Selinexor weekly (Days 1, 8, 22, 29)	Lomustine Day 1 of each cycle	Carmustine (to be substituted if lomustine is not available) Day 1 of each cycle
-1	40 mg	90 mg/m^2	150 mg/m^2
1	60 mg	90 mg/m^2	150 mg/m^2
2	80 mg	90 mg/m^2	150 mg/m^2
2a	60 mg	110 mg/m^2	200 mg/m^2
3	80 mg	110 mg/m^2	200 mg/m^2

Note: If no DLT in Cohort 2, escalate from Dose Level 2 to 3.
If there is a DLT in Cohort 2, and dose escalation to Dose Level 3 is not possible, evaluation of Dose Level 2a as an alternative regimen will be considered.
If Dose Level 3 is not tolerated, Dose Level 2 could be declared as MTD or exploring 2a as an alternative regimen could be considered.

Arm D (S-B): Selinexor with Bevacizumab in 1st rGBM (28 Day Cycle):

Dose Levels	Selinexor weekly	Bevacizumab 10 mg/kg IV Q2W
-1	60 mg (Days 1, 8, 15, 22)	10 mg/kg IV Q2W
1	80 mg (Days 1, 8, 15, 22)	10 mg/kg IV Q2W

Note: Administration of bevacizumab should be performed per label and dose reductions/modifications for bevacizumab are allowed per label.

Bevacizumab will be administered (and dose modified) per label:
First infusion: Administer infusion over 90 minutes.
Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated; administer all subsequent infusions over 30 minutes if infusion over 60 minutes is tolerated.
Dose modifications are allowed per label.

Arm E (S-TTField): Selinexor with TTField in 1st rGBM (28 Day Cycle):

Dose Levels	Selinexor weekly	TTField 200 kHz ≥18h/day
-1	60 mg (Days 1, 8, 15, 22)	200 kHz ≥18h/day
1	80 mg (Days 1, 8, 15, 22)	200 kHz ≥18h/day

Concurrent Therapy

Arms A and B

Concurrent therapy for Arm A and Arm B for the combination and adjuvant periods are presented in the table below.

Concurrent Therapy: Arm A and Arm B:

ARM	Radiation Period (42 days)	Adjuvant Therapy Period (28 days per cycle for 6 cycles and beyond)
A (Phase 1a/b) A Experimental	RT 2 Gy daily Selinexor per dose level	Selinexor 80 mg once weekly until PD
A Control	RT 2 Gy daily TMZ 75 mg/m^2 daily	TMZ started as Cycle 3 at 150 mg/m^2, then increased to 200 mg/m^2 as tolerated per Investigator's judgment in Cycles 4-8 for adjuvant therapy per label on Days 1-5 per 28-day cycle
B (Phase 1a/b) B Experimental	RT 2 Gy daily TMZ 75 mg/m^2 daily Selinexor per dose level	TMZ started as Cycle 3 at 150 mg/m^2, then increased to 200 mg/m^2 as tolerated per Investigator's judgment in Cycles 4-8 for adjuvant therapy per label on Days 1-5 per 28-day cycle Selinexor weekly 60 mg or 80 mg depending on dose level until PD
B Control	Radiation (RT) 2 Gy daily TMZ 75 mg/m^2 daily	TMZ started as Cycle 3 at 150 mg/m^2, then increased to 200 mg/m^2 as tolerated per Investigator's judgment in Cycles 4-8 for adjuvant therapy per label on Days 1-5 per 28-day cycle

RT=radiation therapy; TMZ=temozolomide.
Note: this table is applicable to both Phase 1 and Phase 2. Refer to Table 5 for details.
In Phase 2, radiation 1.8 to 2.0 Gy will be administered.

Radiation Period

Selinexor will be administered orally at an initial dose of 60 mg in treatment Arms A, B, and C, and 80 mg in Arms D and E in Phase 1a, followed by dose escalation scheme as described above. Selinexor should be given about 30 minutes prior to radiation during weeks determined by dose level. With protocol Version 5.0, the planned Dose Level 2 in Arm B, 80 mg QW at Weeks 1, 2, 4, and 5 with concomitant RT and TMZ, was revised due to occurrence of 2 DLTs among the 3 patients enrolled at this dose level.

Standard Fractionated Radiation therapy (RT) using either Radiation Therapy Oncology Group (RTOG) or EORTC methodologies of approximately 60 Gy in 30 fractions. 2 Gy will be administered daily for 5 days in a week (e.g., Monday to Friday, or Sunday to Thursday) unless the treatment schedule requires a change.

Arm B treatment group only and Arms A and B control – During the radiation treatment, oral TMZ will begin on the first day and will be administered orally daily at a dose of 75 mg/m^2 about 1 hour prior to the radiation treatment and about 30 minutes prior to selinexor. Temozolomide will continue at this dose level and schedule until the completion of radiation and then will continue as adjuvant therapy per label. During the adjuvant therapy, oral TMZ can be administered on an empty stomach or at bedtime.

During radiation therapy period, if radiation needs to be stopped due to toxicity, selinexor and TMZ can continue per schedule. If a patient experiences disease progression per modified RANO

criteria, then the patient will discontinue the treatment.

Adjuvant Therapy Period

Post RT, depending on treatment assignment, a patient can continue treatment with weekly selinexor until disease progression, TMZ per label for 6 cycles, or combination of selinexor and TMZ (TMZ for 6 cycles and selinexor continued until progression). Temozolomide will be given per standard of care (see Concurrent Therapy table above).

Arm C

Lomustine will begin on the first day and will be administered orally on Day 1 of each cycle (once every 6-week cycle) at a dose level described in the Arm C table above, up to 6 cycles. Carmustine can be administered for up to 6 cycles, if lomustine is not available.

Selinexor will be administered orally at an initial dose of 60 mg. The first dose will be given on Day 1 Week 1 of each cycle and about 30 minutes before lomustine or carmustine and will thereafter be administered on Day 8, Day 22, and Day 29. Selinexor should be dosed first and it is recommended to give lomustine or carmustine about 30 minutes after selinexor.

Arm D

Selinexor will be dosed weekly. Bevacizumab will be dosed at 10 mg/kg every 2 weeks. Cycles will be defined as 28 days. The first dose of selinexor will be given on Day 1 Week 1 of each cycle and will thereafter be administered on Day 8, Day 15, and Day 22. Selinexor should be dosed first and it is recommended to give bevacizumab after selinexor.

Arm E

Selinexor will be dosed weekly with TTField 200 kHz ≥18h/day. Patients will be encouraged to CCI turned on as much as possible during the day.

Dose Limiting Toxicities per CTCAE v5.0

An AE is considered to be a DLT if it is a clinically significant AE assessed as unrelated to tumor progression, intercurrent illness, or concomitant medications and meets the criteria defined herein and occurs during the radiation period for Arms A and B or Cycle 1 for Arms C, D, and E in Phase 1a. Any DLT must be a toxicity considered at least possibly related to study treatment and the acute effects thereof.

Non-hematologic toxicities

- Grade 3 nausea, vomiting, dehydration, diarrhea, or fatigue lasting >5 days despite optimal supportive medications
- Any other Grade 3/4 non-hematological toxicity with the following exceptions:
  - Electrolyte or laboratory abnormalities that are reversible and/or asymptomatic
  - ALT, AST, or alkaline phosphatase levels in the setting of Grade 2 baseline or elevations from underlying medical conditions

Hematologic toxicities

- Febrile neutropenia
- Grade 4 neutropenia lasting >7 days
- Grade ≥3 thrombocytopenia with clinically significant bleeding

Any AE that results in the following dose modification:

- Missed > 1/3 planned dose for any study treatment (selinexor, radiation, TMZ, lomustine,

bevacizumab, or TTField) due to study drug-related toxicities

- A dose reduction during Cycle 1 due to a study-drug related toxicity
- Discontinuation of a patient before completing Cycle 1, due to study drug-related toxicity

Exceptions:

Adverse events that meet the above definitions but that are clearly unrelated to study drug will not be considered DLTs.

An event may fall within the definition of a DLT, as defined above, but the event may be considered not to be a DLT (e.g., not be clinically meaningful). If this occurs, the Investigator and Sponsor will review the event and supporting data, and the reasons for not considering the event to be a DLT will be clearly documented with supporting rationale.

Phase 1a – Dose Escalation

This study will use a 3+3 design, with 3-6 patients enrolled per dose level to define maximum tolerated dose (MTD). The MTD is the dose level at which no more than 1 of up to 6 patients experience DLT during the first 42-day treatment cycle in Arms A, B, and C and 28-day treatment cycle in Arms D and E, and the dose above that at which at least 2 (of ≤6) patients have DLT as a result of selinexor/RT/TMZ/lomustine/bevacizumab/TTField. If a patient did not experience DLT and did not finish treatment during the radiation period for Arms A and B or first treatment cycle for Arms C, D, and E, he or she will not be evaluable for DLT and will be replaced in the dose level. Enrollment to a dose level would stop if 2 or more patients had a DLT.
In order to accurately characterize MTD/RP2D dose level, based on emerging data and with SRC approval, the number of patients may be increased for the potential MTD and/or RP2D dose level. Intra-patient dose escalation is allowed. If a patient is initially enrolled onto a lower dose cohort and tolerates selinexor well (i.e., without any DLTs; or, any ≥Grade 2 thrombocytopenia or neutropenia during the cycle in which dose escalation is considered), this patient can be moved to a higher dose level that clears DLT evaluation and is determined not to exceed MTD. Patients who have an intra-patient dose escalation will start the next higher dose on Day 1 of the cycle following approval. In the cycle in which their dose is increased, patients in Arms A and B will be followed closely for toxicity with weekly laboratory tests (Days 1, 8, 15, and 22) including complete blood count (CBC) and chemistry. A clinic visit and physical examination will be performed on Day 15 of the cycle in which their dose is increased. For patients in Arm C, weekly laboratory tests will be performed on Days 1, 8, 15, 22, 29, and 36 and a physical examination on Day 22 in the cycle in which the dose is escalated. Note that ±3-day windows for laboratory tests and visits per protocol remain applicable.
Dose escalation will follow the rules outlined in the table below.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter up to 3 patients at the next higher dose level
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose. Up to three (3) additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose.

1 out of 3	Enter up to 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next higher dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Up to three (3) additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level at or below the maximally administered dose	This is the MTD. RP2D can be at or below MTD and will be determined based on the totality of the available safety, efficacy, PK/PDn data from all dose levels. At least 6 patients must be entered at the RP2D.

The number of patients defined in this table are those patients considered evaluable for DLT and MTD evaluation unless they cannot complete the first cycle of therapy for any reason other than a DLT. A patient will be DLT-evaluable if the patient experiences a DLT in Cycle 1, or has taken at least 2 out of the 3, or at least 3 out of the 4, or at least 4 out of the 6 planned selinexor doses (depending on planned dosing frequency) or both doses if a patient is dosed twice in Cycle 1 without experiencing a DLT. A patient who is not DLT-evaluable will be replaced. Dose level review discussions will be held by the Sponsor and Investigators to determine dose escalation, reductions, and dose level expansions.

Phase 1b –Dose Expansion

The Phase 1b Dose Expansion includes Arms A to E to further evaluate safety and explore preliminary signal of efficacy at MTD/RP2D before proceeding to Phase 2. The co-primary endpoints are PFS3, which is defined 3-month progression-free survival rate and OS, defined as the time from initiation of treatment until death due to any cause.

Phase 2 – Efficacy Exploration

The Phase 2 Expansion Phase is a multicenter, open-label, randomized, SoC-controlled portion of the study to further evaluate the safety and efficacy of different combination regimens of SoC therapies with or without selinexor in patients with nGBM or first rGBM.

Open label, randomized study to further evaluate selected combination regimen with and without selinexor

	Arms A & B (nGBM)	**Arm C (rGBM)**
Primary Endpoint	PFS per IRC	OS
Secondary Endpoint	PFS per investigator assessment; PFS6 per IRC and investigator assessment; OS; 1- and 2-year OS rate, safety	PFS, PFS6 (and for Arm C only ORR, DCR, and DOR) per IRC and investigator assessment; 1- and 2-year OS rate, safety

In Phase 2, patients enrolled into each arm will receive the RP2D selected at the end of Phase 1 for that treatment arm. Study treatment may continue until completing protocol-defined treatment duration (for Arm A and B), disease progression per RANO/modified RANO criteria per investigator assessment, unacceptable AEs, etc. Although patients are allowed to discontinue due to PD per investigator assessment, the data used for Phase 2 primary statistical analysis will be provided by an independent review committee (IRC).

Independent Review Committee

An Independent Review Committee (IRC) will be organized to review the radiological and clinical assessments during the Phase 2 portion of the study. The data used for Phase 2 primary statistical analysis will be provided by the IRC. The IRC will develop and follow a data monitoring charter. The IRC will be composed of a minimum of 1 neuro-oncologist and 3 radiologists. The IRC charter will specify that this committee is charged with review and confirmation of radiologic PD and clinical PD per RANO/modified RANO for Phase 2.

Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be established. During the Phase 2 portion of the study, the DSMB will meet approximately every 6 months to review clinical data and provide recommendations to the Sponsor on whether the study should continue. The DSMB may also meet more frequently, if needed.

Supportive Care and Concomitant Medications

Supportive measures for optimal medical care should be provided to all patients in this study. In addition to the required prophylactic therapy outlined below, supportive care per institutional guidelines and/or the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines) should be used as clinically indicated at the discretion of the Investigator.

For Arm A control and for Arm B experimental and control, prophylactic treatment for PCP should be given according to TMZ label and PI's choice.

In order to minimize nausea, all patients should receive 5-HT3 antagonists (ondansetron 8 mg or equivalent), unless contraindicated, starting before each dosing and continued 2 to 3 times daily for 3 days after selinexor dosing. Alternative antiemetic agents may be used if the patient does not tolerate or has inadequate antiemetic effect with 5-HT3 antagonist.

In addition, patients should receive olanzapine 2.5 mg oral daily at bedtime (or minimally available dose based on the available formulation) starting on Day 1 and continuing through radiation therapy and for at least the first 2 cycles of the adjuvant therapy for nGBM in Arm A and B and for at least the first 2 cycles in Arms C, D and E. The dose of olanzapine can be increased as deemed necessary. The olanzapine dose may be dose reduced due to side effects or stopped after 2 months if nausea is well controlled.

Bevacizumab for Suspected Pseudoprogression (Arms A, B, C, and E) in Phase 1a/b:

In Phase 1a/b of the study, for patients in Arms A, B, C, and E with suspected pseudoprogression, short-course bevacizumab (2 to 4 infusions) may be administered for palliation at the Investigator's discretion and after consultation with the Medical Monitor for up to 6 months after RT in Arms A and B or initiation of selinexor in Arms C and E. The dose and schedule of bevacizumab may differ from Arm D per the Investigator's standard practice and may include 5 mg/kg every 2 weeks, 7.5 mg/kg every 3 weeks (Gonzalez 2007; Levin 2011).

Bevacizumab improves PFS but not OS in newly diagnosed (Chinot 2014; Gilbert 2014) and recurrent GBM (Wick 2017). Therefore, use of bevacizumab for palliation of suspected pseudoprogression will not affect assessment of OS.

Duration of Treatment and Follow-up:

The treatment duration of lomustine for Arm C is up to 6 cycles, selinexor will continue at assigned dose until PD.

Patients in Arm D (selinexor + bevacizumab) and Arm E (selinexor + TTField) will continue on treatment until PD, clinical progression, unacceptable toxicity or other discontinuation criteria are met.

Study treatment may continue until completing protocol defined treatment duration (for Arm A and B), disease progression determined by the treating physician per RANO/modified RANO criteria (however patients may stay on treatment if they have documented clinical benefit per the Investigator and after documented approval with the medical monitor), unacceptable AEs or failure to tolerate the study treatment, treatment delay of more than 28 days (except in specific cases with documented approval by the Sponsor), any medically appropriate reason or significant protocol violation (in the opinion of the Investigator), or patient decides to discontinue study treatment, withdraws consent, or becomes pregnant.

After discontinuation of study treatment, patients will be followed for safety up to 30 days after last dose, for PFS approximately every 3 months after end of treatment visit until PD, death or initiation of the subsequent anti-GBM treatment (if a patient discontinues from the treatment due to reasons other than PD), and for survival every 3 months after end of treatment visit until the end of study (i.e., when the last patient in the study has been followed on study treatment for at least 1 year or completed at least 6 months of survival follow-up period after their last dose of study treatment, has withdrawn consent, has died, or has been lost to follow-up, whichever occurs first).

Statistical Methods:

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Analysis Methods for Efficacy Endpoints

Primary Analysis

Phase 1a

- MTD/RP2D
- The occurrence of Grade ≥3 AE, SAEs, and all AEs leading to treatment discontinuation.

Phase 1b

- PFS3 compared to historical benchmarks
- OS: descriptive analysis will be performed

Phase 2

- Progression-free survival (PFS, Arms A and B): the log-rank test will be used to compare the PFS distributions; and Cox proportional hazards regression models will be used to estimate a HR for the risk of progression in the experimental arm vs the control arm treated with SoC regimen.
- The analysis of OS (Arm C): the stratified log-rank test will be used to compare OS distributions; and a stratified Cox proportional hazards regression models will be used to estimate a HR for the risk of survival in the experimental arm vs the control arm.

Secondary Analysis

Phase 1a/b

- TTP will be calculated from the start of selinexor treatment to the date of disease progression, or date of death due to disease progression.
- OS will be calculated from the start of selinexor treatment to the date of death due to any cause.
- PFS will be calculated from the start of selinexor treatment to the date of disease progression, or date of death due to any cause should progression have not occurred.
- To characterize selinexor PK when co-administered with radiation therapy and temozolomide or lomustine/carmustine or bevacizumab or TTField.

- The analysis of time-to-event endpoints will be based on Kaplan-Meier method for estimation of summary statistics and include the median event times and associated 95% CIs, as well as the number and percentage of censored patients.

Arms C, D, and E only:

- ORR will be estimated for each arm separately, by calculating the percentage of patients in that arm who have a response of PR or CR, as assessed by RANO/modified RANO criteria. The exact two-sided 95% CI will be provided.
- DCR will be calculated as the proportion of patients in whom the best overall response is determined as complete response (CR), partial response (PR) or stable disease (SD), as assessed by RANO/modified RANO criteria.
- DOR will be analyzed by Kaplan-Meier descriptive statistics for patients who have achieved overall response, with DOR calculated as the time from the date of first evidence of objective response until progression.

Phase 2

- Comparison of ORR and DCR (For Arm C only), PFS6, OS1, and OS2 between control and experimental arms will be performed using the Chi-squared test. The estimate of the odds ratio and its 95% CI and the p-value for testing the treatment difference will be reported.
- For time-to-event endpoints of DOR (For Arm C only), PFS and OS, the median event time will be estimated with a 95% CI for each treatment arm using the Kaplan-Meier method.
- For endpoints such as ORR, DCR, DOR (For Arm C only), PFS and OS, the median event time will be estimated with a 95% CI for each treatment arm using the Kaplan-Meier method. Comparisons between the 2 treatment arms will be performed using the log-rank test, with HRs and the associated 95% CI estimated by a Cox proportional hazards model, with Efron's method of tie handling, with treatment as the factor.
- For endpoints such as ORR, DCR, DOR (For Arm C only), PFS and PFS6, both analyses per investigator assessment and per IRC will be performed.
- Safety analyses will be performed on the Safety Population which consists of all patients who received at least 1 dose of study treatment and will be presented by actual treatment arm.


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Table 1: Overview of Treatment Arms Evaluated in the Study

	Arm A	Arm B	Arm C	Arm D	Arm E
Population	**nGBM**		**rGBM**		
Methylation status	**u**MGMT	**m**MGMT	**Regardless of methylation status**		
Overall study design	Cycle 1 (42 days with RT), followed by 28-day cycles with selinexor continued until progression	Cycle 1 (42 days with RT), followed by 28-day cycles with selinexor continued until progression and TMZ for 6 cycles	42-day cycles Selinexor continued until progression and lomustine/carmustine[a] for 6 cycles	28-day cycles Selinexor and bevacizumab continued until progression	28-day cycles Selinexor and TTField continued until progression
Phase 1a (Dose-Finding, 3+3)					
Treatment arms	S + RT	S + TMZ + RT	S + Lomustine/ S + Carmustine	S + Bevacizumab	S + TTField
N	9-18 patients	9-18 patients	9-18 patients	9-18 patients	9-18 patients
Primary Endpoint	Assess MTD/RP2D, safety				
Phase 1b (Dose-Expansion; Open-Label)					
Treatment arms	S + RT	S + TMZ + RT	S + Lomustine	S + Bevacizumab	S + TTField
N	11 patients	11 patients	15 patients	17 patients	16 patients
Co-Primary Endpoints	PFS3	PFS3	PFS3	PFS3	PFS3
	OS	OS	OS	OS	OS
Phase 2 (Randomized [1:1], Open-Label)					
Treatment Arm (Experimental)	S + RT	S + TMZ + RT	S + Lomustine	NA	NA
N	54 patients	62 patients	59 patients	NA	NA
Treatment Arm (Control Arm)	TMZ + RT	TMZ + RT	Lomustine	NA	NA
N	54 patients	62 patients	59 patients	NA	NA
Primary Endpoint	PFS by IRC	PFS by IRC	OS	NA	NA

IRC=Independent review committee; MGMT=O6-methylguanine-DNA-methyltransferase; mMGMT=methylated MGMT; MTD=maximum tolerated dose; N=number of patients; NA=not applicable; nMGM= newly diagnosed glioblastoma multiforme; OS=overall survival; PFS3=progression-free survival rate at 3 months; rGBM=recurrent glioblastoma multiforme; RP2D=recommended Phase 2 dose; RT=radiotherapy; S=selinexor; TMZ=temozolomide; TTField=tumor treating fields; uMGMT=unmethylated MGMT.

[a] Carmustine may be substituted for lomustine if lomustine is not available.

Table 2: Schedule of Activities (Arms A and B, Phases 1a/b and 2)

	Screening		Cycle 1 (42 days/cycle)							Cycle 2 containing selinexor (28-day cycle)					Cycles 3-8 for adjuvant therapy with TMZ only, or Cycles 3-8 and beyond for adjuvant therapy containing selinexor (28 days/cycle)				EOT Visit	Safety Follow-up Call	Durability of Response Survival Follow-up[26]
	Prior to start of study		D1	D3	D8	D15	D22	D29	D36	D1	D8	D15	D22	D28	D1	D8	D15	D22	< 14 days after last dose	< 30 days after last dose	Every 3 months after EOT visit
Visit window (days)	≤28 days	≤7 days	± 3 days							± 3 days	± 3 days	± 3 days	± 3 days	- 14 to + 7 days	± 3 days				± 2 days	± 7 days	± 14 days
Study specific ICF[1]	X																				
Randomization[1]	X																				
Inclusion and exclusion criteria	X																				
Demographics	X																				
Medical History[2]	X																				
Confirmation of disease for nGBM	X																				
Archival tissue sample and tissue block[3]																					
Height[4]	X																				
Weight	X		X				X								X				X		X
Physical examination, full (including vital signs)[5,6]	X																		X		
Physical examination, symptom-directed (including vital signs)[5,6]			X				X		X			X[6]			X		X				
Karnofsky assessment [7]	X		X				X								X		X		X		
Neurological assessment per NANO criteria[8]	X													X[8]				X (C4,6,8)	X		
Echocardiogram or MUGA scan[9]	X																				
12 Lead ECG[10]	X																		X		
Hematology (CBC) with differential[11]		X	X		X	X	X	X	X	X		X			X		X		X		
Serum chemistry[11]		X	X		X	X	X	X	X	X		X			X		X		X		
Hematology (CBC) with differential and serum										X[12]	X[12]	X[12]	X[12]		X[12]	X[12]	X[12]	X[12]			

	Screening		Cycle 1 (42 days/cycle)							Cycle 2 containing selinexor (28-day cycle)					Cycles 3-8 for adjuvant therapy with TMZ only, or Cycles 3-8 and beyond for adjuvant therapy containing selinexor (28 days/cycle)				EOT Visit	Safety Follow-up Call	Durability of Response Survival Follow-up[26]
	Prior to start of study		D1	D3	D8	D15	D22	D29	D36	D1	D8	D15	D22	D28	D1	D8	D15	D22	< 14 days after last dose	< 30 days after last dose	Every 3 months after EOT visit
Visit window (days)	≤28 days	≤7 days	± 3 days							± 3 days	± 3 days	± 3 days	± 3 days	- 14 to + 7 days	± 3 days				± 2 days	± 7 days	± 14 days
chemistry for patients with intra-patient dose escalation[12]																					
Serum pregnancy test[13]		X	X[13]												X				X		
Blood draw for PK[14]			X[14]												X[14] (C3 only)						
CCI																					
Assessment of disease status including MRI[16]	X													X				X (C3,4,6,8)	X		
QoL questionnaires EQ-5D, EORTC QLQ-C30, and BN-20[17]	X		X							X					X				X		
CCI																					
Telephone Contact[20]				X																X	X
Selinexor dosing per dose level[21]			X							X					X						
TMZ C1 Daily in treatment Arm B and control groups in Arms A and B. C3-C8 adjuvant dosing regimen[22]			X												X (Adjuvant dosing schedule)						
Radiation Therapy (RT)[23]			2 Gy daily RT for 6-week cycle																		
Concomitant medication[24]	X		X																		
Adverse events	X (SAEs beginning at ICF signing; AEs beginning at first dose) ⟷																				

	Screening		Cycle 1 (42 days/cycle)							Cycle 2 containing selinexor (28-day cycle)					Cycles 3-8 for adjuvant therapy with TMZ only, or Cycles 3-8 and beyond for adjuvant therapy containing selinexor (28 days/cycle)				EOT Visit	Safety Follow-up Call	Durability of Response Survival Follow-up[26]
	Prior to start of study		D1	D3	D8	D15	D22	D29	D36	D1	D8	D15	D22	D28	D1	D8	D15	D22	< 14 days after last dose	< 30 days after last dose	Every 3 months after EOT visit
Visit window (days)	≤28 days	≤7 days	± 3 days							± 3 days	± 3 days	± 3 days	± 3 days	- 14 to + 7 days	± 3 days				± 2 days	± 7 days	± 14 days
Nutritional/Supportive care consultation[25]	X Throughout, as needed but required prior to first dose on C1D1																				

C=cycle; CBC=complete blood count; CT=computed tomography; D=day; ECG=electrocardiogram; EOT=End-of-Treatment; nGBM=newly diagnosed Glioblastoma; ICF=informed consent form; MRI=magnetic resonance imaging; MUGA=multiple gated acquisition; PDn=pharmacodynamics; PK=pharmacokinetics; QoL=quality of life; RT=radiation therapy; TMZ=temozolomide.

In Phase 1 (i.e., dose-finding phase), patients in Arms A and B who have an intra-patient dose escalation will start the next higher dose on Day 1 of the following cycle. In the cycle in which their dose is increased, a clinic visit and physical examination will be performed on Day 15 of the cycle (see Footnote 6) and patients will be followed closely for toxicity with weekly laboratory tests (Days 1, 8, 15, and 22) including CBC and chemistry (see Footnote 12); ±3-day windows for laboratory tests and visits per protocol remain applicable.

[1] Before the first study-specific measures are performed. The Investigator should not repeat procedures that are performed as part of standard of care, if they are within the screening window and are done prior to signing the informed consent form (ICF). Data from standard of care procedures will be part of the patient's medical history and may be used for study purposes. Randomization should be performed ≤14 days prior to the start of study drug.

[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] Archival tissue sample and tissue block can be collected any time during the trial, during Screening or after dosing. The requirement of the sample is mandatory. Proteins and nucleic acids from these samples will be used for correlative studies, which include but are not limited to sequencing and expression analysis.

[4] Body height will be measured at Screening only.

[5] Vital signs: blood pressure, pulse and temperature. Body surface area is calculated based on weight and height.

[6] Full physical examination for baseline and end of treatment visit. Physical examinations during the study should be symptom directed and as clinically indicated. Body surface area is calculated based on weight and height. Physical examination on Cycle 2 Day 15 is **NOT** required for all patients. This is required to be performed **ONLY** for patients in Phase 1 (i.e., dose-finding phase) who have an intra-patient dose escalation and is required to be performed only in the cycle in which their dose was increased.

[7] If Karnofsky assessment was evaluated >3 days before C1D1 during the Screening period, repeat it on C1D1; if ≤3 days before C1D1, don't need repeat it on C1D1. A KPS of 70 is required only at the time of study entry as an inclusion criterion.

[8] A complete neurological assessment per NANO criteria is to be completed at Screening, 4 weeks from the end of Cycle 1 (i.e., in Cycle 2), at the time of each radiological disease response evaluation (to be performed at the visit following the imaging scan), and at end of treatment visit. Neurological examinations during the study should be symptom directed. Any neurological deficits noted during Screening 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. For neurological assessment that is to be performed in Cycle 2, -14 to +7 days visit window is allowed.

[9] Echocardiogram or MUGA scan is applicable for cardiac patients only.

[10] ECGs to be performed predose in supine position. ECGs may be performed as clinically indicated during treatment.

[11] These assessments must be conducted ≤3 days before C1D1. If the results are within required levels, hematology and serum chemistry do not need to be repeated on D1. See Table 19 for a list of parameters. Additional assessment should be conducted as clinically indicated.

[12] For patients in Phase 1 (i.e., dose-finding phase) who have an intra-patient dose escalation, laboratory assessments will be performed weekly on Days 1, 8, 15, and 22 in the cycle following their dose-escalation. Laboratory assessments in the subsequent cycles will follow the schedule as outlined in Footnote 11.

[13] Applicable for women of childbearing potential. Serum β-HCG test at Screening visit, 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. If test was done within up to 3 days prior to dosing, no need to be repeated on dosing day.

[14] Blood draws (2 mL) for PK analysis will be performed on C1D1 and C3D1 at 2, 4, and 6 hrs. postdose. In phase 2, only those patients on the experimental arms (selinexor

CCI

[16] Post-surgery MRI is required, but not necessary to be performed within the Screening Period. Disease status will be measured by contrast-enhanced MRI (or CT for patients unable or unwilling to undergo MRI), including pre-contrast T1/T2/FLAIR, and post-contrast T1, and assessed using the modified RANO criteria at screening, 4 weeks from the end of Cycle 1 (i.e., Cycle 2), end of Cycle 3 (the end of Cycle 3 MRI assessment is only applicable for Phase 1 of the study), end of Cycle 4, and then approximately every 2 cycles (i.e., C6, C8, between Day 22 to Day 28 of the cycle) thereafter, and at the end of treatment. If a patient is unable to undergo MRI post-screening visit, CT will be allowed until the patient is able to resume MRI assessments. For MRI assessment in Cycle 2, −14 to +7 days visit window is allowed. For other neurological assessment, ±3 days visit window is allowed. MRI will be due every 8 weeks for the first year, and then every 12 weeks until progression.

[17]

CCI

[20] Telephone call (or visit) with patient to evaluate supportive care medications, concomitant medications and adverse events, and to adjust supportive care as appropriate. The telephone contact with the patient should take place on Day 3 (+1) following C1D1 selinexor dosing.

[21] Selinexor per dose level, see Section 5.2.1.

[22] TMZ dosed in treatment Arm B and control groups in Arms A and B and in Phase 1 Arm B. Cycle 1 - TMZ 75 mg/m^2 daily. Over Cycles 3-8 - Adjuvant dosing regimen: started at 150 mg/m^2 once daily for 5 consecutive days during Cycle 3; and Cycles 4-8 can increase to 200 mg/m^2 once daily for 5 consecutive days per 28-day treatment cycle as tolerated per investigator's judgment.

[23] Radiation Therapy (RT) performed in treatment and control groups in Arms A and B. Standard Fractionated RT using either RTOG or EORTC methodologies of approximately 60 Gy in 30 fractions. 2 Gy will be administered daily (Days 1-5) unless the treatment schedule requires a change; for Phase 2, radiation 1.8 to 2.0 Gy will be administered.

[24] Concomitant medication: Anti-emetic medication should be given before the first dose and every dose.

[25] Patients must be given documented nutritional consultation to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with study drug. This may be completed within the Screening period for the study and prior to administration of study drug on C1D1. The Investigator or any study staff can provide the nutritional consult in person or by telephone. Nutritional/supportive care is to be provided throughout, as needed.

[26] After discontinuation of study treatment, patients will be followed for PFS approximately every 3 months after end of treatment visit until PD, death or initiation of the subsequent anti-GBM treatment (if a patient discontinues from the treatment due to reasons other than PD), and for survival every 3 months after end of treatment visit until the end of study (i.e., when the last patient in the study has been followed on study treatment for at least 1 year or completed at least 6 months of survival follow-up period after their last dose of study treatment, has withdrawn consent, has died, or has been lost to follow-up, whichever occurs first).

Table 3: Schedule of Activities for Arm C only (Phases 1a/b and 2)

	Screening		Cycle 1 (42 days/cycle)							Cycle 2 and beyond (42 days/cycle)						EOT Visit	Safety Follow-up Call	Durability of Response Survival Follow-up[26]
	Prior to start of study		D1	D3	D8	D15	D22	D29	D36	D1	D8	D15	D22	D29	D36	< 14 days after last dose	< 30 days after last dose	Every 3 months after EOT visit
Visit window (days)	≤28 days	≤7 days	± 3 days							± 3 days						± 2 days	± 7 days	± 14 days
Study specific ICF[1]	X																	
Inclusion and exclusion criteria	X																	
Demographics	X																	
Medical History[2]	X																	
Confirmation of disease progression for rGBM	X																	
Archival tissue sample and tissue block[3]																		
Height[4]	X																	
Weight	X		X				X			X						X		X
Full physical examination with vital signs[5,6]	X															X		
Symptom directed physical examination with vital signs[5,6]			X				X		X	X			X					
Pulmonary function test[7]	X														X[7] (C3 and C6)	X		
Karnofsky assessment[8]	X		X				X			X			X			X		
Neurological assessment per NANO criteria[9]	X								X						X	X		
Echocardiogram or MUGA scan[10]	X																	
12 Lead ECG[11]	X															X		
Hematology (CBC) with differential[12]		X	X		X	X	X	X	X	X	X	X	X	X	X	X		
Serum chemistry[12]		X	X		X	X	X	X	X	X			X			X		
Serum chemistry in patients with intra-patient dose escalation[13]										X[13]	X[13]	X[13]	X[13]	X[13]	X[13]			
Serum pregnancy test[14]		X	X[14]							X						X		
Blood draw for PK[15]			X[15]							X[15] (C2 only)								

CCI

	Screening		Cycle 1 (42 days/cycle)							Cycle 2 and beyond (42 days/cycle)						EOT Visit	Safety Follow-up Call	Durability of Response Survival Follow-up[26]
	Prior to start of study		D1	D3	D8	D15	D22	D29	D36	D1	D8	D15	D22	D29	D36	< 14 days after last dose	< 30 days after last dose	Every 3 months after EOT visit
Visit window (days)	**≤28 days**	**≤7 days**	**± 3 days**							**± 3 days**						**± 2 days**	**± 7 days**	**± 14 days**
Assessment of disease status including MRI[17]	X								X						X	X		
QoL questionnaires[18] EQ-5D, EORTC QLQ-C30, and BN-20	X		X							X						X		
CCI																		
Telephone Contact[21]				X													X	X
Selinexor dosing per dose level[22]			X															
Lomustine/carmustine in treatment and control groups in Arm C[23]			X							X								
Concomitant medication[24]	X		X															
Adverse events	X (SAEs beginning at ICF signing; AEs beginning at first dose)																	
Nutritional/Supportive care consultation[25]	X Throughout, as needed but required prior to first dose on C1D1																	

C=cycle; CBC=complete blood count; CT=computed tomography; D=day; ECG=electrocardiogram; rGBM=recurrent glioblastoma; EOT= End-of-Treatment; ICF=informed consent form; MRI=magnetic resonance imaging; MUGA=multiple gated acquisition; PDn=pharmacodynamics; PK=pharmacokinetics; QoL=quality of life.
In Phase 1 (i.e., dose-finding phase), patients in Arm C who have an intra-patient dose escalation will start the next higher dose on Day 1 of the following cycle. In the cycle in which their dose is increased, patients will be followed closely for toxicity with weekly laboratory tests (Days 1, 8, 15, 22, 29, and 36) including CBC and chemistry and a physical examination on Day 22 (±3-day windows for laboratory tests and visits per protocol remain applicable).

[1] Before the first study-specific measures are performed. The Investigator should not repeat procedures that are performed as part of standard of care, if they are within the screening window and are done prior to signing the informed consent form (ICF). Data from standard of care procedures will be part of the patient's medical history and may be used for study purposes.

[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] Archival tissue sample and tissue block can be collected any time during the trial, during Screening or after dosing. The requirement of the sample is mandatory. Proteins and nucleic acids from these samples will be used for correlative studies which include but are not limited to sequencing and expression analysis.

[4] Body height will be measured at Screening only.

[5] Vital signs: blood pressure, pulse and temperature. Body surface area is calculated based on weight and height.

[6] Full physical examination for baseline and end of treatment visit. Physical examinations during the study should be symptom directed and as clinically indicated. Body surface area is calculated based on weight and height.

[7] Pulmonary function test, including the predicted Forced Vital Capacity (FVC) and Carbon Monoxide Diffuse Capacity (DLCO), will be performed during the screening, on Day 36 of Cycles 3 and 6, and at the EoT visit; and may be performed as clinically indicated during treatment and after completion of 6 cycles of lomustine/carmustine.

[8] If Karnofsky assessment was evaluated >3 days before C1D1 during the Screening period, repeat it on C1D1; if ≤3 days before C1D1, not required to be repeated on C1D1. A KPS of 60 is required only at the time of study entry as an inclusion criterion.

[9] A complete neurological assessment per NANO criteria is to be completed at Screening, at the time of each radiological disease response evaluation (to be performed at the visit following the imaging scan), and at end of treatment visit. Neurological examinations during the study should be symptom directed. Any neurological deficits noted during screening 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.

[10] Echocardiogram or MUGA scan is applicable for cardiac patients only.

[11] ECGs to be performed predose in supine position ECGs may be performed as clinically indicated during treatment.

[12] These assessments must be conducted ≤3 days before C1D1. If the results are within required levels, hematology and serum chemistry do not need to be repeated on D1. See Table 19 for a list of parameters. Additional assessment should be conducted as clinically indicated.

[13] For patients in Phase 1 (i.e., dose-finding phase) who have an intra-patient dose escalation, serum chemistry will be performed weekly on Days 1, 8, 15, 22, 29, and 36 in the cycle in which dose is increased. Laboratory assessments in the subsequent cycles will follow the schedule as outlined in Footnote 12.

[14] Applicable for women of childbearing potential. Serum β-HCG test at Screening visit, 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. If test was done within up to 3 days prior to dosing, no need to be repeated on dosing day.

[15] Blood draws (2 mL) for PK analysis will be performed on C1D1 and C2D1 at 2, 4, and 6 hrs. postdose. In phase 2, only those patients on the experimental arms (selinexor

CCI

Disease status will be measured by contrast-enhanced MRI (or CT for patients unable or unwilling to undergo MRI), including pre-contrast T1/T2/FLAIR, and post-contrast T1 and assessed using the RANO criteria at Screening, at the end of Cycle 1, at the end of every cycle thereafter, and at the end of treatment. If a patient is unable to undergo MRI post-screening visit CT will be allowed until the patient is able to resume MRI assessments. A +3 days visit window prior to the start of next cycle is allowed.

CCI

A sub cohort of patients, up to 70 patients in Phase 1b, and up to 350 patients in Phase 2 will be asked to wear the smart activity watch during Screening period to establish a baseline, and then continuously until EOT visit.

[21] Telephone call (or visit) with patient to evaluate supportive care medications, concomitant medications and adverse events, and to adjust supportive care as appropriate. The telephone contact with the patient should take place on Day 3 (+1) following C1D1 selinexor dosing.

[22] Selinexor per dose level, see Section 5.2.1.

[23] Lomustine dosed in treatment and control groups in Arm C. Carmustine may be substituted if lomustine is not available.

[24] Concomitant medication: Anti-emetic medication should be given before the first dose and every dose.

[25] Patients must be given documented nutritional consultation to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with study drug. This may be completed within the Screening period for the study and prior to administration of study drug on C1D1. The Investigator or any study staff can provide the nutritional consult in person or by telephone. Nutritional/supportive care is to be provided throughout, as needed.

[26] After discontinuation of study treatment, patient will be followed for PFS approximately every 3 months after end of treatment visit by coming to the clinic for imaging and/or clinical assessment until PD, death or initiation of the subsequent anti-GBM treatment (if a patient discontinues from the treatment due to reasons other than PD), and for survival every 3 months after end of treatment visit until the end of study (i.e., when the last patient in the study has been followed on study treatment for at least 1 year or completed at least 6 months of survival follow-up period after their last dose of study treatment, has withdrawn consent, has died, or has been lost to follow-up, whichever occurs first).

Table 4: Schedule of Activities for Arms D and E (Phase 1a/b)

	Screening		Cycle 1 (28 days/cycle)					Cycle 2 and beyond (28 days/cycle)				EOT Visit	Safety Follow-up Call	Durability of Response Survival Follow-up[25]
	Prior to start of study		D1	D3	D8	D15	D22	D1	D8	D15	D22	< 14 days after last dose	< 30 days after last dose	Every 3 months after EOT visit
Visit window (days)	≤ 28 days	≤ 7 days	± 3 days					± 3 days				± 2 days	± 7 days	± 14 days
Study specific ICF[1]	X													
Inclusion and exclusion criteria	X													
Demographics	X													
Medical History[2]	X													
Confirmation of disease progression for rGBM	X													
Archival tissue sample and tissue block[3]														
Height[4]	X													
Weight	X		X				X	X				X		X
Full physical examination with vital signs[5,6]	X											X		
Symptom directed physical examination with vital signs[5,6]			X				X	X			X			
Blood pressure[7]	X		X			X		X		X		X	X	
Karnofsky assessment[8]	X		X				X	X			X	X		
Neurological assessment per NANO criteria[9]	X										X	X		
Echocardiogram or MUGA scan[10]	X													
12 Lead ECG[11]	X											X		
Hematology (CBC) with differential[12]		X	X			X		X		X		X		

	Screening		Cycle 1 (28 days/cycle)					Cycle 2 and beyond (28 days/cycle)				EOT Visit	Safety Follow-up Call	Durability of Response Survival Follow-up[25]
	Prior to start of study		D1	D3	D8	D15	D22	D1	D8	D15	D22	< 14 days after last dose	< 30 days after last dose	Every 3 months after EOT visit
Visit window (days)	≤ 28 days	≤ 7 days	± 3 days					± 3 days				± 2 days	± 7 days	± 14 days
Serum chemistry[12]		X	X			X		X		X		X		
Urine dipstick (Arm D only)[13]		X	X			X		X		X		X	X	
Serum pregnancy test[14]		X	X[14]					X				X		
Blood draw for PK[15]			X[15]					X[15] (C2 only)						
CCI														
Assessment of disease status including MRI[17]	X										X (C2, C3, C4, and every 2 cycles)	X		
CCI														
Telephone Contact[20]				X									X	X
Selinexor dosing per dose level[21]			X					X						
Bevacizumab in Arm D[22]			X			X		X		X				
TTField in Arm E[22]			X (Daily continuously)											
Concomitant medication[23]	X		X											
Adverse events	X (SAEs beginning at ICF signing; AEs beginning at first dose)													
Nutritional/Supportive care consultation[24]	X Throughout, as needed but required prior to first dose on C1D1													

C=cycle; CBC=complete blood count; CT=computed tomography; D=day; ECG=electrocardiogram; rGBM=recurrent Glioblastoma; EOT=End-of-Treatment; ICF=informed consent form; MRI=magnetic resonance imaging; MUGA=multiple gated acquisition; PDn=pharmacodynamics; PK=pharmacokinetics; TTField=tumor treating field.

[1] Before the first study-specific measures are performed. The Investigator should not repeat procedures that are performed as part of standard of care, if they are within the screening window and are done prior to signing the informed consent form (ICF). Data from standard of care procedures will be part of the patient's medical history and may be used for study purposes.

[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] Archival tissue sample and tissue block can be collected any time during the trial, during Screening or after dosing. The requirement of the sample is mandatory. Proteins and nucleic acids from these samples will be used for correlative studies which include but are not limited to sequencing and expression analysis.

[4] Body height will be measured at Screening only.

[5] Vital signs: blood pressure, pulse and temperature. Body surface area is calculated based on weight and height.

[6] Full physical examination for baseline and end of treatment visit. Physical examinations during the study should be symptom directed and as clinically indicated. Body surface area is calculated based on weight and height.

[7] Blood pressure will be assessed at Screening, each visit, more frequently if patient develops hypertension or otherwise clinically indicated, <14 days and <30 days after last dose.

[8] If Karnofsky assessment was evaluated >3 days before C1D1 during the Screening period, repeat it on C1D1; if ≤3 days before C1D1, not required to be repeated on C1D1. A KPS of 60 is required only at the time of study entry as an inclusion criterion.

[9] A complete neurological assessment per NANO criteria is to be completed at Screening, at the time of each radiological disease response evaluation (to be performed at the visit following the imaging scan) i.e., at the end of Cycle 2, end of Cycle 3, end of Cycle 4, and at the end of every 2 cycles thereafter for 1 year (i.e., end of Cycle 6, Cycle 8, etc.) and every 3 cycles after 1 year, and at end of treatment visit. Neurological examinations during the study should be symptom directed. Any neurological deficits noted during Screening 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.

[10] Echocardiogram or MUGA scan is applicable for cardiac patients only.

[11] ECGs to be performed predose in supine position ECGs may be performed as clinically indicated during treatment.

[12] These assessments must be conducted ≤3 days before C1D1. If the results are within required levels, hematology and serum chemistry do not need to be repeated on D1. See Table 19 for a list of parameters. Additional assessment should be conducted as clinically indicated.

[13] For Arm D, urine dipstick for protein at Screening and each visit prior to infusion, < 14 days and < 30 days after last dose, continue after 30 days as clinically indicated. 24-hour urine collection will be performed for patients with a 2+ or greater urine dipstick assessment.

[14] Applicable for women of childbearing potential. Serum β-HCG test at screening visit, 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. If test was done within up to 3 days prior to dosing, no need to be repeated on dosing day.

[15] Blood draws (2 mL) for PK analysis will be performed on C1D1 and C2D1 at 2, 4, and 6 hrs. postdose.

CCI

[17] Disease status will be measured by contrast-enhanced MRI (or CT for patients unable or unwilling to undergo MRI), including pre-contrast T1/T2/FLAIR, and post-contrast T1 and assessed using the modified RANO for Arm D and RANO for Arm E criteria at Screening, at the end of Cycle 2, end of Cycle 3, end of Cycle 4, and at the end of every 2 cycles at least thereafter for 1 year (i.e., end of Cycle 6, Cycle 8, etc.) and every 3 cycles after 1 year, and at the end of treatment. If a patient is unable to undergo MRI post-Screening visit CT will be allowed until the patient is able to resume MRI assessments. A ±3 days visit window prior to the start of next cycle is allowed. Scans can be

CCI

[20] Telephone call (or visit) with patient to evaluate supportive care medications, concomitant medications and adverse events, and to adjust supportive care as appropriate. The telephone contact with the patient should take place on Day 3 (+1) following C1D1 selinexor dosing.

[21] Selinexor per dose level, see Section 5.2.1. The first dose of selinexor will be given on Day 1 Week 1 of each cycle and before bevacizumab and will thereafter be administered on Day 8, Day 15, and Day 22.

[22] Bevacizumab will be administered every 2 weeks in Arm D and arrays for TTField will be worn daily in Arm E by the patients.

[23] Concomitant medication: Anti-emetic medication should be given before the first dose and every dose.

[24] Patients must be given documented nutritional consultation to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with study drug. This may be completed within the Screening period for the study and prior to administration of study drug on C1D1. The Investigator or any study staff can provide the nutritional consult in person or by telephone. Nutritional/supportive care is to be provided throughout, as needed.

[25] After discontinuation of study treatment, patient will be followed for PFS approximately every 3 months after end of treatment visit by coming to the clinic for imaging and/or clinical assessment until PD, death or initiation of the subsequent anti-GBM treatment (if a patient discontinues from the treatment due to reasons other than PD), and for survival every 3 months after end of treatment visit until the end of study (i.e., when the last patient in the study has been followed on study treatment for at least 1 year or completed at least 6 months of survival follow-up period after their last dose of study treatment, has withdrawn consent, has died, or has been lost to follow-up, whichever occurs first).

Table 5: Phase 1 and Phase 2 Dosing Schedule

ARM A Experimental Cycle 1 Radiation Period (42-day Cycle)

Treatment	Week 1							Week 2							Week 3							Week 4							Week 5							Week 6						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28	D29	D30	D31	D32	D33	D34	D35	D36	D37	D38	D39	D40	D41	D42
RT 2Gy daily	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		
Sel dose level-1 60 mg	X																					X																				
Sel dose level 1 60mg	X							X														X							X													
Sel dose level 2 80mg	X							X														X							X													
Sel dose level 3 80mg	X							X							X							X							X							X						

D=Study Day; QW=once weekly; Sel=selinexor oral; RT=radiation therapy.

ARM A Control Cycle 1 Radiation Period (42-day Cycle)

Treatment	Week 1							Week 2							Week 3							Week 4							Week 5							Week 6						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28	D29	D30	D31	D32	D33	D34	D35	D36	D37	D38	D39	D40	D41	D42
RT 2Gy daily	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		
TMZ 75 mg/m2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

D=Study Day; RT=radiation therapy; TMZ=temozolomide.

ARM A Cycle 2

Treatment	Week 1							Week 2							Week 3							Week 4						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28
Sel dose 80 mg	X														X													

D=study day; Sel=selinexor oral.
[1] Selinexor 80 mg on Day 1 and Day 15 in the post-radiation period.

ARM A Experimental Cycles Adjuvant Therapy Period (28-day Cycle) Until PD

Treatment	Week 1							Week 2							Week 3							Week 4						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28
Sel dose 80 mg	X							X							X							X						

D=Study Day; Sel=selinexor oral.

ARM A Control Cycles 3-8 Adjuvant Therapy Period (28-day Cycle) for 6 Cycles

Treatment	Week 1							Week 2							Week 3							Week 4						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28
TMZ 150 mg/m^2	X	X	X	X	X																							

D=Study Day; TMZ=temozolomide.

[1] Temozolomide will be restarted as Cycle 3 at 150 mg/m^2/day for 5 days out of 28 days. Subsequent cycles can increase to 200 mg/m^2/day as tolerated per Investigator's judgment. (only for Phase 2, control arms).

ARM B Experimental Cycle 1 Radiation Period (42-day Cycle)

Treatment	Week 1							Week 2							Week 3							Week 4							Week 5							Week 6						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28	D29	D30	D31	D32	D33	D34	D35	D36	D37	D38	D39	D40	D41	D42
RT 2 Gy daily	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		
TMZ 75 mg/m^2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sel DL −1 60 mg	X																					X																					
Sel DL 1 60 mg	X							X														X							X													
Sel DL 2 80 mg	X							X														X							X													
Sel DL 2a 40 mg	X		X												X		X												X		X											
Sel DL 2b 80 mg	X														X														X													
Sel DL 3a 60 mg	X		X												X		X												X		X											

D=Study Day; DL=dose level; Sel=selinexor oral; RT=radiation therapy; TMZ=temozolomide.

ARM B Control Cycle 1 (42-day Cycle)

Treatment	Week 1							Week 2							Week 3							Week 4							Week 5							Week 6						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28	D29	D30	D31	D32	D33	D34	D35	D36	D37	D38	D39	D40	D41	D42
RT 2Gy daily	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		
TMZ 75 mg/m2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

D=Study Day; RT=radiation therapy; TMZ=temozolomide.

ARM B Cycle 2

Treatment	Week 1							Week 2							Week 3							Week 4							
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28
Sel DL 2a 60 mg[1]	X														X													
Sel DL 3a or DL 2b 80 mg[1]	X														X													

D=study day; Sel=selinexor oral.
[1] Selinexor on Day 1 and Day 15 in the post-radiation period.

ARM B Experimental Cycles 3-8 Adjuvant Therapy Period (28-day Cycle)

Treatment	Week 1							Week 2							Week 3							Week 4						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28
TMZ 150 mg/m^2	X	X	X	X	X																							
Sel DL 2a 60 mg[1]	X							X							X							X						
Sel DL 3a or DL 2b 80 mg[1]	X							X							X							X						

D=Study Day; DL=dose level; Sel=selinexor oral; TMZ=temozolomide
Note: Temozolomide will be restarted as Cycle 3 at 150 mg/m^2/day for 5 days out of 28 days. Cycles 4-8 can increase to 200 mg/m^2/day as tolerated per investigator's judgment. (Phase 1 Arm B and Phase 2 Arm B experimental arm).
[1] Selinexor weekly 60 mg or 80 mg. At Cycle 8, TMZ will be stopped and selinexor will continue until PD.

ARM B Control Cycles 3-8 Adjuvant Therapy Period (28-day Cycle) for 6 Cycles

Treatment	Week 1							Week 2							Week 3							Week 4						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28
TMZ 150 mg/m^2	X	X	X	X	X																							

Abbreviations: D=Study Day; TMZ=temozolomide

[1] Temozolomide will be restarted as Cycle 3 at 150 mg/m^2/day for 5 days out of 28 days. Subsequent cycles can increase to 200 mg/m^2/day as tolerated per Investigator's judgment (only for Phase 2, control arm).

ARM C Experimental ALL Cycles (42-day Cycle)

Treatment	Week 1							Week 2							Week 3							Week 4							Week 5							Week 6						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28	D29	D30	D31	D32	D33	D34	D35	D36	D37	D38	D39	D40	D41	D42
Lomustine dose levels -1,1,2 90 mg/m2	X																																								
Lomustine dose levels 2a,3 110 mg/m2	X																																								
Sel dose level-1 40mg	X							X														X							X												
Sel dose level 1 60mg	X							X														X							X												
Sel dose level 2 80mg	X							X														X							X												
Sel dose level 2a 60mg	X							X														X							X												
Sel dose level 3 80mg	X							X														X							X												

Abbreviations: D=Study Day; Sel=selinexor oral

Note: Carmustine may be substituted, if lomustine is not available.

ARM C Control ALL Cycles (42-day Cycle)

Treatment	Week 1							Week 2							Week 3							Week 4							Week 5							Week 6						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28	D29	D30	D31	D32	D33	D34	D35	D36	D37	D38	D39	D40	D41	D42
Lomustine 110 mg/m2	X																																								

Abbreviations: D=Study Day.
Note: Carmustine may be substituted, if lomustine is not available.

ARM D ALL Cycles (28-day Cycle) (Phase 1a/b only)

Treatment	Week 1							Week 2							Week 3							Week 4						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28
Bev 10 mg/kg IV	X														X													
Sel DL −1 60 mg	X							X							X							X						
Sel DL 1 80 mg	X							X							X							X						

Abbreviations: Bev=Bevacizumab; D=Study Day; DL=dose level; Sel=selinexor.
Note: Dose modifications for Bevacizumab allowed per label.

ARM E ALL Cycles (28-day Cycle) (Phase 1a/b only)

Treatment	Week 1							Week 2							Week 3							Week 4						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28
TTField	Daily																											
Sel DL −1 60 mg	X							X							X							X						
Sel DL 1 80 mg	X							X							X							X						

Abbreviations: D=Study Day; Sel=selinexor; TTField=Tumor Treating Fields.

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AUC	Area under the concentration curve
BIW	Twice weekly
CxDx	Cycle x Day x
CE	Contrast enhancement
CNS	Central nervous system
CPGO	Clinical Practice Guidelines in Oncology
CR	Complete response
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DLBCL	Diffuse large B-cell lymphoma
DLCO	Carbon Monoxide Diffuse Capacity
DLT	Dose limiting toxicity
DOR	Duration of response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End-of-treatment
EU	European Union
FDA	Food and Drug Administration
FLAIR	Fluid-attenuated Inversion Recovery
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GBM	Glioblastoma multiforme
Hb	Hemoglobin
hCG	Human chronic gonadotropin
HR	Hazard ratio

IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDH	Isocitrate Dehydrogenase
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
IRC	Independent review committee
KPS	Karnofsky Performance Score
MedDRA	Medical Dictionary for Regulatory Activities
MGMT	O6-methylguanine-DNA-methyltransferase
MM	Multiple myeloma
mMGMT	Methylated MGMT
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition
NCCN	National Comprehensive Cancer Network
nGBM	Newly diagnosed GBM
NPC	Nuclear pore complex
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PDn	Pharmacodynamic
PFS	Progression-free survival
PFS3	Progression-free survival rate at 3 months
PFS6	Progression-free survival rate at 6 months
PI	Principal Investigator
PK	Pharmacokinetic(s)
PR	Partial response
PT	Preferred term
PTV	Planned target volume
QoL	Quality of life

QW	Once weekly
Q2W	Every 2 weeks
R2PD	Recommended Phase 2 dose
RANO	Response Assessment in Neuro-Oncology
REB	Research Ethics Board
rGBM	Recurrent GBM
rRNA	Ribosomal RNA
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SINE	Selective inhibitor of nuclear export
S-L	Selinexor with lomustine
snRNA	Small nuclear RNA
SoC	Standard of care
SOC	System Organ Class
SRC	Safety Review Committee
S-RT	Selinexor with radiation therapy
S-TRT	Selinexor with radiation therapy and temozolomide
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
TGI	Tumor growth inhibition
TMZ	Temozolomide
TSP	Tumor suppressor protein
TTP	Time-to-progression
TTField	Tumor Treating Fields
ULN	Upper limit of normal
uMGMT	Unmethylated MGMT
USA	United States of America
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
XPO1	Exportin-1

1. INTRODUCTION

1.1. Glioblastoma

Glioblastomas (Grade IV tumors of glial cell origin in the brain) are also known as glioblastoma multiforme (GBM) and World Health Organization Grade IV astrocytoma. GBM is both the most common and most aggressive sub-type of glioma. The average age-adjusted incidence rate is 3.2 per 100,000 population (Ostrom 2015; Ostrom 2014). GBMs present at a median age of 64 years (Thakkar 2014) but can occur at any age, including childhood. Incidence is slightly higher in men than women (1.58:1) and in Caucasians relative to other ethnicities (Ellor 2014).

GBM is an incurable disease with few treatment advances for many years. The prognosis of GBM is poor due in part to its aggressive and extensive infiltration of surrounding central nervous system (CNS) tissue and its frequent inaccessibility for surgical resection within the brain. In addition, the blood-brain barrier presents an obstacle for many chemotherapeutic agents, with only small, lipophilic molecules able to reach the tumor (Upadhyay 2014). Moreover, GBM is frequently refractory to cytotoxic agents that can penetrate the blood-brain barrier, and the 1- and 5-year overall survival (OS) rates are 29% and 5%, respectively. Median survival of patients with newly diagnosed GBM (nGBM) is 15 months (Thakkar 2014). Recurrence of disease is common, and median survival of recurrent disease is approximately 5-7 months (Lombardi 2019).

1.1.1. Standard First-Line Therapy for Patients with Newly Diagnosed GBM

In recent years, surgical resection (debulking), followed by a combination of radiation therapy (RT) and temozolomide (TMZ) has been established as the standard first-line therapy for patients with GBM.

Patients with O6-methylguanine-DNA-methyltransferase (MGMT) promotor methylated (mMGMT) disease or MGMT unmethylated (uMGMT) disease, may be treated with or without TMZ, respectively (Sadones 2009). TMZ, the standard alkylating agent used in the treatment of GBM, is cytotoxic to cells by inducing DNA damage, but this damage can be rapidly repaired by MGMT. Methylation of the MGMT promoter reduces MGMT expression and compromises DNA repair (Qian 1997). The methylation status of the MGMT promoter has been identified as an independent prognostic factor of survival in GBM patients undergoing treatment with TMZ, with significant survival benefit for patients with a mMGMT promoter (~45% of GBM patients) (Stupp 2005; Stupp 2009). In addition, some patients may or may not receive adjuvant TMZ treatment which may depend on methylation status, TMZ tolerability or other factors.

Alternating electric field therapy is the most recent addition in the treatment of newly diagnosed GBM. The Phase 3 randomized trial for nGBM (EF-14) showed that patients treated with alternating electric field therapy had statistically significant improvement in OS, as well as in the 2-, 3-, 4 and 5-year survival rates (Stupp 2016;Stupp 2015). This treatment is not widely used yet.

Unfortunately, a recent attempt to add chemotherapy or biotherapy (such as bevacizumab, cilengitide, Rindopepimut, etc. [Chinot 2014; Stupp 2014; Nabors 2015; Weller 2017; Schuster 2015]) to the concomitant chemoradiation for nGBM has not shown incremental survival benefit. Further studies of immunotherapy for treatment of

nGBM using dendritic cell vaccine, heat shock protein vaccine, and immune checkpoint inhibitors are under way.

In summary, although radiation has been shown to improve outcomes in patients with nGBM, median survival remains poor. Even with the addition of TMZ to surgical resection and radiotherapy, most GBMs will recur in field or adjacent to the high dose radiation volume.

Selinexor has been found to have the effect to sensitize GBM cells to radiation in non-clinical study (Section 1.2.3).

1.1.2. Treatment Options for Patients with Recurrent GBM

Despite first line treatment with maximal safe resection, chemoradiation and TMZ, glioblastomas eventually recur. The TMZ/RT regimen is not curative and patients with nGBM have a high risk for relapse within 6 months - 1 year after the primary treatment. Although the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab was approved for recurrent GBM (rGBM) in 2009, there is still no established standard treatment for rGBM (Gallego 2015). Options at recurrence include surgical resection, bevacizumab, Tumor Treatment Field (TTField), cytotoxic chemotherapy (e.g., lomustine; procarbazine, lomustine, and vincristine [PCV]; TMZ), regorafenib, and clinical trials per NCCN guidelines. Most studies have shown at best modest progression-free survival (PFS) and OS improvements so there remains a high unmet medical need for new therapies to address the poor prognosis of patients with rGBM.

Treatment decisions for patients with recurrent or progressive high-grade GBM must be individualized, taking into account the patient's functional status, tumor burden, and prior treatments. If possible, clinical trials should be considered for patients with good functional status. Since systemic therapy is not curative and there are no randomized trials that directly compare active intervention versus supportive care, the benefit of reintervention must be balanced by the risk of iatrogenic neurotoxicity and its impact on quality of life (QoL). The management of patients with recurrent or progressive disease includes surgery, reirradiation therapy, and systemic therapy.

The most commonly used systemic therapy for recurrent high-grade GBM are nitrosourea-based regimens, e.g., carmustine or lomustine (CCNU) alone or combined with procarbazine and vincristine (PCV). Six-month PFS (PFS6) rates of approximately 20% were seen (Happold 2009; Westphal 2003; Brandes 2004; Kappelle 2001).

GBM was found to be one of the most vascularized human tumors with a high expression of VEGF. Vascular endothelial growth factor expression is associated with a poor prognosis. Promising results were obtained with targeted therapies such as the monoclonal antibody bevacizumab (an antiangiogenic agent) that binds to VEGF inhibiting its activity, for which PFS6 is 25% to 46%. Bevacizumab also showed a positive impact on QoL (Gil-Gil 2013; Bokstein 2008; Vredenburgh 2007; Poulsen 2009; Batchelor 2007; Kesselheim 2011; Chinot 2012). Bevacizumab received accelerated approval for recurrent glioblastoma in 2009 based on 2 studies (Friedman 2009; Kreisl 2009) and full approval in 2017 in the US based on durable objective response rather than survival benefit (Wick 2017).

Alternating TTField were approved for recurrent glioblastoma based upon the results of the EF-11 trial (Stupp 2012). Patients were randomized to TTField versus Investigator's choice active chemotherapy. The primary endpoint was OS. The study failed to show improved survival with TTField, but endpoints with TTField were shown to be equivalent to chemotherapy: OS 6.6 and 6.0 months, 1-year survival 20% and 20% and PFS6 21.4% and 15.1%, respectively.

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

In a non-clinical in vitro study, GBM cell lines treated with varying combinations of lomustine and selinexor demonstrated enhanced cytoxicity when compared to single agent incubations. The current study will also evaluate the effects of selinexor added to the most commonly used systemic therapy, lomustine/carmustine, bevacizumab, and TTField in patients with rGBM upon first relapse.

1.2. Selinexor and Rationale of Evaluating Selinexor in GBM

This study will evaluate the effects of selinexor added to the standard RT therapy in patients with uMGMT nGBM and added to the TMZ/RT therapy in patients with mMGMT nGBM. This study will also evaluate the effects of selinexor added to the most commonly used systemic therapy, lomustine, in patients with rGBM upon first relapse.

1.2.1. Exportin 1 (XPO1) as a Therapeutic Target in GBM

Exportin 1 (XPO1) may be a new, novel target in GBM. XPO1 is overexpressed in GBM and high-grade gliomas, and the degree of XPO1 over-expression correlates with higher tumor grade and poor survival (Liu 2016; Shen 2009). In eukaryotic cells, RNAs are transcribed in the nucleus and exported to the cytoplasm through the nuclear pore complex (NPC). XPO1 is the major export receptor implicated in one of the two distinct RNA export pathways across the NPC (Okamura 2015). This pathway is responsible for exporting ribosomal RNAs (rRNAs), small nuclear RNAs (snRNAs) and a certain subset of messenger RNAs (mRNAs) (Grosshans 2001; Fornerod 1997). Additionally, XPO1 is the sole nuclear exporter of many tumor suppressor proteins (TSPs), including p53 and p27, and is overexpressed in many cancers (Green 2015). In a study of XPO1 expression in gliomas, high XPO1 expression was shown to be correlated with poor patient survival and was dramatically increased in GBM compared to lower grade tumors (Shen 2009). As such, XPO1 has become a protein of interest for targeting in treatment of high-grade gliomas.

1.2.2. Mechanism of Action of Selinexor

Selinexor is an oral, first-in-class, slowly reversible, potent selective inhibitor of nuclear export (SINE) compound that specifically blocks XPO1.

XPO1 is responsible for the unidirectional export of ~220 different cargo proteins from the nucleus to the cytoplasm (Garg 2017; Xu 2012). XPO1 is overexpressed in many cancers, including GBM.

The anti-neoplastic activity of SINE compounds is mediated through at least three distinct pathways involving TSPs, oncoproteins, and the glucocorticoid receptor. First,

SINE compounds induce nuclear localization and functional activation of multiple TSPs, leading to rapid apoptosis of MM (Tai 2014) and other malignant cells. By forcing the nuclear localization and activation of TSPs, all cell types exposed to SINE compounds undergo G1 ± G2 cell cycle arrest, followed by a 'genomic fidelity' review. Cells with genomic damage (i.e., malignant cells) are induced to undergo apoptosis both in vitro and in vivo. Normal cells, with an intact genome, remain in transient, reversible cell cycle arrest until the XPO1 block is relieved (Crochiere 2017; Garg 2017). A second anti-neoplastic effect of SINE compounds is mediated through the mRNA cap-binding protein eIF4E, which is also an XPO1 cargo (Li 2016). Among other functions, eIF4E is responsible for the efficient nuclear export and delivery of several growth-promoting (oncoprotein) mRNAs to cytoplasmic ribosomes for translation (Culjkovic-Kraljacic 2012; Culjkovic 2006). By forcing the nuclear retention of the eIF4E bound to XPO1, SINE compounds reduce the cytoplasmic ribosomal synthesis of oncoprotein mRNAs including c-Myc, hDM2, cyclin D1 and Bcl-XL (Golomb 2012; Tai 2014; Tan 2014). Finally, SINE compounds also lead to restoration of anti-myeloma glucocorticoid receptor signaling in the presence of glucocorticoids; selinexor and other SINE compounds do not appear to exacerbate the hyperglycemic effects of glucocorticoids. Thus, by inhibiting the key nuclear/cytoplasmic control protein XPO1, SINE compounds exhibit broad and deep anti-cancer activities across tumor types (Abdul Razak 2016).

Selinexor's mechanism of action consists of forming slowly reversible covalent bonds to the cysteine 528 cargo pocket of XPO1, thus shutting down XPO1 nuclear export activity. This results in marked nuclear accumulation of TSPs and their functional reactivation of p53, p21, Rb, Ikb, FOXO1A, etc. (Crochiere 2016, Kashyap 2016, Turner 2016) as well as reduced translation of protooncogene proteins (c-myc, bcl-2, mdm2, etc. Golomb 2012, Culjkovic-Kraljacic 2012). Activation of TSPs and downregulation of proto-oncogenes block the cell division cycle and induce apoptosis in both solid and hematologic malignancies, while, at the same time, sparing normal cells.

CCI

1.2.3.1. Selinexor Single Agent Activity

Selinexor demonstrated potent anti-glioma activity in ex vivo patient derived high-grade glioma cell lines (4 adult, 3 pediatric). In addition, selinexor demonstrated single agent activity in a xenograft model of glioma and in a murine orthotopic patient-derived xenograft model of GBM (Green 2015). Importantly, the anti-glioma activity observed in the orthotopic model suggests that therapeutically relevant levels of selinexor are achieved in the brain.

1.2.3.2. Selinexor as a Radiosensitizer

Selinexor has been shown to reduce the expression of DNA damage repair proteins thereby potentiating DNA damage therapy in various cancer models (Kashyap 2014). Consistently, selinexor enhanced the radiosensitivity of GBM stem like cell lines in vitro and in orthotopic xenograft models (Wahba 2018). Similar results were observed in vitro in cell lines resistant to radiotherapy (Green 2015). A recent study investigating

colorectal tumor cells also showed that selinexor enhanced in vitro radiosensitivity. In that study, the proposed mechanism of radiosensitivity was prevention of survivin export into the cytoplasm resulting in increased in radiation-induced apoptosis (Ferreiro-Neira 2016).

1.2.3.3. Selinexor in Combination with Alkylating Agents

Selinexor in combination with many chemotherapeutic agents (such as taxane, platinum, etc.) has been tested in many in vivo models and a synergy effect has been observed.

Selinexor has demonstrated preclinical activity in combination with the alkylating agents TMZ and lomustine (unpublished data). Specifically, LN18 and LN229 cell lines treated with varying combinations of lomustine and selinexor demonstrated enhanced cytoxicity when compared to single agent incubations. Synergy was confirmed in LN18 GBM cells, using the Compusyn software which utilizes the Chou Talaly method, at clinically relevant concentrations of selinexor. In vivo, mice harboring U87-MG tumors were treated with selinexor alone, TMZ alone, or selinexor in combination with TMZ. Mice in the combination arm experienced enhanced tumor growth inhibition (TGI; 97%) when compared to either single agent arm (selinexor 23% TGI, TMZ 68% TGI). These data suggest a combinatorial benefit when using selinexor together with DNA damage inducing GBM therapies.

1.2.3.4. Selinexor in Combination with Bevacizumab

Selinexor showed significant tumor growth inhibition in combination with bevacizumab in a preclinical ovarian cancer model (Miyake 2013).

1.2.3.5. Selinexor in Combination with TTField

Preclinical data shows that combined treatment with selinexor and TTField is favorable. In vitro, the combined treatment of TTField and selinexor demonstrate enhanced efficacy as compared to each treatment alone in LN229, A172 and F98 glioma cell line. In vivo, in F98 intracranial rat glioma model, the combined treatment of TTField (200kHz, 7 days) and 10 mg/kg BIW selinexor (3 doses overall), lead to highest reduction in tumor volume fold increases on the last day of TTField application (Day 14) as compared to the control ($p<0.05$) and to selinexor and TTField alone (the results did not reach statistical significance) (internal unpublished Novocure data).

1.2.4. Overall Clinical Experience

Selinexor has been administered to over 3400 patients worldwide in various cancers such as MM, lymphomas, gynecological cancers, sarcomas, glioblastoma, etc. Selinexor was granted accelerated approval by the US Food and Drug Administration (FDA) in July 2019 in combination with dexamethasone for the treatment of adult patients with relapsed/refractory MM who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38-targeted monoclonal antibody. Selinexor is also approved in the US and in the EU for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy (approved June 2020). Selinexor is

also approved (in US) in combination with bortezomib and dexamethasone for treatment of adult patients with multiple myeloma who have received at least 1 prior therapy.

The most commonly reported treatment-emergent adverse events (TEAEs) among patients in company-sponsored studies have been predominantly low-grade and reversible nausea, fatigue, anorexia (including "decreased appetite"), vomiting, and diarrhea. TEAEs of thrombocytopenia and anemia, which can be higher grade, were reported primarily in patients with hematologic malignancies.

Selinexor treatment has not been associated with any significant major organ toxicity. A pooled safety dataset of company-sponsored studies (Studies KCP-330-001, KCP-330-008, KCP-330-009, KCP-330-010, KCP-330-012, KCP-330-013) showed similar percentages of Grade 3/4 TEAEs among patients with moderate (90%), mild (85.7%) and normal (87.9%) hepatic functions. Moreover, clinically relevant cumulative toxicities have not been observed during long-term treatment. These results suggest that selinexor may be administered long term with acceptable tolerability and offers promise when used in combination with a wide range of other anti-cancer therapies.

Preliminary findings from ongoing clinical studies have shown that selinexor demonstrates therapeutic benefit across a broad range of R/R hematologic and solid tumor cancers, including MM, DLBCL, endometrial cancer, dedifferentiated liposarcoma, and GBM, which is consistent with its proposed mechanism of action.

More information about the clinical safety and efficacy of selinexor is available in the selinexor IB.

1.2.4.1. Clinical Data in GBM - KCP-330-004

KCP-330-004 (KPT-330 in rGBM, KING) is a Phase 2, multiple-arm study with selinexor monotherapy for rGBM patients (Lassman 2020).

Arm A was a surgical arm to explore intra-tumoral pharmacokinetics (PK) (50 mg/m^2 selinexor BIW). The results showed that selinexor can cross the blood-brain barrier with adequate intra-tumoral penetration. The average selinexor tumor concentrations of 136 nM were achieved approximately 2 hours postdose (n=6), which are similar to the selinexor in vitro IC_{50} of 133 nM achieved in patient-derived GBM cells (Green 2015).

Arms B, C, and D were safety and efficacy exploration arms. Arm B (50 mg/m^2 selinexor BIW) was not well-tolerated, leading to closure of this arm and randomization to Arms C and D (60 mg BIW and 80 mg once weekly (QW) fixed dose). The fixed dose once and twice weekly regimens used in this trial appeared to be better tolerated without a large loss of efficacy.

Results from Arms C and D demonstrated singe agent efficacy in patients with >2 median prior treatments, with durable responses and disease stabilization observed in this patient population with a very poor prognosis. The PFS6 of selinexor at 80 mg QW was 17%. Furthermore, overall response rate (ORR) was 10% including very durable response observed in heavily pretreated patients (e.g., 1 partial response [PR] observed in a patient with uMGMT GBM who had received 2 prior systemic therapies; the patient remained on treatment for >3 years. One complete response [CR] was observed in a mMGMT patient who had received 2 prior systemic therapies and the patient remained on treatment for >1 year. Treatment-related hematological adverse events (AEs) included

thrombocytopenia with Grade 1/2 in 6 (20.0%) patients and Grade 3 in 1 (3.3%) patient at the 80 mg QW. Gastrointestinal toxicity was observed, mainly nausea and anorexia, which can be mitigated with the appropriate supportive care (Lassman 2020). Based on the efficacy and favorable toxicity profile of selinexor in this study, the 80 mg weekly dosing was determined to be the recommended Phase 2 dose (RP2D) for further development in GBM.

The rationale for this study is based on the preclinical activity of selinexor in combination with RT (Wahba 2018) and with TMZ or lomustine (unpublished data), good penetration through the blood-brain barrier, as well as the clinical efficacy and favorable side-effect profile of monotherapy selinexor in patients with rGBM.

1.2.4.2. Pharmacokinetics

Oral selinexor PK are predictable, approximately dose-proportional, and exhibit moderate- to moderately-high interpatient variability across a wide dose range in male and female patients with advanced hematological malignancies or solid tumors. The maximum concentration (C_{max}) is typically reached within 4 hours following oral administration of selinexor and the mean half-life is 6 to 8 hours following a single dose of selinexor. The clearance of selinexor is mediated mainly by metabolism catalyzed by CYP3A, UDP-glucuronosyltransferases, and glutathione S-transferases (unpublished data).

Additional details are available in the KPT-330 Investigator's Brochure.

1.3. Study and Dose Rationale

1.3.1. Selinexor Dose Schedule Rationale

Based on preliminary observations from the Phase 1 studies in patients with advanced hematological and solid tumors, selinexor shows a reasonably wide therapeutic range as a single agent, with activity ranging from ~6 mg/m^2 to ≥85 mg/m^2 (approximately 10 mg to 120 mg oral).

In dose escalation studies in patients with advanced hematologic and solid tumor malignancies (Studies KCP-330-001 and KCP-330-002, respectively), selinexor was dosed once or twice weekly and exhibited linear PK and dose-proportional exposure (AUC and C_{max}). In Study KCP-330-002 in solid tumors, the maximum tolerated dose (MTD) of selinexor monotherapy was defined at 65 mg/m^2 using a BIW (Days 1 and 3) dosing schedule, which is approximately equivalent to 110 mg BIW or adult patients with solid tumors assuming the average adult body surface area of 1.7 m^2.

Selinexor single agent at doses of 60 mg BIW and 80 mg QW was found to be well tolerated in the "KING" (KCP-330-004) study (Section 1.2.4.1; Lassman 2020). In this study, selinexor showed antitumor activity with durable responses and disease stabilization in patients with rGBM who were pretreated with median of 2 prior lines of systemic therapy including TMZ/RT, a patient population who usually have a very poor prognosis. At the dose of 80 mg QW, the PFS6 was 17%. Furthermore, ORR was 10% including very durable response observed in heavily pretreated patients (Section 1.2.4.1). Treatment-related hematological AEs included thrombocytopenia with Grade 1/2 in 6 (20.0%) patients and Grade 3 in 1 (3.3%) patient at the 80 mg QW. Gastrointestinal

toxicity was observed, mainly nausea and anorexia, which can be mitigated with the appropriate supportive care (Lassman 2020). Based on the efficacy and favorable toxicity profile of selinexor in this study, the 80 mg weekly dosing was recommended for further development in GBM.

In terms of selinexor doses used in combination study, a dose at 100 mg QW has been evaluated in clinical studies, including an ongoing Phase 3, randomized, controlled, open-label study of a combination of bortezomib and dexamethasone plus or minus selinexor 100 mg QW; as of 15 Feb 2021, enrollment in the study was completed (BOSTON, NCT 03110562).

Furthermore, a dose of 60 mg selinexor QW in combination with a cytotoxic agent, docetaxel, at the standard of care (SoC) dose per label (75 mg/m^2 every 3 weeks) has been selected for patients with non-small cell lung cancer (NSCLC). In an ongoing Investigator-sponsored Phase 1/2 NSCLC study (Texas, USA, NCT03095612), selinexor 60 mg or 80 mg QW in combination with docetaxel 75 mg/m^2 every 3 weeks was evaluated in patients with heavily pretreated NSCLC with KRAS mutation. Based on available safety data, the recommended dose of selinexor is 60 mg QW with docetaxel 75 mg/m^2 every 3 weeks. At the time of the protocol development, 5 patients had post-treatment restaging and best responses included 2 PRs (1 at selinexor 60 mg and 1 at 80 mg, respectively), 2 SD (including 1 patient with 29% target lesion decrease from baseline; both at 60 mg) and 1 with progressive disease (PD).

As safety and tolerability of selinexor have not been assessed in combination with RT, TMZ, lomustine/carmustine, bevacizumab, or TTField, selinexor starting dose in this study will be set at 60 mg QW to provide an appropriate safety margin, with standard 3+3 escalation to determine the MTD and RP2D. Activity has been seen in single agent studies within this dose range and it is anticipated that these doses will provide substantial benefit in combination with RT with or without TMZ, and in combination with lomustine.

In the protocol Version 5.0, the dose level 2 in Arm B (selinexor 80 mg QW at Weeks 1, 2, 4, and 5 with concomitant RT and TMZ) was revised due to occurrence of DLTs at this level. Refer to Section 5.2.1 for further details.

Dosing rationale for concurrent treatments in the study:

Radiation will be given 2 Gy daily for 42 days per current SoC (for Phase 2, radiation 1.8 to 2.0 Gy will be administered).

TMZ will be dosed at 75 or 150 mg/m^2 which is consistent with current SoC.

Lomustine will be dosed at 90 mg/m^2 or 110 mg/m^2 and carmustine will be dosed at 150 mg/m^2 to 200 mg/m^2 intravenously every 6 weeks which is consistent with current SoC.

Bevacizumab will be dosed at 10 mg/kg every 2 weeks which is consistent with current SoC.

TTField will be given at a dose of 200 kHz ≥18h/day. Patients will be encouraged to wear the arrays and have the device turned on as much as possible during the day which is consistent with current SoC.

1.3.2. Potential Benefit and Risk Assessment

Selinexor has been clinically evaluated in over 3400 patients. In clinical studies evaluating selinexor, broad antitumor activity has been observed with continual selinexor treatment in many hematological malignancies and solid tumors including GBM. Selinexor in combination with dexamethasone was approved under accelerated approval for the treatment of adult patients with R/R MM who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody. Selinexor is also approved in the US for the treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy (approved June 2020).

In ongoing clinical studies, the most common adverse events (AEs) reported as at least possibly related to selinexor have been predominantly low-grade and reversible nausea, vomiting, diarrhea, fatigue, and anorexia (decreased appetite). TEAEs of thrombocytopenia and anemia, which can be higher grade, were reported primarily in patients with hematologic malignancies. Most of these AEs can be managed effectively with dose modification and/or supportive care initiated prior to first dose. In addition, 8 tumor lysis syndrome cases have been reported (as of 31 March 2020).

Please refer to the KPT-330 Investigator's Brochure for the most current safety information.

Patients with newly diagnosed GBM (nGBM) and rGBM have few viable treatment options. As described in Section 1.2.3 and Section 1.2.4.1, anti-GBM activity and synergy between selinexor and radiation, TMZ, lomustine, bevacizumab, and TTField have been observed either clinically or non-clinically.

Given the limited treatment options for patients with GBM, the preliminary efficacy signals observed with single-agent selinexor and the consistent safety profile observed, the combination regimens proposed to be evaluated in this study represent a positive benefit/risk assessment for these patients.

Besides the potential synergistic effect, overlapping toxicity with the proposed combination might also be expected. 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. Emerging safety signals, especially common side effects of the agents in the combination regimen (such as myelosuppression effect, GI issues, etc.) will be carefully and closely reviewed by Investigators and Sponsor Medical Monitor. If toxicities are encountered, adjustments will be made to study treatment as detailed in Section 5.5. The safety review committee (SRC) will meet regularly to review the totality of safety data from all patients treated at all dose levels.

1.3.3. Reproductive Risks of Selinexor

Based on data from animal studies and its mechanism of action, selinexor can cause fetal harm when administered to a pregnant woman. Selinexor administration to pregnant animals during organogenesis resulted in structural abnormalities and alterations to growth at exposures below those occurring clinically at the recommended dose.

Pregnant women should be advised of the potential risk to a fetus. Females of reproductive potential and males with a female partner of reproductive potential should be advised to use effective contraception during treatment with selinexor and for 6 months after the last dose (Section 5.12.3.2). Please see the KPT-330 Investigator's Brochure for additional information.

2. STUDY OBJECTIVES

2.1. Primary Objectives

This is a Phase 1/2 study of selinexor in combination with SoC therapy for nGBM or rGBM. This study will be conducted in 2 phases. The modified RANO criteria will be used for assessment in Arms A, B, and D; and RANO criteria for Arms C and E.

The specific primary objectives are as follows:

Objectives	Endpoints
Primary Objectives **Phase 1a** (for all arms) • To assess the MTD per arm • To evaluate the RP2D per arm	**Primary Endpoints** **Phase 1a** (for all arms) • MTD/RP2D per arm • The occurrence of Grade ≥3 AEs, all serious adverse events (SAEs), and all AEs leading to treatment discontinuation
Phase 1b (for all arms) • To determine the efficacy of selinexor in all patients as determined by the 3-month PFS (PFS3) rate with PFS assessment as per RANO/modified RANO per Investigator assessment • To determine the efficacy of selinexor in all patients as determined by the OS	**Phase 1b** (for all arms) • All Arms: PFS3 (survival probability of having PFS ≥3 months as estimated by Kaplan-Meier method per Investigator assessment) • OS, defined as the time from initiation of treatment until death due to any cause
Phase 2 • Arms A and B: to determine the efficacy of selinexor in all nGBM patients as determined by PFS per modified RANO per independent review committee (IRC) in patients randomized to the experimental arm (S-RT in Arm A and S-TRT in Arm B) vs the control arm treated with SoC regimen (TRT) in the targeted population • Arm C: to compare OS in all rGBM patients randomized to the experimental arm (selinexor + lomustine/or carmustine) vs the control arm treated with SoC regimen (lomustine/carmustine) in the targeted population	**Phase 2** • Arms A and B: PFS, defined as the time from date of randomization until the first date of PD or death due to any cause per IRC assessment • Arm C: OS, defined as the time from randomization until death due to any cause

2.2. Secondary Objectives

The specific secondary objectives are as follows. The modified RANO criteria will be used for assessment in Arms A, B, and D; and RANO criteria for Arms C and E.

Secondary Objectives	Secondary Endpoints
Phase 1a • To assess OS for each arm independently	**Phase 1a** • OS
Phase 1a/b • To assess time-to-progression (TTP) and PFS for each arm independently • For Arm C, D, and E only: To evaluate the overall response rate (ORR) and disease control rate (DCR) based on RANO/modified RANO criteria • For Arm C, D, and E only: To assess duration of response (DOR) • To assess selinexor PK in plasma when administered with radiation therapy, temozolomide, and/or lomustine/ carmustine, bevacizumab, and TTField	**Phase 1a/b** • TTP, defined as time from date of first study treatment until progression or death due to progression • PFS • For Arm C, D, and E only: ORR, defined as the proportion of patients who have a response of partial response (PR) or complete response (CR) • For Arm C, D, and E only: DCR, defined as the proportion of patients in whom the best overall response is determined as CR, PR or stable disease (SD) • For Arm C, D, and E only: DOR, defined as time from date of first occurrence of objective response (PR or CR) until progression • Selinexor PK parameters (e.g., clearance [CL], area under the concentration curve [AUC], maximum concentration [C_{max}])
Phase 1b • To obtain additional safety, tolerability data.	**Phase 1b** • To further characterize the occurrence of Grade ≥3 AE, all serious adverse events (SAEs), and all AEs leading to treatment discontinuation and confirm tolerability at the MTD/RP2D.
Phase 2 • Arms A and B: to determine the efficacy of selinexor in all nGBM patients as determined by PFS per modified RANO criteria per investigator assessment in patients randomized to the experimental arm vs the control arm treated with SoC regimen in the targeted population • Arms A and B: to compare OS in all nGBM patients randomized to the experimental arm vs the control arm treated with SoC regimen in the targeted population	**Phase 2** • Arms A and B: PFS per Investigator assessment • Arms A and B: OS for patients with nGBM

• Arm C: to determine PFS per RANO criteria per IRC and investigator assessment in all rGBM patients randomized to the experimental arm vs the control arm treated with SoC regimen in the targeted population.	• Arm C: PFS per IRC assessment • Arm C: PFS per Investigator assessment
• Arm C only: to compare the ORR and DCR based on the response per RANO per Investigator assessment and per IRC in patients randomized to the experimental arm vs the control arm treated with SoC regimen in the targeted population. • Arm C only: to compare the DOR per RANO per Investigator assessment and per IRC in patients randomized to the experimental arm vs the control arm	• Arm C only: ORR per IRC and Investigator assessment • Arm C only: DCR per IRC and Investigator assessment • Arm C only: DOR per IRC and Investigator assessment
• All Arms: to determine the efficacy of selinexor in all patients as determined by the (PFS6) rate where PFS assessment is per RANO/modified RANO per IRC and investigator assessment	• All Arms: PFS6 (survival probability of having PFS ≥ 6 months as estimated by Kaplan-Meier method per IRC and investigator assessment)
• All Arms: to assess the 1 and 2-year OS rate of patients in experimental and control arm	• All Arms: 1-year OS (OS1) and 2-year OS (OS2) rate as estimated by Kaplan-Meier method
• All Arms: to assess the safety and tolerability of treatment in patients randomized to the experimental arm vs the control arm treated with SoC regimen in the targeted population	• All Arms: Safety • All Arms: Incidence of selected Grade ≥3 AEs, including hematological abnormalities, gastrointestinal disorders (nausea, vomiting, and diarrhea), and fatigue • All Arms: Incidence of all SAEs. • All Arms: Incidence of AEs leading to treatment discontinuation


CCI


CCI

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a global, multicenter, open-label, clinical study with Dose Escalation (Phase 1a) followed by Phase 1b (Dose Expansion) and (Phase 2 randomized efficacy exploration) to independently assess the MTD, efficacy, and safety of selinexor in combination with SoC therapy for nGBM or rGBM. The study will independently evaluate 5 different combination regimens in 5 treatment arms in patients with nGBM (Arms A and B) or with rGBM (Arm C, D, and E).

- Arm A: evaluating the combination of selinexor with RT (S-RT) in nGBM patients with uMGMT
- Arm B: evaluating the combination of selinexor with RT and TMZ (S-TRT) in nGBM patients with mMGMT
- Arm C: evaluating the combination of selinexor with lomustine (or carmustine if lomustine is not available) (S-L/C) in rGBM patients regardless of MGMT status
- Arm D: evaluating the combination of selinexor with bevacizumab in rGBM patients regardless of MGMT status
- Arm E: evaluating the combination of selinexor with TTField in rGBM patients regardless of MGMT status

An overview of all study arms is provided in Table 1.

Approximately 465 to 510 patients will be enrolled. For nGBM Arm A, B and rGBM Arm C, Arm D, and Arm E approximately 9 to18 evaluable patients will be enrolled for each arm for a total of 45 to 90 patients. With emerging data and upon SRC agreement, selected dose level can be expanded with additional patients to better understand the safety, anti-tumor activity and PK/pharmacodynamics (PDn) of that dose.

3.1.1. Phase 1a: Dose Escalation Arms

An independent 3+3 dose escalation of selinexor will be performed in each arm (approximately 2~3 dose levels) until the MTD and/or RP2D for that Arm is reached. Safety Review Committee meetings will occur between each dose level to review dose-limiting toxicities (DLTs). Consensus among SRC to proceed to the next dose level will be documented. The SRC is comprised of Investigators and Sponsor Medical Monitors.

In each Arm, based on emerging data and upon SRC approval, selected dose level can be expanded to better understand safety, efficacy, and PK/PDn of that dose. Intra-patient dose escalation is allowed. If a patient is initially enrolled onto a lower dose cohort and tolerates selinexor well (i.e., without any DLTs; or, any ≥Grade 2 thrombocytopenia or neutropenia during the cycle in which dose escalation is considered), this patient can be moved to a higher dose level that clears DLT evaluation and is determined not to exceed MTD. The RP2D to be used in the Phase 2 portion for each Arm will be determined by the SRC, based on the MTD and the totality of efficacy and safety data seen in the Phase 1 dose escalation study.

For more details of Phase 1 dosing and evaluation, see Section 5.4.

3.1.2. Phase 1b: Dose Expansion Phase

The open label Dose Expansion Phase (Phase 1b), will confirm safety of the MTD/RP2D and preliminary signal of efficacy (PFS rate at 3 months [PFS3] compared to historical benchmarks) and OS in patients with nGBM and rGBM before proceeding to Phase 2. Patients will receive the RP2D determined in the Phase 1a in each arm and further information on safety and efficacy will be obtained.

- Arm A: nGBM uMGMT, approximately 11 patients are required with a 1-sided 95% confidence interval
- Arm B: nGBM mMGMT approximately 11 patients are required with a 1-sided 95% confidence interval
- Arm C: rGBM regardless of MGMT status, approximately 15 patients are required with a 1-sided 95% confidence interval
- Arm D: rGBM regardless of MGMT status, approximately 17 patients are required with a 1-sided 95% confidence interval
- Arm E: rGBM regardless of MGMT status, approximately 16 patients are required with a 1-sided 95% confidence interval

3.1.3. Phase 2: Efficacy Exploration/Randomization Phase

During Phase 2, patients will receive the RP2D in each arm in an open-label, randomized design. The number of patients for each arm in the Phase 2 portion will be evaluated again at the end of the Phase 1 portion.

- Arm A: nGBM uMGMT approximately 108 patients (54 patients in S+RT experimental arm and 54 patients in TRT control arm).
- Arm B: nGBM mMGMT approximately 124 patients (62 patients in S+TRT experimental arm and 62 patients in TRT control arm).
- Arm C: rGBM regardless of MGMT status, approximately 118 patients (59 patients in S+L/C experimental arm and 59 patients in L/C control arm).

Randomization in Arm C (Section 7.2) will be stratified based on:

- Number of prior lines of anti-GBM regimens (1 versus >1)

It is planned to randomize patients in a 1:1 allocation to treatment and control arm.

Patients will continue to receive treatment until disease progression (however, patients may stay on treatment if they have documented clinical benefit per the Investigator and after documented approval with the medical monitor), death, toxicity (i.e., AEs that cannot be managed with medical care), or withdrawal from the study.

For more details of Phase 2 dosing and evaluation, see Section 5.4.7.

3.1.4. Concurrent Therapy

Concurrent therapies in this study are:

- Standard Fractionated RT using either Radiation Therapy Oncology Group (RTOG) or EORTC methodologies of approximately 60 Gy in 30 fractions.
- TMZ
- Lomustine (or carmustine, if lomustine is not available)
- Bevacizumab
- TTField

Concurrent therapy will be administered at time points throughout the study according to Table 6.

For more details of concurrent therapy, see Section 5.4.6.

3.1.5. Adjuvant Therapy

Depending on a patient's treatment in Arm A or Arm B, a patient will continue to receive selinexor with or without temozolomide. Temozolomide will be given per SoC in treatment Arms A and B. For more details of adjuvant therapy, see Section 5.4.6.1.2.

3.2. Rationale for Study Design

The results in rGBM (from the Phase 2 KING study) provided guidance for use of selinexor in earlier stages of GBM and to evaluate the use of combination therapies with selinexor. Preclinical data shows that selinexor sensitizes GBM stem-like cells in vitro and in vivo, and colorectal cells in vitro to radiation (Wahba 2018; Ferreiro-Neira 2016). Wahba, et al, demonstrated with polysome profiling that selinexor enhances radiosensitivity in vitro and in vivo by decreasing gene translational efficiency and that translational efficiency recovers to baseline at about 48 hours (Wahba 2018). This suggests that selinexor may be a more effective radiosensitizer when given twice weekly. The rationale for this study is based on the preclinical activity of selinexor in combination with RT (Wahba 2018) and with TMZ or lomustine (unpublished data), good penetration through the blood-brain barrier (as demonstrated in KING study as well as preclinical models averaging 0.72 in rats and 0.61 in cynomolgus monkeys [Green 2015]), as well as the clinical efficacy and favorable side-effect profile of monotherapy selinexor in patients with rGBM.

Arms D (selinexor plus bevacizumab) and E (selinexor plus TTField) were added to the protocol (Protocol Version 5.0) based on the preclinical activity observed with selinexor in combination with bevacizumab and in combination with TTField, the lack of significant overlapping toxicities between selinexor and bevacizumab and TTField, and the poor prognosis and unmet need of patients with recurrent glioblastomas. Arms D and E will be evaluated in Phase 1a and 1b of the study and could be evaluated further in Phase 2 of the study based on the data from Phase 1.

3.3. Study Duration and Dates

For Arms A and B, depending on the treatment arm assignment

- If a patient is only receiving TMZ as adjuvant therapy, after completing the planned 6-cycle adjuvant therapy per label, patients will discontinue study treatment and continue with PFS and survival follow-up.
- If a patient is only receiving selinexor as adjuvant therapy, dosing with selinexor will continue until PD.
- If a patient is receiving both TMZ and selinexor as adjuvant therapy, TMZ dosing will end after the planned 6-cycle adjuvant therapy per label, but selinexor dosing will continue until PD.

The treatment duration of lomustine for Arm C is up to 6 cycles, selinexor will continue at assigned dose until PD.

Patients in Arm D (selinexor + bevacizumab) and Arm E (selinexor + TTField) will continue on treatment until PD, clinical progression, unacceptable toxicity or other discontinuation criteria are met.

Study treatment may continue until completing protocol defined treatment duration (for Arms A and B), disease progression determined by the treating physician per RANO/modified RANO criteria (however patients may stay on treatment if they have documented clinical benefit per the Investigator and after documented approval with the Medical Monitor), unacceptable AEs or failure to tolerate the study treatment, treatment delay of more than 28 days (except in specific cases with documented approval from the Sponsor), any medically appropriate reason or significant protocol violation (in the opinion of the Investigator), or patient decides to discontinue study treatment, withdraws consent, or becomes pregnant.

After discontinuation of study treatment, patients will be followed for safety up to 30 days after last dose, for PFS approximately every 3 months after end of treatment visit until PD, death or initiation of the subsequent anti-GBM treatment (if a patient discontinues from the treatment due to reasons other than PD), and for survival every 3 months after end of treatment visit until the end of study (i.e., when the last patient in the study has been followed on study treatment for at least 1 year or completed at least 6 months of survival follow-up period after their last dose of study treatment, has withdrawn consent, has died, or has been lost to follow-up, whichever occurs first).

4. STUDY POPULATION

4.1. Inclusion Criteria

Patients meeting all of the following inclusion criteria are eligible to enroll in this study:

1. Written informed consent in accordance with federal, local, and institutional guidelines.
2. Age ≥18 years at the time of informed consent and ≥ 22 years for Arm E.
3. Pathologically confirmed glioblastoma (including all histological variants; documentation to be provided) that are newly diagnosed (for Arms A and B) or relapsed disease (for Arms C, D, and E) after 1 to 2 lines of systemic therapy (RT ± TMZ or RT ± TMZ in combination with other drug) (surgical resection of recurrent disease allowed). For Arms A and B, MGMT status should be available.
4. Prior therapy:
   a. Arms A and B: patients who have not received RT or any systemic therapy for brain tumor and must be eligible for definitive external beam RT and TMZ.
   b. Arms C, D, and E: patients must have received prior treatment with RT with or without TMZ and only 1 prior line of therapy) (RT ± TMZ in combination with other drug is allowed).
5. Measurable disease according to RANO/modified RANO guidelines is required only for Arms C, D, and E; it is not required for Arms A or B.
6. Patients enrolling into Arms C, D, and E must be on a stable or decreasing dose of corticosteroids (or none) for at least 5 days prior to the baseline magnetic resonance imaging (MRI).
7. KPS greater than or equal to 70 (for Arms A and B) and 60 (for Arms C, D, and E).
8. Patients must have adequate organ function ≤2 weeks of study treatment as defined by the following laboratory criteria:
   a. Hematological function ≤7 days prior to C1 D1: absolute neutrophil count (ANC) ≥1.5 x 10^9/L; platelet count ≥150 x 10^9/L; and hemoglobin (Hb) ≥10.0 g/dL. Transfusion is not allowed within 7 days prior to C1D1.
   b. Hepatic function: bilirubin ≤2 x the upper limit of normal (ULN), ALT (alanine transaminase) ≤2.5 x ULN, AST ≤2.5 x ULN; unless bilirubin elevation is related to Gilbert's Syndrome for which bilirubin must be <4 x ULN.
   c. Renal function: calculated (Cockcroft-Gault) or measured creatinine clearance ≥30 mL/min.
9. Female patients of childbearing potential must have a negative serum pregnancy test at Screening and agree to use highly effective methods of contraception throughout the study and for 6 months following the last dose of study treatment.
10. Fertile male patients who are sexually active with a female of childbearing potential must use highly effective methods of contraception throughout the study and for 6 months following the last dose of study treatment.

11. For Arms A and B: patients must have had surgery and/or biopsy not greater than 8 weeks prior to initial screening.
12. Patients must consent to provide tumor tissue and blood samples to be used for future molecular testing for correlative studies.
13. Limited to supratentorial disease for Arm E only.

4.2. Exclusion Criteria

Patients meeting any of the following exclusion criteria are not eligible to enroll in this study:

1. Patients who are receiving any other investigational agents and/or have had prior therapy including:

   For Arms A and B only:

   a. Patients who have previously received RT to the brain.
   b. Patients who received chemotherapy for the treatment of their glioma.
   c. Patients who are being treated with implanted Gliadel wafers.

   For Arm C:

   d. Prior nitrosoureas.

   For Arms C, D, and E:

   e. <4 weeks from prior TMZ or other chemotherapy, or <4 weeks or 5 half-lives (whichever is shorter) for investigational agents prior to start of study treatment.
   f. Prior treatment bevacizumab or other direct VEGF/VEGFR inhibitors. For any questions of the definition of a direct VEGF/VEGFR inhibitor, consult the study Medical Monitor.
   g. Any AE which has not recovered to Grade ≤1, or returned to baseline, related to the previous GBM therapy, except alopecia, and some other Grade 2 AEs that have been stabilized (upon Medical Monitor approval).
2. Patients who are being treated or plan to be treated during this study with TTField for patients in Arms A to D.
3. Major surgery <2 weeks prior to the start of study treatment for Arms A to C and E, <4 weeks for Arm D.
4. History of allergic reactions attributed to compounds of similar chemical or biological composition to selinexor or other study treatment.
5. Patients must not have significantly diseased or obstructed gastrointestinal tract malabsorption, uncontrolled vomiting or diarrhea, or inability to swallow oral medication.
6. Patients with coagulation problems and medically significant bleeding in the month prior to start of treatment (peptic ulcers, epistaxis, intracranial hemorrhage, spontaneous bleeding). Prior history of deep vein thrombosis (DVT) or pulmonary embolism (PE) is not exclusionary.
7. Currently pregnant or breastfeeding.

8. For Arms A and B: patients with pre-existing known or suspected radiation sensitivity syndromes will be excluded due to potential confounding effect on outcome.
9. Any life-threatening illness, active medical condition, organ system dysfunction, or serious active psychiatric issue which, in the Investigator's opinion, could compromise the patient's safety or the patient's ability to remain compliant with study procedures.
10. Uncontrolled (i.e., clinically unstable) infection requiring parenteral antibiotics, antivirals, or antifungals within 7 days prior to first dose of study treatment; however, prophylactic use of these agents is acceptable even if parenteral.
11. Patients with mutated Isocitrate Dehydrogenase (IDH) should be excluded for Phase 2.
12. For patients in Arm C, forced vital capacity (FVC) or carbon monoxide diffusing capacity (DLCO) below 70% of predicted.
13. For Arm E: implanted active electronic medical devices such as programmable intraventricular shunts, spinal cord, vagus nerve or deep brain stimulators, pacemakers or implantable automatic defibrillators, skull defect (i.e. missing bone with no replacement), sensitivity to conductive hydrogels as used in ECGs, an underlying serious scalp condition that may interfere with placement of arrays, or bullet fragments, or documented clinically significant arrythmias.

5. STUDY TREATMENTS

5.1. Treatments Administered

5.1.1. Study Drugs

A summary of characteristics for each investigational medicinal product (IMP), including dose formulation, unit dose strength(s), and route of administration is provided in Table 6. In addition to IMP, patients in Arm A and Arm B will receive RT 2 Gy daily with a 5 days on/2 days off schedule for the 6 weeks of Cycle 1. In Phase 2, radiation 1.8 to 2.0 Gy will be administered.

The investigational drug in this study, selinexor, is blue, round, bi-convex and film-coated 20 mg tablets with “K20” debossed on one side and nothing on the other side. Selinexor tablets are packaged in blister packs.

Table 6: Study Drugs Administered

Arm Name	Arms A, B, C, D, E	Arm A and Arm B	Arm C		Arm D	Arm E
Intervention Name	Selinexor (KPT-330)	Temozolomide (TMZ)	Lomustine (CCNU)	Carmustine (BiCNU)	Bevacizumab	Tumor Treating Fields
Type	Drug	Drug	Drug	Drug	Drug	Wearable Portable Device
Dose Formulation	Tablet	Capsule	Capsule	Lyophilized powder in a single dose vial for reconstitution	Single use vial	Electrical fields generator with transducer arrays.
Unit Dose Strength(s)	20 mg	5, 20, 100, 140, 180, or 250 mg	10, 40 or 100 mg	100 mg	100 mg/4 mL and 400 mg/16 mL	≥18h/day
Dose to be administered	Per dose level	75 or 150 mg/m^2	90 or 110 mg/m^2	150 to 200 mg/m^2	10 mg/kg	TTField 200 kHz
Dosage Frequency	QW continuously or with drug holiday depending on dose level assigned	Daily	Q6W on Day 1 of each cycle	Q6W on Day 1 of each cycle (42-day cycle)	Q2W 28-Day cycles	Daily
Route of Administration	Oral	Oral	Oral	Intravenous	Intravenous	Scalp application of transducer arrays
Use	Experimental intervention	Concomitant SoC therapy	Concomitant SoC therapy	Concomitant SoC therapy	Concomitant SoC therapy	Concomitant SoC therapy
Sourcing	Provided centrally by the Sponsor	Provided locally by the trial site, subsidiary, or designee	Provided locally by the trial site, subsidiary, or designee	Provided locally by the trial site, subsidiary, or designee	Provided locally by the trial site, subsidiary, or designee	Provided locally by the trial site, subsidiary, or designee
Packaging and Labeling	Selinexor 20 mg tablets will be provided in packaging labeled as required per country requirement	TMZ will be provided to patients in standard manufacturer packaging and will be labeled as required per country requirement	Lomustine will be provided to patients in standard manufacturer packaging and will be labeled as required per country requirement	Carmustine will be provided to patients in standard manufacturer packaging and will be labeled as required per country requirement	Bevacizumab will be provided to patients in standard manufacturer packaging and will be labeled as required per country requirement	TTField will be provided to patients in standard manufacturer packaging and will be labeled as required per country requirement

BiCNU=carmustine; CCNU=lomustine; QW=once weekly; Q2W=once every 2 weeks; Q6W=once every 6 weeks; SoC=standard of care; TMZ=temozolomide; TTField=tumor treating fields.

5.2. Drug Administration

5.2.1. Selinexor

Selinexor will be administered orally at an initial dose of 60 mg in treatment Arms A, B, and C and 80 mg in Arms D and E in Phase 1, and thereafter administered according to the drug administration and dose-escalation schedule provided in Section 5.4 to establish the MTD and RP2D for each treatment arm for Phase 2.

The first dose level of selinexor in treatment Arms A and B will be given on Day 1 of radiation and will thereafter be administered weekly on the first day of radiation during weeks determined by dose level. If this dose level is tolerated, a new dose level will open with SRC approval and the new dose will be escalated to 80 mg on Weeks 1, 2, 4, and 5. If the first dose level is not tolerated, a new dose level will open with SRC approval and the selinexor dose of 60 mg will be given at reduced frequency on Weeks 1 and 4 only (Section 5.4.1). and Section 5.4.2).

With protocol Version 5.0, the planned dose level 2 in Arm B, 80 mg QW at Weeks 1, 2, 4, and 5 with concomitant RT and TMZ, was revised due to occurrence of 2 DLTs among the 3 patients enrolled at this dose level. The DLTs included 1 patient who missed 2 of 4 doses of selinexor due to Grade 2 to 4 thrombocytopenia, and another patient who developed Grade 4 neutropenia > 7 days.

Three new dosing levels are being introduced: 2a, 2b, and 3a each of which will maintain the 3+3 design.

- Dose level 2a will evaluate 40 mg Days 1 and 3, Weeks 1, 3, 5.
- Dose level 2b will evaluate 80 mg Day 1 of Weeks 1, 3, 5. This dose level reduces the number of doses during the 6 weeks of the concomitant phase of treatment with RT and TMZ from the current 4 to 3 while maintaining the 80 mg dose.
- Dose level 3a will evaluate 60 mg Days 1 and 3, Weeks 1, 3, 5.

Dose levels 2a and 2b will enroll concurrently and patients will be randomly assigned to dose level 2a and 2b until either of these 2 dose levels stops enrollment.

- If Dose level 2a clears the DLT evaluation period per the SRC, the next dose level, 3a, will enroll at 60 mg, Days 1 and 3, Weeks 1, 3, 5. The dose of 60 mg twice weekly is the approved dose of XPOVIO for DLBCL and was evaluated in Arm C in KCP-330-004 (KING) in recurrent GBM.

If dose level 2b clears the DLT evaluation period, there will be no further dose escalation. This will be the MTD at this schedule.

In treatment Arm C, selinexor will be given on Day 1, Day 8, Day 22, and Day 29. If the first dose level is tolerated, a new dose level will open with SRC approval and the new dose will be escalated to 80 mg on Weeks 1, 2, 4, and 5. If the first dose level is not tolerated, the dose of 40 mg will be given on Weeks 1, 2, 4, and 5 (Section 5.4.3).

In treatment Arms D and E, selinexor will be given at 80 mg on Day 1, Day 8, Day 15, and Day 22. If this dose level is not tolerated, the dose of 60 mg will be given on Day 1, Day 8, Day 15, and Day 22.

All dosages prescribed to the patient and all dose changes during the study must be recorded on the electronic case report form (eCRF).

5.2.2. Temozolomide

Temozolomide will be administered orally daily at a dose of 75 mg/m^2 in Cycle 1 in treatment Arms A and B only (Arms A and B control arms, Arm B experimental arm, and Arm B Phase 1). The first dose will be given on the first day or evening prior to Day 1 of radiation and will be administered daily thereafter until the completion of RT. Post-RT, temozolomide will be administered orally daily as adjuvant therapy in treatment Arms A and B (Arms A and B control arms, Arm B experimental arm, and Arm B Phase 1) per SoC at a dose of 150 mg/m^2 on Days 1 to 5 of 28 days in Cycle 3; and increased to 200 mg/m^2 as tolerated per Investigator's judgment in Cycle 4 to 8. Further details are provided in the drug administration and dose escalation schedule in Section 5.4 and the concurrent therapy table in Table 13.

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

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.

5.2.3. Lomustine

Lomustine will be dosed orally in treatment Arm C according to the dose administration and dose escalation schedule provided in Section 5.4. The first dose will be given on the first day (C1D1) and thereafter will be administered every 6 weeks on Day 1 of the cycle (once per cycle) at a dose of 90 mg/m^2 for dose level -1, level 1, and level 2. If tolerated, lomustine will be escalated to 110 mg/m^2 for dose level 2a and level 3.

If lomustine is not available, carmustine can be substituted and should be administered intravenously according to the dose administration and dose escalation schedule provided in Section 5.4 and as per the carmustine label.

The first dose will be given on the first day (C1D1) and thereafter will be administered every 6 weeks on Day 1 of the cycle (once per cycle) at a dose of 150 mg/m^2 for dose level -1, 1, and 2. If tolerated, carmustine will be escalated to 200 mg/m^2 for dose level 2a and 3. Carmustine dosing, premedications, and dose modifications will be in accordance with the carmustine label.

The Investigator or responsible site personnel will administer lomustine or carmustine on-site as per protocol. Study drug will be administered 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.

5.2.4. Bevacizumab

Bevacizumab will be administered intravenously in treatment Arm D according to the dose administration and dose escalation schedule provided in Section 5.4. The first dose will be given on the first day (C1D1) and thereafter will be administered every 2 weeks at a dose of 10 mg/kg.

The Investigator or responsible site personnel will administer bevacizumab on-site as per protocol. Study drug will be administered 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.

5.2.5. Tumor Treating Fields

Tumor Treating Fields (TTField) is a wearable, portable, FDA-approved device. TTField will be administered in Arm E at a dose 200 kHz for ≥18 hours daily in 28-days cycles according to the dose administration and dose escalation schedule provided in Section 5.4. The treatment will be initiated on the first day (C1D1) and thereafter will be administered daily.

The Investigator or responsible site personnel will initiate TTField therapy on-site as per protocol and patients will be instructed to continue using TTField daily. All details regarding dosing prescribed to the patient and any changes during the study must be recorded in the eCRF. Information regarding number of hours that the TTField device is worn daily will be collected.

5.3. Study Drug Dosing and Administration

5.3.1. Labeling

Each drug container will be labeled in accordance with current International Council for Harmonisation (ICH), Good Clinical Practice (GCP), and specific regulatory requirements, e.g., FDA, Health Canada, European Medicines Agency, etc. Containers for take-home use may require additional in-pharmacy labeling with take-home and patient-specific instructions (such as exact dose) depending on country-specific regulations or laws.

All treatments will be labeled in accordance with current ICH, GCP, FDA, Health Canada, and European Medicines Agency regulations and guidelines. Labels will include the medication name, storage conditions, and batch number, and will comply with language and legal requirements of Canada, the European Union (EU), and the US.

5.3.2. Dispensing Directions

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

5.3.3. Dosing Information

For doses of study medication that are to be taken on non-clinic days, the patient will be provided with oral study drugs (including selinexor, temozolomide, lomustine) by the hospital pharmacy.

The doses of study treatments for individual patients should remain constant throughout the study unless dose modification needs to be implemented due to toxicity or upon SRC recommendation. Selinexor dose escalation in Phase 1 to determine the RP2D for the Expansion Phase will occur according to directions in Section 5.4. Note: No patient's dose of selinexor may exceed 70 mg/m^2 (approximately 100 mg).

5.3.4. Dosing Instructions for Patients

Study medications will be dosed according to the schedules provided in Section 5.4.

For doses of oral medications to be taken on non-clinic days, patients will be provided with medication to take home.

Selinexor tablets should be taken orally with at least 120 mL (4 ounces) of water. Selinexor can be taken with or without food. In order to avoid contact with skin, tablets must be swallowed whole and should not be broken, chewed, crushed, or divided.

On Day 3 following C1D1 selinexor dosing, a telephone call (or visit) with the patient must take place to evaluate supportive care medications, concomitant medications and adverse events, and to adjust supportive care as appropriate.

5.4. Dose Schedules for Evaluation

This study will use a 3+3 design, with 3-6 patients enrolled per dose level to define MTD. The MTD is the dose level at which no more than 1 of up to 6 patients experience DLT during the first 42-day treatment cycle in Arms A, B, and C and 28-day treatment cycle in Arms D and E, and the dose above that at which at least 2 (of ≤6) patients have DLT as a result of selinexor/RT/TMZ/lomustine/bevacizumab/TTField. If a patient did not experience DLT and did not finish treatment during the radiation period for Arm A and B or first treatment cycle for Arm C, D, and E, he or she will not be evaluable for DLT and will be replaced in the dose level. Enrollment to a dose level would stop if 2 or more patients had a DLT.

In order to accurately characterize MTD/RP2D dose level, based on emerging data and with SRC approval, the number of patients may be increased for the potential MTD and/or RP2D dose level.

Intra-patient dose escalation is allowed. If a patient is initially enrolled onto a lower dose cohort and tolerates selinexor well (i.e., without any DLTs; or, any ≥Grade 2 thrombocytopenia or neutropenia during the cycle in which dose escalation is considered), this patient can be moved to a higher dose level that clears DLT evaluation and is determined not to exceed MTD. Patients who have an intra patient dose escalation will start the next higher dose on Day 1 of the cycle following approval. In the cycle in which their dose was increased, patients in Arms A and B will be followed closely for toxicity with weekly laboratory tests (Days 1, 8, 15, and 22) including complete blood count (CBC) and chemistry. A clinic visit and physical examination will be performed on Day 15 of the cycle in which their dose was increased. For patients in Arm C, weekly laboratory tests will be performed on Days 1, 8, 15, 22, 29, and 36 and a physical examination on Day 22 in the cycle in which the dose is escalated. Note that ±3-day windows for laboratory tests and visits per protocol remain applicable.

Dose-escalation will follow the rules outlined below in Table 7.

Drug administration and dose-escalation by treatment arm will follow the Drug Administration and Dose Escalation Schedule provided in Table 8 through Table 12.

Table 7: Dose Escalation Rules

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enroll 3 patients at the next higher dose level
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose. Up to 3 additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enroll 3 more patients at this dose level. • If 0 of these 3 additional patients experience DLT, proceed to the next higher dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Up to 3 additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level at or below the maximally administered dose	This is the MTD. RP2D can be at or below MTD and will be determined based on the totality of the available safety, efficacy, PK/PDn data from all dose levels. At least 6 patients must be entered at the RP2D.

DLT=dose-limiting toxicity; MTD=maximum tolerated dose.

The number of patients defined in this table are those patients considered evaluable for DLT and MTD evaluation unless they cannot complete the first cycle of therapy for any reason other than a DLT. A patient will be DLT-evaluable if the patient experiences a DLT in Cycle 1, or has taken at least 2 out of the 3, or at least 3 out of the 4, or at least 4 out of the 6 planned selinexor doses (depending on planned dosing frequency) or both doses if a patient is dosed twice only in Cycle 1 without experiencing a DLT. A patient who is not DLT-evaluable will be replaced. Dose level review discussions will be held by the Sponsor and Investigators to determine dose escalation, reductions, and dose level expansions.

5.4.1. Arm A (S-RT): Selinexor in nGBM uMGMT

Selinexor will be dosed QW with or without drug holiday in a 42-day cycle in patients registered to treatment Arm A with nGBM uMGMT using the schedule and guidelines for dose-escalation provided in Table 8.

Table 8: Dose Escalation Schedule for Arm A (S-RT): Selinexor in nGBM uMGMT

Dose Levels	Selinexor, Day 1 of each treatment week during radiation period; **Then QW at 80 mg after radiation stops**[1]	Radiation Treatment Daily; continue until radiation stops (42-day treatment duration unless stopping early for toxicity)
-1	60 mg Weeks 1, 4	2 Gy
1	60 mg, Weeks 1, 2, 4, 5	2 Gy
2	80 mg, Weeks 1, 2, 4, 5	2 Gy
3	80 mg, Weeks 1, 2, 3, 4, 5, 6	2 Gy

QW=once weekly.
[1] The dose regimen specified in the table is for radiation period (Cycle 1) only. After the radiation stops, selinexor 80 mg will be dosed on Day 1 and Day 15 in Cycle 2, and subsequently will continue at 80 mg QW as adjuvant therapy until PD (see Table 13).

5.4.2. Arm B (S-TRT): Selinexor in nGBM mMGMT

Selinexor will be dosed QW with or without drug holiday in a 42-day cycle in patients registered to treatment Arm B with nGBM or mMGMT using the schedule and guidelines for dose-escalation provided in Table 9.

As discussed in Section 5.2.1, with protocol Version 5.0, the planned dose level 2 in Arm B, 80 mg QW at Weeks 1, 2, 4, and 5 with concomitant RT and TMZ, was revised due to occurrence of 2 DLTs among the 3 patients enrolled at this dose level. The DLTs included 1 patient who missed 2 of 4 doses of selinexor due to Grade 2 to 4 thrombocytopenia, and another patient who developed Grade 4 neutropenia > 7 days.

Three new dosing levels are being introduced: 2a, 2b, and 3a each of which will maintain the 3+3 design.

- Dose level 2a will evaluate 40 mg Days 1 and 3, Weeks 1, 3, 5.
- Dose level 2b will evaluate 80 mg Day 1 of Weeks 1, 3, 5. This dose level reduces the number of doses during the 6 weeks of the concomitant phase of treatment with RT and TMZ from the current 4 to 3 while maintaining the 80 mg dose.
- Dose level 3a will evaluate 60 mg Days 1 and 3, Weeks 1, 3, 5.

Dose levels 2a and 2b will enroll concurrently and patients will be randomly assigned to dose level 2a and 2b until either of these 2 dose levels stops enrollment.

- If Dose level 2a clears the DLT evaluation period per the SRC, the next dose level, 3a, will enroll at 60 mg, Days 1 and 3, Weeks 1, 3, 5. The dose of 60 mg

twice weekly is the approved dose of XPOVIO for DLBCL and was evaluated in Arm C in KCP-330-004 (KING) in recurrent GBM.

If dose level 2b clears the DLT evaluation period, there will be no further dose escalation. This will be the MTD at this schedule.

Table 9: Dose Escalation Schedule for Arm B (S-TRT): Selinexor in nGBM mMGMT

Dose Levels	Selinexor Day 1 of each treatment week during radiation period; Then once weekly after radiation stops[a]	TMZ Once daily (QD) for 42 days; Then adjuvant therapy per label after radiation stops[a]	RT Daily Continue until RT stops (42-day treatment duration unless stopping early for toxicity)
-1	60 mg, Weeks 1, 4	75 mg/m^2	2 Gy
1	60 mg, Weeks 1, 2, 4, 5	75 mg/m^2	2 Gy
2	80 mg, Weeks 1, 2, 4, 5	75 mg/m^2	2 Gy
2a	40 mg, Days 1 and 3, Weeks 1, 3, 5	75 mg/m^2	2 Gy
2b	80 mg, Day 1, Weeks 1, 3, 5	75 mg/m^2	2 Gy
3a	60 mg, Days 1 and 3, Weeks 1, 3, 5	75 mg/m^2	2 Gy

RT=radiotherapy; TMZ=temozolomide.
[a] The dose regimen specified in the table is for radiation period only. After the radiation stops, TMZ will continue as adjuvant therapy per label for 6 cycles (Cycles 3-8). Selinexor will be dosed at 60 mg (dose level 2a) or 80 mg (dose level 2b and 3a) on Day 1 and Day 15 in Cycle 2, and subsequently continued at the same dose once weekly until PD.

5.4.3. Arm C (S-L/C): Selinexor in rGBM

Selinexor will be dosed QW on a 42-day cycle in patients registered to treatment Arm C with rGBM using the schedule and guidelines for dose-escalation provided in Table 10.

Table 10: Dose Escalation Schedule for Arm C (S/L): Selinexor in rGBM (42-Day Cycle)

Dose Levels	Selinexor weekly (Days 1, 8, 22, 29)	Lomustine Day 1 of each cycle	Carmustine (to be substituted if lomustine is not available) Day 1 of each cycle
-1	40 mg	90 mg/m^2	150 mg/m^2
1	60 mg	90 mg/m^2	150 mg/m^2
2	80 mg	90 mg/m^2	150 mg/m^2
2a	60 mg	110 mg/m^2	200 mg/m^2
3	80mg	110 mg/m^2	200 mg/m^2

Note: If no DLT in Cohort 2, escalate from Dose Level 2 to 3.
If there is a DLT in Cohort 2, and dose escalation to Dose Level 3 is not possible, evaluation of Dose Level 2a as an alternative regimen will be considered.

If Dose Level 3 is not tolerated, Dose Level 2 could be declared as MTD or exploring 2a as an alternative regimen could be considered.

5.4.4. Arm D: Bevacizumab: Selinexor in rGBM

Selinexor will be dosed QW on a 28-day cycle in patients enrolled in treatment Arm D with rGBM using the schedule and guidelines for dose-escalation provided in Table 11.

Table 11: Dose Escalation Schedule for Arm D (S-Bev): Selinexor in rGBM (28-Day Cycle)

Dose Levels	Selinexor weekly	Bevacizumab 10 mg/kg IV Q2W
-1	60 mg (Days 1, 8, 15, 22)	10 mg/kg IV Q2W
1	80 mg (Days 1, 8, 15, 22)	10 mg/kg IV Q2W

Q2W=every 2 weeks.
Note: Administration of bevacizumab should be performed per label and dose reductions/modifications for bevacizumab are allowed per label.

5.4.5. Arm E (S-TTField): Selinexor in rGBM

Selinexor will be dosed QW on a 28-day cycle in patients enrolled in treatment Arm E with rGBM using the schedule and guidelines for dose-escalation provided in Table 12.

Table 12: Dose Escalation Schedule for Arm E (S-TTField): Selinexor in rGBM (28-Day Cycle)

Dose Levels	Selinexor weekly	TTField 200 kHz ≥18h/day
-1	60 mg (Days 1, 8, 15, 22)	200 kHz ≥18h/day
1	80 mg (Days 1, 8, 15, 22)	200 kHz ≥18h/day

5.4.6. Concurrent Therapy

5.4.6.1. Arms A & B

Concurrent therapy for Arm A and Arm B for the combination and adjuvant periods are presented in Table 13.

Table 13: Concurrent Therapy (Arm A and Arm B)

Arm	Radiation Period (42 days)	Adjuvant Therapy Period (28 days per cycle for 6 cycles or beyond)
A (Phase 1a/b) A Experimental	RT 2 Gy daily Selinexor per dose level	Selinexor 80 mg once weekly until PD
A Control	RT 2 Gy daily TMZ 75 mg/m^2 daily	TMZ started as Cycle 3 at 150 mg/m^2, then increased to 200 mg/m^2 as tolerated per Investigator's judgment in Cycles 4-8 for adjuvant therapy per label on Days 1-5 per 28-day cycle
B (Phase 1a/b) B Experimental	RT 2 Gy daily TMZ 75 mg/m^2 daily Selinexor per dose level	TMZ started as Cycle 3 at 150 mg/m^2 then increased to 200 mg/m^2 as tolerated per Investigator's judgment in Cycles 4-8 for adjuvant therapy per label on Days 1-5 per 28-day cycle Selinexor weekly 60 mg or 80 mg depending on dose level until PD
B Control	RT 2 Gy daily TMZ 75 mg/m^2 daily	TMZ started as Cycle 3 at 150 mg/m^2, then increased to 200 mg/m^2 as tolerated per Investigator's judgment in cycles 4-8 for adjuvant therapy per label on Days 1-5 per 28-day cycle

RT=radiation therapy; TMZ=temozolomide.
Note: this table is applicable to both Phase 1 and Phase 2. Refer to Table 5 for details.
In Phase 2, radiation 1.8 to 2.0 Gy will be administered.

5.4.6.1.1. Radiation Period

Selinexor will be administered orally at an initial dose of 60 mg in treatment Arms A, B, and C, and 80 mg in Arms D and E in Phase 1a, followed by dose escalation scheme as described above. Selinexor should be given about 30 minutes prior to radiation during weeks determined by dose level.

Standard Fractionated Radiation therapy (RT) using either RTOG or EORTC methodologies of approximately 60 Gy in 30 fractions. 2 Gy will be administered daily for 5 days in a week (e.g., Monday to Friday, or Sunday to Thursday) unless the treatment schedule requires a change.

Arm B treatment group only and Arms A and B control: During the RT oral TMZ will begin on the first day and will be administered orally daily at a dose of 75 mg/m^2 about 1 hour prior to the radiation treatment and 30 minutes prior to selinexor. Temozolomide will continue at this dose level and schedule until the completion of radiation and then

will continue as adjuvant therapy per label. During the adjuvant therapy, oral temozolomide can be administered on an empty stomach or at bedtime.

During RT period, if radiation needs to be stopped due to toxicity, selinexor and temozolomide can continue per schedule. If a patient experiences disease progression per modified RANO criteria, then the patient will discontinue the treatment.

5.4.6.1.2. Adjuvant Therapy Period

Post RT, depending on treatment assignment, a patient can continue treatment with weekly selinexor until disease progression, TMZ per label for 6 cycles, or combination of selinexor and TMZ (TMZ for 6 cycles and selinexor continued until progression). Temozolomide will be given per standard of care (see Table 13).

5.4.6.2. Arm C

Lomustine will begin on the first day and will be administered orally on Day 1 of each cycle (once every 6-week cycle) at a dose level described in Table 10, up to 6 cycles. Carmustine can be administered at a dose level described in Table 10 for up to 6 cycles, if lomustine is not available.

Selinexor will be administered orally at an initial dose of 60 mg. The first dose will be given on Day 1 Week 1 of each cycle and about 30 minutes before lomustine and will thereafter be administered on Day 8, Day 22, and Day 29. Selinexor should be dosed first and it is recommended to give lomustine about 30 minutes after selinexor.

5.4.6.3. Arm D

Selinexor will be dosed weekly. Bevacizumab will be dosed at 10 mg/kg every 2 weeks. Cycles will be defined as 28 days. The first dose of selinexor will be given on Day 1 Week 1 of each cycle and will thereafter be administered on Day 8, Day 15, and Day 22. Selinexor should be dosed first and it is recommended to give bevacizumab after selinexor.

Bevacizumab will be administered (and dose modified) per label:

First infusion: Administer infusion over 90 minutes.

Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated; administer all subsequent infusions over 30 minutes if infusion over 60 minutes is tolerated.

Dose modifications are allowed per bevacizumab label.

The start and stop timings of bevacizumab infusion will be documented.

5.4.6.4. Arm E

Selinexor will be dosed weekly with TTField 200 kHz ≥18h/day. Patients will be encouraged to CCI [redacted] turned on as much as possible during the day.

5.4.6.5. Dose-Limiting Toxicities

An AE is considered to be a DLT if it is a clinically significant AE (based on CTCAE v5.0) assessed as unrelated to tumor progression, intercurrent illness, or concomitant medications and meets the criteria defined herein and occurs during the radiation period for Arms A and B or Cycle 1 for Arms C, D , and E in Phase 1a. Any DLT must be a toxicity considered at least possibly related to study treatment and the acute effects thereof.

5.4.6.5.1. Non-hematologic DLTs

Non-hematologic DLTs include the following:

- Grade 3 nausea, vomiting, dehydration, diarrhea, or fatigue lasting >5 days despite optimal supportive medications
- Any other Grade 3/4 non-hematological toxicity with the following exceptions:
  - Electrolyte/laboratory abnormalities including hyponatremia that are reversible and/or asymptomatic
  - ALT, AST, or alkaline phosphatase levels in the setting of Grade 2 baseline or elevations from underlying medical conditions

5.4.6.5.2. Hematologic DLTs

Hematologic DLTs include the following:

- Febrile neutropenia
- Grade 4 neutropenia lasting >7 days
- Grade ≥3 thrombocytopenia with clinically significant bleeding

5.4.6.5.3. Other DLTs

Any AE that results in the following dose modification are also considered DLTs:

- Missed > 1/3 planned dose for any study treatment (selinexor, radiation, TMZ, lomustine, bevacizumab, or TTField) due to study drug-related toxicities
- A dose reduction during Cycle 1 due to a study drug-related toxicity
- Discontinuation of a patient before completing Cycle 1, due to a study drug-related toxicity

5.4.6.5.4. DLT Exceptions

AEs that meet the above definitions but that are clearly unrelated to study drug will not be considered DLTs.

An event may fall within the definition of a DLT, as defined above, but the event may be considered not to be a DLT (e.g., not clinically meaningful). If this occurs, the Investigator and Sponsor will review the event and supporting data, and the reasons for not considering the event to be a DLT will be clearly documented with supporting rationale.

5.4.6.6. Required Prophylactic Supportive Care

Supportive measures for optimal medical care should be provided to all patients in this study. In addition to the required prophylactic therapy outlined below, supportive care per institutional guidelines and/or the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines) should be used as clinically indicated at the discretion of the Investigator.

Anti-emetic Medications

Ondansetron

In order to minimize nausea, unless contraindicated, all patients should receive 5-HT3 antagonists (ondansetron 8 mg or equivalent), starting before each dosing and continued 2-3 times daily for 3 days after selinexor dosing. Alternative antiemetic agents may be used if the patient does not tolerate or has inadequate antiemetic effect with 5-HT3 antagonists.

Olanzapine

In addition, patients should receive olanzapine 2.5 mg oral daily at bedtime (or minimally available dose based on the available formulation) starting on Day 1 and continuing through radiation therapy and for at least the first 2 cycles of the adjuvant therapy for nGBM in Arms A and B and for at least the first 2 cycles in Arms C, D, and E. The dose of olanzapine can be increased as deemed necessary. The olanzapine dose may be dose reduced due to side effects or stopped after 2 months if nausea is well controlled.

Alternatively, AKYNZEO (Netupitant/Palonosetron) may be used as per label in patients intolerant to olanzapine or 5HT3 antagonists other than palonosetron (AKYNZEO may not be used in combination with other 5HT3 receptor antagonists or NK1 receptor antagonists).

Additional options can be found in the NCCN Clinical Practice Guidelines in Oncology (CPGO) for antiemesis and anorexia/cachexia (palliative care).

Additional supportive care and other treatments may be administered as described below:

- Appetite stimulants: megestrol acetate at a dose of 400-800 mg daily.
- Additional options, including benzodiazepine, cannabinoid, phenothiazine and D2 receptor antagonists, can be found in the NCCN Guidelines for antiemesis and anorexia/cachexia (palliative care).
- 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.

For Arm A control and for Arm B experimental and control, prophylactic treatment for PCP should be given according to TMZ label and Principal Investigator's choice.

Premedications and supportive care for other drugs used in combination with selinexor should be given as per drug label and institutional protocols.

5.4.6.7. Dose Adjustments for Tolerability

Patients who have low-grade tolerability symptoms and derive clinical benefit from the treatment may receive a dose schedule reduction after consultation with the Medical Monitor and documented approval from sponsor. Patients whose dose or schedule is reduced may subsequently have their previous dose schedule adjusted upwards, according to the above guidelines, after consultation with the Medical Monitor and documented approval from sponsor (see Section 5.5).

5.4.7. Phase 2: Expansion Phase

The Phase 2 Expansion Phase is a multicenter, open-label, randomized, SoC-controlled portion of the study to further evaluate the safety and efficacy of different combination regimens of SoC therapies with or without selinexor in patients with nGBM or first rGBM. The Phase 2 Expansion Phase endpoints are as follows:

	Arms A & B (nGBM)	**Arm C (rGBM)**
Primary Endpoint	PFS per IRC	OS
Secondary Endpoint	PFS per Investigator assessment; PFS6, per IRC and Investigator assessment; OS; 1- and 2-year OS rate, safety	PFS, PFS6, (and for Arm C only ORR, DCR, and DOR) per IRC and Investigator assessment; 1- and 2-year OS rate, safety

In Phase 2, patients enrolled into each arm will receive the RP2D selected at the end of Phase 1 for that treatment arm. Study treatment may continue until completing protocol-defined treatment duration (for Arms A and B), disease progression per RANO/modified RANO criteria per Investigator assessment, unacceptable AEs, etc. Although patients are allowed to discontinue due to PD per Investigator assessment, the data used for Phase 2 primary statistical analysis will be provided by an IRC.

Patients will be enrolled into an arm according to characteristics of GBM and treatment history. On Day 1, patients enrolled into each arm will be randomized to either the experimental arm or the SoC control. Patients will be assigned a unique number in ascending numerical order at each study site.

Study medication will be dispensed at the study visits summarized in the Schedule of Activities. Returned study medication should not be re-dispensed to study patients.

Dose modifications to manage tolerability will be allowed during the Expansion Phase. The Investigator should exercise professional judgment to determine if the doses should be adjusted for individual patients by referring to Section 5.4.

5.5. Dose Modification and Supportive Care Guidelines

All dose modifications during dose escalation must be reviewed and discussed with the medical director before implementation. During the Phase 1 dose escalation, if dose reduction occurs but is not defined as a DLT per criteria, then this patient will be considered not evaluable for DLT.

Based on observations from multiple studies in patients with advanced hematological and solid tumors, selinexor shows a reasonably wide therapeutic range, with activity ranging from ~6 mg/m^2 to 85 mg/m^2 (approximately 10 mg to 120 mg oral). Therefore, in order

to optimize specific anti-tumor activity and tolerability, dose reductions and/or schedule modifications will be allowed as described in Section 5.4. **Patients should also be treated aggressively with supportive care to reduce toxicities** (Section 5.12.1).

Toxicity will be graded according to CTCAE v.5.0; the therapy modifications described below are to be applied according to severity grading. If more than one type of AE occurs concurrently, the most severe grade will determine the modification.

Each dose modification or treatment delay must be documented and captured in the eCRF, including the respective reason. Dose modifications due to drug toxicity should be associated in the eCRF with the AE requiring the modification.

Re-escalation of selinexor is allowed as outlined in Section 5.4. If drug-related toxicity requires a treatment delay of more than 28 days, Investigators need to contact the Medical Monitor before the end of this period. Depending on the clinical situation (e.g., response status to study drugs, seriousness of AE) and in the patient's best interest, additional time off study drugs may be approved by the Medical Monitor.

For all Grade ≥3 hematological or non-hematological AEs that are NOT selinexor-related, after documented consultation with the Medical Monitor and at the discretion of the Investigator, selinexor dosing may be maintained.

Table 8, Table 9, and Table 10 summarize the selinexor dose levels to be evaluated in the study; Table 14 describes supportive care and dose adjustment guidelines. General supportive care recommendations are provided in Section 5.12.1. Deviations from the guidelines are permitted after documented discussion between the Medical Monitor and the treating physician.

5.5.1. Selinexor

Dose modifications to manage tolerability will be allowed. Selinexor dose will be reduced by 20 mg during each dose reduction. Supportive care and selinexor dose adjustment guidelines for AEs related to selinexor in patients in all arms are provided in Table 14.

Table 14: Supportive Care and Selinexor Dose Adjustment Guidelines for AEs Related to Selinexor

Adverse Event	Occurrence	Action
Hematologic Adverse Events		
Thrombocytopenia		
Grade 2-3: Platelet count 25 × 10^9/L to <75 × 10^9/L	Any	• Reduce selinexor by 1 dose lower • Consider additional supportive care and discuss with Sponsor's Medical Monitor
Grade 3: Grade 2-3 with bleeding Platelet count 25 × 10^9/L to <75 × 10^9/L with concurrent bleeding	Any	• Interrupt selinexor • Restart selinexor at 1 dose level lower after bleeding has resolved (see Section 5.4) • Consider additional supportive care and discuss with Sponsor's Medical Monitor
Grade 4 Platelet count <25 × 10^9/L	Any	• Interrupt selinexor

Adverse Event	Occurrence	Action
		• Monitor until platelet count returns to at least 50×10^9/L • Restart selinexor at 1 dose level lower • Consider additional supportive care and discuss with Sponsor's Medical Monitor
Neutropenia		
Grade 3 ANC 0.5 to 1.0×10^9/L without fever	Any	• Proactively initiate growth factor support if ANC $<1.0 \times 10^9$/L • Maintain the dose
Grade 4 or 3/4 with fever ANC $<0.5 \times 10^9$/L OR febrile neutropenia	Any	• Interrupt selinexor • Initiate growth factor support • Monitor until ANC returns to $\geq 1.0 \times 10^9$/L • Restart selinexor at 1 dose level lower
Anemia		
Hb <8.0 g/dL	Any	• Administer blood transfusions and/or other treatments per clinical guidelines
Life-threatening consequences (urgent intervention indicated)	Any	• Interrupt selinexor • Monitor until Hb returns to ≥8.0 g/dL • Restart selinexor at 1 dose level lower • Administer blood transfusions and/or other treatments per clinical guidelines
Nonhematologic Adverse Events		
Hyponatremia		
Sodium ≤130 mmol/L	First	• Interrupt selinexor and provide appropriate supportive care • Monitor until sodium returns to >130 mmol/L • Restart selinexor at same dose
	Second	• Interrupt selinexor and provide appropriate supportive care • Monitor until sodium returns to >130 mmol/L • Restart selinexor at one dose lower
Fatigue		
Grade 2 lasting >7 days OR Grade 3	Any	• Interrupt selinexor and provide appropriate supportive care • Add methylphenidate • Monitor until fatigue resolves to Grade 1 or baseline • Restart selinexor at 1 dose level lower
Nausea and Vomiting		
Grade 1 or 2 nausea OR Grade 1 or 2 vomiting	Any	• Maintain selinexor and initiate additional anti-nausea medications

Adverse Event	Occurrence	Action
Grade 3 nausea OR Grade ≥3 vomiting	Any	• Interrupt selinexor • Monitor until nausea or vomiting has resolved to ≤Grade 2 or baseline. • Initiate additional anti-nausea medications • Restart selinexor at 1 dose level lower
Diarrhea		
Grade 2	First	• Maintain selinexor and institute supportive care
	Second and subsequent	• Reduce selinexor by 1 dose level • Institute supportive care
Grade ≥3	Any	• Interrupt selinexor and institute supportive care • Monitor until diarrhea resolves to Grade ≤2 • Restart selinexor at 1 dose level lower
Weight Loss and Anorexia		
Weight loss of 10% to <20% OR anorexia associated with significant weight loss or malnutrition	Any	• Interrupt selinexor and institute supportive care • Monitor until weight returns to >90% of baseline weight • Restart selinexor at 1 dose level lower
Other Nonhematologic Adverse Events		
Grade 3 or 4	Any	• Interrupt selinexor and institute supportive care • Monitor until resolved to ≤Grade 2 • Restart selinexor at 1 dose level lower

Abbreviations: ANC=absolute neutrophil count; Hb=hemoglobin.
Note: All dose modifications should be based on the worst preceding toxicity.
Note: It is strongly encouraged that the Investigator dose reduces or interrupts one drug at a time for those AEs that are thought to have multifactorial causes.
[a] For all Grade ≥3 hematological or non-hematological AEs that are NOT selinexor- or temozolomide-related, after consultation with the Medical Monitor and at the discretion of the Investigator, selinexor may be maintained.
[b] For all selinexor-related AEs, if the below prescribed dose reductions/interruptions result in a stabilization of ≥4 weeks, a re-escalation may be considered after approval from the Medical Monitor.

5.5.1.1. Management of Thrombocytopenia and Neutropenia

Thrombocytopenia and neutropenia are potential overlapping toxicities for selinexor with other combination drugs. If a patient experiences drug-induced thrombocytopenia and/or neutropenia while receiving the combination under investigation in this study, the Investigator should attempt to determine which drug may be responsible and treat appropriately, including dose modifications and delays, as necessary. In case of overlapping toxicities, the Investigator should follow the guidelines of the higher grade (see Table 14). If during the management of an AE for an individual patient receiving both selinexor and another drug(s), the Investigator suspects that one of the drugs may be the cause of that event, the Investigator should discuss the case with the Medical Monitor. If the cause cannot be attributed to a single drug, it is strongly recommended that the

Investigator dose reduces or interrupts 1 drug at a time. Please refer to Table 14 for dose adjustments of regimens containing investigational treatment (selinexor) or refer to manufacturer guidelines in the prescribing information for dose adjustment of combination drugs (not containing investigational treatment). Any dose reductions should be documented in the patient's research record and the eCRF.

5.5.1.2. Infection

Patients with active uncontrolled or suspected infections should have treatment withheld until the infection has clinically resolved and/or the patient is clinically stable. After the infection has resolved clinically or the patient's clinical condition has stabilized and when ready to resume dosing, treatment may continue at the original dose. Patients may continue antibiotic therapy for prolonged periods while re-initiating their treatment at the discretion of the Investigator.

5.5.1.3. Renal Insufficiency

Selinexor is not significantly eliminated by the kidney. Therefore, no dose alteration of selinexor/placebo is required in patients with renal dysfunction.

5.5.1.4. Conditions Not Requiring Selinexor Dose Reduction

The following conditions are exceptions to the dose-modification guidelines. Selinexor does not need to be held for the following cases:

- Alopecia of any grade
- Electrolytes or serum analyte (e.g., urate) abnormalities that are reversible with standard interventions.

5.5.2. Radiation Therapy

Standard Fractionated Radiation therapy using either RTOG or EORTC methodologies of approximately 60 Gy in 30 fractions. Modifications to the radiation treatment plan will be made at the discretion of the radiation oncologist. Ideally, radiation therapy will be delivered uninterrupted. Occasionally, deviations from this schedule may be required secondary to expected toxicity or life events.

5.5.3. Temozolomide

5.5.3.1. During Concomitant Radiation Therapy

A complete blood count should be obtained weekly. Adjustments to the dose of temozolomide and selinexor will be made at the direction of the treating physician upon discussion with the Medical Monitor. Supportive care and dose adjustment guidelines for toxicity and intensity experienced with dosing temozolomide and selinexor during concomitant radiotherapy are provided in Table 13 and Table 15.

Table 15: Supportive Care and Dose Adjustment Guidelines for Toxicity and Intensity during Concomitant Radiotherapy

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
Platelets	
100-75k	Hold TMZ, continue Selinexor
>50-75k	Hold TMZ Continue Selinexor Continue RT Recheck CBC, when platelets >75k restart TMZ
25-50k	Hold TMZ Hold Selinexor Continue RT Recheck CBC, when platelets >75k restart TMZ and Selinexor
<25k	Hold TMZ Hold Selinexor Hold RT Recheck CBC, when platelets >50k restart RT When platelets >75 k restart TMZ and Selinexor (dose decreased level)
ANC	
>1.5	Continue both TMZ and Selinexor
>1-1.5	Hold TMZ Continue Selinexor Continue RT Recheck CBC when ANC 1.5 restart TMZ
0.5-1	Hold TMZ Hold Selinexor Continue RT Recheck CBC, when ANC >1.5 restart TMZ and Selinexor
<0.5	Hold TMZ Hold Selinexor Continue RT Recheck CBC, when ANC >1.5 restart TMZ and Selinexor (dose decrease one level.

ANC=absolute neutrophil count; CBC=complete blood count; RT=radiation therapy; TMZ=temozolomide.

5.5.3.2. Following Concomitant Radiation Therapy

Post-RT, TMZ will be given per standard of care (Table 13).

5.5.4. Selinexor Dose Adjustment in the Setting of Infection

Patients with active uncontrolled or suspected infections should have selinexor treatment withheld until the infection has clinically resolved or the patient is clinically stabilized. Dexamethasone should be adjusted per institutional guidelines, and adrenal suppression considered. After the infection has resolved clinically, or the patient's clinical condition has stabilized, treatment with selinexor may continue at the original dose. Missed doses will not be replaced. Patients may continue on antibiotics or other anti-microbial agents for prolonged periods while re-initiating their selinexor regimen at the discretion of the Investigator.

5.5.5. Missed or Vomited Doses

Missed Doses

Missed doses for selinexor should be managed as follows:

- **If a dose of selinexor is missed**, administer the missed dose if the time for next scheduled dose is ≥48 hours. Do not administer the missed dose if the time for next scheduled dose is <48 hours (the next dose will be taken as per schedule).
- **If a dose of selinexor is skipped** (e.g., due to recommendation of Investigator), the next dose will be taken as per schedule. Doses should not be administered <48 hours apart and all missed and delayed doses should be documented.

If a patient missed a full one- or two-week period of dosing for non-study drug-related events (e.g., a required medical procedure or an unanticipated personal emergency), the days missed will not be replaced.

Missed doses for other drugs used in the study in the combination treatments will be handled as per the individual study drug label.

Vomited Doses

If a dose is vomited within 1 hour of ingestion and all intact selinexor tablets are seen, the dose will be replaced. If vomiting occurs more than 1 hour after dosing, it will be considered a complete dose.

5.6. Medication Storage

Selinexor tablets should be stored at or below 86°F (30°C) in a locked and secured area with access restricted to the site staff pharmacist or designee(s) at room or refrigerated temperature. Room temperature storage is preferred. The tablets should not be stored at freezer temperatures or frozen. See Appendix 2 for detailed information on selinexor storage, stability, and administration.

All other study medications should be stored as described on their respective product labels.

5.7. Study Drug Accountability

Selinexor will be provided to study sites. Commercial co-therapies should be sourced locally by the study sites. Karyopharm will not provide commercial co-therapies. All

co-therapies should be reimbursed by insurance or designated healthcare systems. Instructions for ordering selinexor are provided in the *Pharmacy Manual*.

Study drug accountability records will be maintained at the site pharmacy and will be available for review by the study monitor during scheduled monitoring visits. Drug accountability will be performed on selinexor only. “All-selinexor” accountability must be reviewed by the study monitor. Study sites are required to maintain a temperature log where study medication is stored.

Selinexor should not be used for any purpose outside the scope of this protocol, nor may selinexor be transferred or licensed to any party not participating in the clinical study. Data for selinexor are confidential and proprietary and shall be maintained as such by the Investigators.

5.8. Selection and Timing of Dose for Each Patient

5.9. Method of Assigning Patients to Treatment Arms/Dose Levels

During Phase 1 of the study, patients will be assigned to a treatment Arm by the Investigator based on the patient's diagnosis and treatment history.

During Phase 2, patients will be enrolled into each arm based on the patient’s diagnosis and treatment history and will be randomized to investigational treatment or SoC based on the *Randomization Plan* on file at the Sponsor. The use of IRT systems will facilitate the randomization process.

5.10. Blinding

Not applicable; this is an open-label study.

5.11. Treatment Compliance

The Investigator or other study staff will supervise study drug treatment given in the clinic and instruct the patient on study medication self-administration.

Patients will be asked to bring their study medication containers with them at each visit and compliance with protocol-defined study drug intake will be checked by pill count.

Compliance to study medication will be recorded by study personnel after discussion with the patient and drug accountability. Compliance to study medication will be done by the Investigator (or designee) and recorded in source documents. The date will be recorded as per study drug schedule. The Investigator (or designee) will account for the number of tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the eCRF and drug accountability logs with the reasons for dosing deviations.

5.12. Concomitant Therapy

5.12.1. Supportive Care

Supportive measures for optimal medical care should be provided to patients during participation in this study. In ongoing clinical studies, the most common AEs reported as at least possibly related to selinexor have been low-grade nausea, fatigue, anorexia,

thrombocytopenia, and vomiting. Most of these AEs can be managed effectively with dose modification and/or supportive care initiated prior to first dose. In addition to the required prophylactic therapy outlined below, supportive care per institutional guidelines and/or the National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) should be used as clinically indicated at the discretion of the Investigator.

Anti-emetic Medications

Ondansetron

In order to minimize nausea, unless contraindicated, all patients should receive 5-HT3 antagonists (ondansetron 8 mg or equivalent), starting before each dosing and continued 2-3 times daily for 3 days after selinexor dosing. Alternative antiemetic agents may be used if the patient does not tolerate or has inadequate antiemetic effect with 5-HT3 antagonists.

Olanzapine

In addition, patients should receive olanzapine 2.5 mg oral daily at bedtime (or minimally available dose based on the available formulation) starting on Day 1 and continuing through radiation therapy and for at least the first 2 cycles of the adjuvant therapy for nGBM in Arms A and B and for at least the first 2 cycles in Arms C, D and E. The dose of olanzapine can be increased as deemed necessary. The olanzapine dose may be dose reduced due to side effects or stopped after 2 months if nausea is well controlled.

Both ondansetron and olanzapine should be given before the dose. Olanzapine can be given a day before dosing as well.

Alternatively, AKYNZEO (Netupitant/Palonosetron) may be used as per label in patients intolerant to olanzapine or 5HT3 antagonists other than palonosetron (AKYNZEO may not be used in combination with other 5HT3 receptor antagonists or NK1 receptor antagonists).

Additional options can be found in the NCCN CPGO for antiemesis and anorexia/cachexia (palliative care).

Additional supportive care and other treatments may be administered as described below:

- Appetite stimulants: megestrol acetate at a dose of 400-800 mg daily.
- Additional options, including benzodiazepine, cannabinoid, phenothiazine and D2 receptor antagonists, can be found in the NCCN Guidelines for antiemesis and anorexia/cachexia (palliative care).
- 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.

Premedications and supportive care for other drugs used in combination with selinexor should be given as per drug label and institutional protocols.

Supportive care guidelines for managing AEs are provided in Table 14.

5.12.2. Bevacizumab for Suspected Pseudoprogression (Arms A, B, C, and E) in Phase 1a/b

Pseudoprogression is characterized by transiently increased enhancement and vasogenic edema that mimics tumor progression with or without neurological decline but without true tumor progression. It is caused by increased vascular permeability from cytotoxic therapies (Brandsma 2008; Ellingson 2017) and diagnosed retrospectively by improvement even resolution of radiological changes on subsequent imaging per mRANO (Ellingson 2017). Radiological changes usually resolve without intervention while symptomatic pseudoprogression is usually managed with corticosteroids. Bevacizumab has been shown to reduce vascular permeability and cerebral edema in radiation necrosis (Gonzalez 2007; Levin 2011) and pseudoprogression (Nguyen 2019; Miyatake 2013; Foster 2015), and can improve symptoms and QOL and spare patients the effects of corticosteroids.

In Phase 1a/b of the study, for patients with suspected pseudoprogression, short-course bevacizumab (2 to 4 infusions) may be administered for palliation at the Investigator's discretion and after consultation with the Medical Monitor for up to 6 months after RT in Arms A, B or initiation of selinexor in Arms C and E. The dose and schedule of bevacizumab may differ from Arm D per the Investigator's standard practice and may include 5 mg/kg every 2 weeks, 7.5 mg/kg every 3 weeks (Gonzalez 2007; Levin 2011).

Bevacizumab improves PFS but not OS in newly diagnosed (Chinot 2014; Gilbert 2014) and recurrent GBM (Wick 2017). Therefore, use of bevacizumab for palliation of suspected pseudoprogression will not affect assessment of OS.

5.12.3. Non-study Related Concomitant Medication and Treatment

Concomitant medications include any prescription or over-the-counter preparation, including vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations taken during the study. Patients may continue their baseline medication(s), unless listed below under Restrictions (Section 5.13) or Prohibited Medications (Section 5.14). 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, if applicable.

5.12.3.1. Permitted Concomitant Medication

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

5.12.3.2. Contraception Requirements

Female patients of childbearing potential must have a negative serum pregnancy test at Screening. Test sensitivity for human chronic gonadotropin (hCG) must be ≥25 mIU/mL.

Patients should not become pregnant or father a child while on this study because the study treatments in this study can affect an unborn baby.

Female patients should not breastfeed a baby while on this study. It is important that patients understand the need to use birth control while on this study.

Female patients of childbearing potential and fertile male patients who are sexually active with a female of childbearing potential must use highly effective methods of contraception throughout the study and for a period of 6 months for both female as well as male patients following the last dose of study treatment.

Highly effective methods and effective contraceptive methods of contraception are listed in Section 6.16.1.

Please see Section 1.3.3 for additional safety information related to pregnancy.

5.13. Restrictions

Medications

Prescribing Information for each dose level's non-selinexor drug (e.g., temozolomide) should serve as a reference for potential restrictions and/or prohibitions.

Acetaminophen

There are no restrictions on the use of acetaminophen or acetaminophen-containing products in combination with study treatment, EXCEPT on days on study treatment dosing, when acetaminophen must not exceed a total daily dose of 1 gram

Diet

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

5.14. Prohibited Medications

Concurrent therapy with any approved or investigative anticancer therapeutic outside of those included in this study is not allowed. Use of any immunosuppressive agents during the study must be confirmed by the Medical Monitor.

5.15. Radiation Therapy Guidelines

5.15.1. Scheduling

Radiation therapy will be administered per standard of care daily Monday-Friday. All the protocol related follow-up appointments will occur at the clinical site.

5.15.2. Technique

Standard Fractionated Radiation therapy (RT) using either RTOG or EORTC methodologies of approximately 60 Gy in 30 fractions. Radiation therapy dose will be administered on consecutive treatment days, 5 fractions per week via a linear accelerator using 6 MV photons or greater. Interruptions for holidays will be permitted, and any missed days will be added on to the end of treatment. Computerized tomography (CT) simulation will be performed in the treatment position with the patient immobilized using a thermoplastic mask.

Both EORTC and RTOG treatment volumes are permitted as described below in Table 16.

Table 16: EORTC and RTOG Treatment Volumes Guidance

EORTC treatment volumes (single phase)	RTOG treatment volumes (two phases)
Single Phase (Treated to 60 Gy in 30 fractions	Phase 1 (Treated to 46 Gy in 23 fractions)
GTV: Surgical resection cavity plus any residual enhancing tumor (postcontrast T1 weighted MRI scans) CTV: GTV plus a margin of 2 cm PTV: CTV plus a margin of 3-5 mm	GTV1: Surgical resection cavity plus any residual enhancing tumor (postcontrast T1 weighted MRI scans) plus surrounding edema (hyperintensity on T2 or FLAIR MRI scans). CTV1: GTV1 plus a margin of 2 cm (if no surrounding edema is present, the CTV is the contrast enhancing (CE) tumor plus 2.5 cm. PTV1: CTV plus a margin of 3-5 mm
	Phase 2 (Treated to 14 Gy in 7 fractions)
	GTV2: Surgical resection cavity plus any residual enhancing tumor (postcontrast T1 weighted MRI scans) CTV2: GTV2 plus a margin of 2 cm PTV2: CTV2 plus a margin of 3-5 mm

EORTC=European Organisation for Research and Treatment of Cancer; RTOG=Radiation Therapy Oncology Group; FLAIR=fluid-attenuated inversion recovery; MRI=magnetic resonance imaging; CTV=clinical target volume; GTV=gross tumor volume; PTV=planned target volume.

5.15.3. Target Coverage and Dose Limits

The volume of planned target volume (PTV) covered by the prescription dose must represent ≥95% of the PTV. A variation of ≥90% coverage of the PTV will be accepted. As per International Commission on Radiation Units criteria, the max point dose shall not exceed 107% of the prescribed dose.

5.15.4. Critical Structures

The organs at risk in the field to be contoured include brain, brainstem, optic nerves, and optic chiasm. Normal tissue dose limits will be employed as per Table 17 below.

Table 17: Organs at Risk

Organs at Risk	Objective
Brainstem	$D_{max} \leq 54$ Gy 1-10 cc> 59 Gy (Periphery)
Chiasm	$D_{max} < 55$ Gy
Cochlea	Ideally one side mean <45 Gy
Eyes	Macula<45 Gy
Optic Nerves	D_{max} <55 Gy

D_{max}=maximum dose.

6. STUDY PROCEDURES

6.1. Informed Consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), Institutional Review Board (IRB), Independent Ethics Committee (IEC), or Research Ethics Board (REB)-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e., all procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's Informed Consent Form (ICF) was actually signed will be captured in their eCRFs. Patients will be required to re-consent to updated versions of the ICF throughout the trial until the 30-Day safety follow-up visit. Re-consent during the survival follow-up phase will not be required.

The Investigator should not repeat procedures that are performed as part of standard of care, if they are within the screening window and are done prior to signing the ICF. Data from standard of care procedures will be part of the patient's medical history and may be used for study purposes.

Karyopharm will provide to Investigators, in a separate document, a proposed ICF that is considered appropriate for this study and complies with ICH GCP guidelines and regulatory requirements. Karyopharm or their designee must agree to any Investigator suggested changes to this ICF *before* submission to the IRB/IEC/REB. Karyopharm must also agree to any suggested ICF revisions made by the IRB/EC/REB in their review of the consent form. A copy of the approved version must be provided to Karyopharm or designee after IRB/IEC/REB approval.

Additionally, consent will be required to obtain DNA samples extracted from tumor biopsies, which may be stored for potential exploratory biomarker studies. Patient participation in this study is dependent on the collection and use of these samples. Samples will be stored for up to 15 years for potential future genomic biomarker analysis, as warranted in this rapidly evolving field. Samples will be single coded, allowing individual samples to be retrieved and destroyed if the patient withdraws consent at a later date. Each patient's ICF will reflect that samples collected may be used for pharmacogenomic investigations.

6.2. Study Patient Number

Each patient will be assigned a unique patient number and will keep this number for the duration of the study. Patient numbers will not be reassigned or reused for any reason. Patients will be identified to the Sponsor by their assigned number, date of birth, and sex. The Investigator should maintain a patient master log.

6.3. Medical History

During Screening, a complete medical history will be obtained from each patient. Medical history will include baseline symptoms as well as a detailed history of prior procedures for GBM and other prior cancer therapies (i.e., chemotherapy, radiotherapy, surgery, etc.), including start and stop dates, best response, disease progression during or

after therapy, as well as discontinuations due to intolerability or toxicity. Smoking history will be recorded. A detailed history of disease-specific diagnostic and prognostic testing and test results (such as phenotypic and cancer molecular profiling, including but not limited to MGMT methylation, EGFR alterations, IDH1 mutation, and status of chromosomes 1p/19q) will also be collected. Data from SoC procedures will be part of the patient's medical history and may be used for study purposes.

6.4. Concomitant Medications

Concomitant medications will be documented for each patient at each scheduled visit. A detailed history of medications will be documented during Screening and C1D1. Subsequently, at each study visit, patients will be asked whether they have taken any medication other than the study medication (from Screening through the End of Treatment visit). All concomitant medications as well as changes in medication, will be recorded on the eCRFs.

Necessary supportive care is allowed (see Section 5.12.1).

6.5. Physical Examination, Vital Signs, and KPS Score

Full physical examinations will be performed, including neurological examinations per NANO criteria. All other physical examinations during the study should be limited, symptom-directed physical examinations, including body systems as appropriate.

Information about the physical examinations must be present in the source documentation at the study site. Clinically relevant findings made after the start of study dosing, which meet the definition of an AE, must be recorded on the AE eCRF.

The actual value and change from baseline (Day 1, prior to the first administration of study treatment) to each on study evaluation will be summarized for vital signs (Section 7.8.3). Body surface area is calculated based on weight and height.

Karnofsky performance status will be provided during the study (see Appendix 1).

6.6. GBM Assessment and Response Criteria

Disease status will be measured by contrast-enhanced MRI (or computed tomography [CT] for patients unable or unwilling to undergo MRI) scans including pre-contrast T1/T2/FLAIR and post-contrast T1 and assessed using the Modified Response Assessment in Neuro-Oncology (modified RANO) criteria in Arms A, B, and D, and RANO in Arms C and E (Table 18). MRI is the required methodology during the study; however, if a patient is unable to undergo MRI post-screening visit CT will be allowed until the patient is able to resume undergoing MRI scans.

Response will be assessed by RANO/modified RANO criteria (as applicable) and as such, the first imaging following completion of radiation will be considered the baseline for response assessment as per Ellingson 2017. For patients in Arm C and Arm E, a repeat MRI scan for confirmation of PD is not required if the Investigator's clinical impression is PD as patients in Arm C and Arm E are receiving lomustine or TTField, respectively, which is not associated with pseudoprogression or pseudoresponse.

Pseudoprogression: If imaging shows progressive changes, the patient may continue on study treatment for confirmatory imaging at 4 to 8 weeks after the initial scan that

showed progressive changes irrespective of which study arm the patient is enrolled into if the Investigator suspects pseudoprogression and feels that the patient continues to benefit for Arms A and B as per mRANO and after consultation with the Medical Monitor for Arms C and E.

Table 18: Modified RANO Response Criteria

Response	Modified RANO Response Criteria
Complete Response (CR)	Requires *all* of the following: 1. Disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. 2. No new lesions. 3. Patients must be off corticosteroids (or on physiologic replacement doses only). 4. Stable or improved clinical assessments (i.e., neurological examinations). Note: Patients with non-measurable disease only cannot have achieve CR; the best response possible is SD
Partial Response (PR)	Requires *all* of the following: 1. ≥50% decrease in sum of products of perpendicular diameters or ≥65% decrease in total volume of all measurable enhancing lesions compared with baseline, sustained for at least 4 weeks. If the second scan exhibits PD with respect to the "preliminary PR" scan, then the response is not sustained, noted as pseudoresponse, PsR, and is now considered "preliminary PD" (note confirmed PD requires at least two sequential increases in tumor volume [a]). If the second scan exhibits SD, PR, or CR, it is considered a *durable PR* and the patient should continue on therapy until confirmed PD is observed. 2. No new lesion. 3. Steroid dose should be the same or lower compared with baseline scan. 4. Stable or improved clinical assessments.
Progressive Disease (PD)[a]	1. At least two sequential scans separated by at ≥4 weeks both exhibiting ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in total volume of enhancing lesions. 2. In the case where the baseline or best response demonstrates no measurable enhancing disease

	(visible or not visible), then any new *measurable* (>10mm x 10mm) enhancing lesions are considered PD *after* confirmed by a subsequent scan ≥4 weeks exhibiting ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in total volume of enhancing lesions relative to the scan first illustrating new measurable disease. 3. Clear clinical deterioration not attributable to other causes apart from tumor (e.g., seizures, medication adverse effects, therapy complications, stroke, infection) or attributable to changes in steroid dose. 4. Failure to return for evaluation as a result of death or deteriorating condition.
Stable disease (SD)[a]	1. Does not qualify for CR, PR, or PD as defined above. Note this also applies to patients that demonstrate PsR when the confirmation scan does not show PD or PsP when the confirmation scan does not show PR/CR. 2. In the event that corticosteroid dose was increased (for new symptoms/signs) without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that the steroid increase was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

CR=complete response; PD=progressive disease; PR=partial response; PsP=pseudoprogression; PsR=pseudoresponse; RANO=Response Assessment in Neuro-Oncology; SD=stable disease.
[a] Repeat scan is not required for confirmation of PD in Arm C and Arm E if Investigator's clinical impression is PD.

Additional endpoints to assess efficacy of selinexor in combination with SoC therapy in patients with nGBM or rGBM based on RANO/modified RANO criteria will include:

Progression-free survival	*Time frame of PFS up to disease progression or end of study*
Overall survival	*Time to death or lost to follow-up; measured from the date of randomization (Phase 2) until death due to any cause or until lost to follow-up for all patients.*
Overall response rate	*ORR based on outcome assessments based on modified RANO criteria.*
Progression-free survival rate at 6 months (PFS6)	*Estimated survival probability of having PFS ≥ 6 months based on Kaplan-Meier method (time frame: 6 months).*

Disease Control Rate	*Proportion of patients in whom the best overall response is determined as CR, PR, or SD.*

6.7. Safety Assessments

Safety evaluations will be conducted as described below.

6.7.1. Echocardiography and Electrocardiography

An echocardiogram or multiple gated acquisition (MUGA) scan to assess baseline cardiac function and risk of cardiac dysfunction, including cardiomyopathy will be conducted during Screening. The decision to perform an echocardiogram or MUGA will be at the discretion of the Investigator. Additional echocardiograms or MUGA scans may be performed during subsequent visits if clinically appropriate, per Investigator discretion.

A standard 12-lead ECG will be performed. It is recommended that patients rest in a supine position for at least 5 minutes prior to the ECG recording. The Investigator will interpret the ECG using one of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant. The date and time the ECG is performed, and the following parameters will be recorded in the eCRF: heart rate, PR interval, QT interval, QRS interval, and QT corrected using Fridericia's correction formula.

6.7.2. Pulmonary Function Tests

In Arm C only, pulmonary function test, including predicted FVC and DLCO, will be performed during Screening, at Day 36 of Cycles 3 and 6, and at the EoT visit; and may be performed as clinically indicated during treatment and after completion of 6 cycles of lomustine/carmustine.

6.7.3. Clinical Safety Laboratory Tests

Clinical laboratory tests (detailed in Table 19) will be performed by the sites' local laboratories. In addition, laboratory tests will be collected and analyzed at times specified in Table 2. More frequent assessments may be performed if clinically indicated, or at the Investigator's discretion and these should be recorded on the eCRF.

Table 19: Clinical Safety Laboratory Tests

Hematology (Blood sample: whole blood; EDTA) tests including)				
Hemoglobin	Hematocrit	WBC count	Lymphocytes[a]	Neutrophils[a]
Platelets				
Serum Chemistry (Blood sample: serum)				
Glucose	Calcium	BUN/urea	Creatinine	Sodium
Potassium	Albumin	Alkaline phosphatase	Total bilirubin[b]	Total protein
AST	ALT	LDH[c]		

ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; EDTA=ethylenediaminetetraacetic acid; LDH=lactate dehydrogenase; WBC=white blood cell
[a.] Absolute counts will be collected, not percent values.

[b] If the total bilirubin concentration is increased >1.5 × ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.
[c] Per Investigator's discretion.

For patients in Arm D, for monitoring of proteinuria, urine dipstick for protein at Screening and each visit prior to infusion, < 14 days and < 30 days after last dose will be performed. The assessment should be continued after 30 days of last dose as clinically indicated. A 24-hour urine collection will be performed for patients with a 2+ or greater urine dipstick assessment.

Blood chemistry will be analyzed at each study center by a certified laboratory. The Investigator or designee will review the laboratory report after receipt of the results and assess the clinical significance of all abnormal values. Results must be reviewed prior to dosing and appropriate action taken for any clinically significant abnormal values.

At any time during the study, abnormal laboratory values that are clinically relevant (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs or require therapeutic intervention), whether specifically requested in the protocol or not, must be documented in the eCRF.

If any abnormal laboratory value or test result constitutes an AE, then these must be recorded on the AE eCRF. Values will be documented on the laboratory report until stabilized, or the laboratory value returns to a clinically acceptable range (regardless of relationship to study treatment) or baseline. Any laboratory value that remains abnormal at the end-of-treatment (EOT) visit that is considered clinically significant will be followed according to accepted medical standards for up to 30 days or until resolution of the abnormality or return to baseline levels. Toxicity will be assessed using the NCI CTCAE v5.0.

Estimated creatinine clearance is calculated at Screening using the Cockcroft-Gault formula:

([140-age] × body weight [kg]/[72 × creatinine (mg/dL)]) × 0.85 if the patient is female

Karyopharm must be provided with a copy of the laboratory certification and, when available, normal ranges for each parameter measured. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Karyopharm must be provided with a copy of the certification and normal ranges for that laboratory.

6.7.4. Safety Review Committee

The Safety Review Committee (SRC) will include, at a minimum, the Karyopharm Medical Monitor and the Investigators. Additional information is provided in the *Safety Review Plan.*

A review of the pre-defined study data by the SRC is required prior to escalating study drugs within each dose level. The following data for all visits during Cycle 1 should be available in the eCRF:

- Study Drug Administration
- AEs
- Hematology and Biochemistry Results

- Concomitant Medications

Additional information from the site may also be requested by Karyopharm. Requested information must be entered into the electronic data capture (EDC) system by sites in a timely manner per contract, as the information will be used to assess safety at that dose level and determine the feasibility of proceeding to a new dose level.

This data review process will also be followed to determine the MTD (per dose level) and the RP2D (per arm).

The RP2D will be based on discussion between the Investigators and the Sponsor and will be either the established MTD or a dose lower than MTD based on the totality of the safety and tolerability.

The Sponsor will determine whether a dose level will be re-evaluated, a dose level will be expanded, if there will be a dose modification/escalation, or if an arm will move into Phase 2, etc.

6.8. Pharmacokinetic Assessments

Blood samples of approximately 2 mL will be collected for the measurement of plasma concentrations of selinexor at 2, 4, and 6 hours post selinexor dose on C1D1 and C3D1 in Arms A and B, and C1D1 and C2D1 in Arms C, D, and E. In Phase 2, only those patients on the experimental arms (selinexor containing) will have blood drawn for PK. Instructions for the collection and handling of biological samples are provided in the *Laboratory Manual*. The actual date and time (24-hour clock time) of each sample collection and selinexor dosing will be recorded. If a patient experiences emesis within 6 hours postdose on the days of PK sampling, no further PK samples will be collected on that day.

Plasma PK samples will be shipped to a bioanalytical laboratory for analysis. Details for collection and processing of PK samples can be found in the *Laboratory Manual*. Plasma samples will be analyzed via a validated high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS) method for plasma selinexor. Selinexor PK may be assessed using a population PK modeling approach and subsequent exposure-response analyses would be performed if deemed necessary.

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6.11. Adverse Events Assessments

6.11.1. Definitions

- *Adverse event (AE)*: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. 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 study treatment, whether or not considered related to the study treatment.
- *Life-threatening adverse event or life-threatening suspected adverse reaction*: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- *Treatment-emergent adverse event (TEAE)*: Any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.
- *Serious adverse event (SAE):* Any untoward medical occurrence that, at any dose, results in death; is life threatening (i.e., an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. (See Section 6.11.2 or additional information about SAE reporting.)
- *Suspected adverse reaction*: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse

reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

- *Unexpected adverse event or unexpected suspected adverse reaction*: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not but are not specifically mentioned as occurring with the particular drug under investigation.

6.11.2. Recording of Adverse Events

AE will be reported and recorded in the eCRF from the time of the first dose of study drug through 30 days after the last dose of study drug or until the start of subsequent antineoplastic therapy, whichever occurs first. That is, if a patient begins a new antineoplastic therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started.

Any SAE that occurs after the informed consent has been signed, regardless of whether dosing with study drug has commenced should also be recorded on the AE eCRF.

Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

Any treatment-emergent abnormal laboratory result that is clinically significant, i.e., meeting one or more of the following conditions, must be recorded as a single diagnosis on the AE page in the eCRF:

- Accompanied by clinical symptoms
- Leading to a change in study treatment (e.g., dose modification, interruption or permanent discontinuation)
- 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)

When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

A Grade 3 or 4 event (considered to be severe or life-threatening per NCI CTCAE, v5.0) does not automatically indicate an SAE unless it meets the definition of serious as defined in Section 6.11.3 and/or as per the opinion of the Investigator.

The Investigator should ask the patient non-leading questions to determine if AEs occur during the study. AEs may also be recorded when they are volunteered by the patient, or through physical examination, laboratory tests, or other clinical assessments.

An AE should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome.

All AEs occurring during the study are to be followed up in accordance with good medical practice until they are resolved, stabilized or judged no longer clinically significant or, if a chronic condition, until fully characterized.

6.11.2.1. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (i.e., are considered to be clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin).

Laboratory abnormalities that meet the criteria for an AE should be followed until they have returned to baseline levels (as measured during the Screening visit) or are deemed no longer clinically significant. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

A laboratory abnormality that does not meet the definition of an AE should not be reported as an AE. A Grade 3 or 4 event (considered to be severe per NCI CTCAE v5.0) does not automatically indicate an SAE unless it meets the definition of serious as defined in Section 6.11.1 and/or as per the opinion of the Investigator. A laboratory abnormality that results in a dose being held or modified would, by definition, be an AE and must be recorded as such in the eCRFs.

6.11.3. Adverse Event Severity

AEs will be evaluated for severity (or intensity), relatedness to study treatment and seriousness.

The term “severe” is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., ‘severe’ headache). This is not the same as “serious”. Seriousness of AEs is based on the outcome of an AE and usually associated with events that pose a threat to a patient’s life or functioning.

The term “severe” is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., ‘severe’ headache). This is not the same as a “serious” AE.

The severity of the AE will be graded by the Investigator according to the NCI CTCAE Grading Scale, v5.0 (the NCI CTCAE files can be accessed online at the following URL: http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

Events that are not specifically defined in CTCAE v5.0 should be assessed according to the definitions provided on page 2 of the CTCAE v5.0 document.

6.11.4. Adverse Event Causality

The Investigator will make a judgment regarding the relationship of the AE to study treatment, as outlined in Table 20.

Table 20: Classification of Adverse Events by Causality

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

6.12. Serious Adverse Events Assessments

A SAE is any untoward medical occurrence that occurs at any dose (including after the ICF is signed and prior to dosing) that:

- Results in death
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Please note that SAEs that occur at any time between the signing of the ICF up to the first dose of study treatment must be reported (in addition to SAEs that occur after the first dose of study treatment).

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

6.13. Events That Do Not Meet the Definition of a Serious Adverse Event

Elective hospitalizations to administer or to simplify trial treatment or trial procedures (i.e., an overnight stay to facilitate 24-hour urine collection) or other medical procedures

are not considered SAEs. A 'serious' hospitalization is defined as any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. An emergency room visit is not considered a hospitalization unless it results in an official admission as an inpatient to the hospital (e.g., undesirable effects of any administered treatment) and must be documented as an SAE.

Progression of the malignancy/disease (including fatal outcomes), events that are clearly consistent with the expected pattern of progression of the underlying disease, should NOT be reported as an SAE during the study or within the safety reporting period (see Section 6.13.2). Sudden or unexplained death should be reported as an SAE. If there is any uncertainty about a finding being due solely to progression of malignancy/disease, the finding should be reported as an AE or SAE, as appropriate.

6.13.1. Recording of Serious Adverse Events

It is the responsibility of the Investigator to record and document all SAEs occurring from the time when the ICF is signed until at least 30 days after the patient has stopped study treatment. All SAEs must be reported on the designated Sponsor's SAE Report Form (paper or electronic) in addition to being recorded in the AE eCRF. When technically possible, SAEs should be reported electronically via the "Medication Error and SAE report form" eCRF, which serves as an electronic SAE Report Form. When this eCRF is not available to use for SAE reporting, the paper SAE Report Form must be used, and the original copy must be retained in the Investigator's site file.

All applicable sections of the eCRFs and SAE Report Form must be completed in order to provide a clinically thorough report. The Investigator must assess and record the relationship of each SAE to study treatment and complete the SAE documentation form in English.

See ICH E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting) for key data elements that are required for expedited reporting.

6.13.2. Reporting of Serious Adverse Events

Every SAE, regardless of the causal relationship to the study treatment, occurring after the patient has signed informed consent form, until at least 30 days after the patient has stopped study treatment, must be reported to the Karyopharm Pharmacovigilance Department as soon as possible and not exceeding *24 hours* of learning of its occurrence. The investigational site personnel must use the SAE Report Form (paper or electronic) provided by Karyopharm for reporting any SAE to the Karyopharm Pharmacovigilance Department.

To complete the electronic SAE Report Form, a Log Line must first be completed in the Adverse Events eCRF. The SAE will then be linked to an electronic SAE Report Form. It is then necessary to complete a Log Line in the corresponding SAE Report Form eCRF within 24 hours of learning of the SAE's occurrence. It is not necessary to submit a paper SAE Report Form if the SAE was originally declared using the electronic SAE Report Form.

If the SAE is to be reported via a paper SAE Report Form, upon completion, the SAE Report Form must be immediately emailed or faxed to:

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

Any SAE observed after the 30-day follow-up period should only be reported to Karyopharm if the Investigator suspects that the SAE has a causal relationship to study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information.

An SAE should be followed until its resolution or until it is judged to be permanent. An assessment should be made at each study visit (or more frequently, if necessary) of any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome of the event.

6.13.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Karyopharm to be related to the study treatment administered. All SUSARs will be collected and reported to the competent authorities and relevant ethics committees in accordance with the FDA's "Safety Reporting Requirements for Investigational New Drugs and Bioanalytical/Bioequivalence Studies" or as per national regulatory requirements in participating countries.

If required by local regulations, the Investigator is responsible for notifying his/her IRB or local ethics committee of all SAEs.

6.14. Adverse Event and Serious Adverse Event Follow-up

All AEs and SAEs occurring during the study are to be followed up in accordance with good medical practice until they are resolved, stabilized or judged no longer clinically significant or, if a chronic condition, until fully characterized. Any AEs that are considered drug-related must be followed until resolution or until stabilization.

6.15. Post-Study Adverse Events and Serious Adverse Events

All unresolved AEs should be followed by the Investigator until the events are resolved, the patient is lost to follow-up, or the AE is otherwise explained. Karyopharm should also be notified if the Investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that has participated in this study

6.16. Procedures for Handling Special Situations

6.16.1. Pregnancy and Breastfeeding

Note: Pregnancy per se is not considered to be an AE; however, it is discussed here because of the importance of reporting pregnancies that occur during studies and because a medical occurrence observed in the mother or fetus/newborn would be classified as an AE.

Female patients of childbearing potential and fertile male patients will be informed as to the potential risk of conception while participating in this study and will be advised to use 2 methods of reliable birth control simultaneously: 1 highly effective contraception listed below (i.e., results in a low failure rate when used consistently and correctly) and 1 additional effective contraceptive method – male latex or synthetic condom, diaphragm, or cervical cap, during the dosing period and for a period of at least 6 months for both female as well as male patients following the discontinuation of study treatment.

Highly effective methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

Effective methods may include barrier methods (male condom, female condom, cervical cap, diaphragm, sponge).

A pregnancy test will be performed on each premenopausal female patient of childbearing potential prior to the first dose of study drug on Day 1 of Cycles ≥2 while on treatment, and again at treatment discontinuation during the End-of-Treatment visit. A negative pregnancy test must be documented prior to administration of study drug.

If a patient is confirmed pregnant during the study, study drug administration must be discontinued immediately. The Investigator must immediately notify the Sponsor's Medical Monitor of the event and record the pregnancy on the Pregnancy Form (provided by Karyopharm). The initial information regarding a pregnancy must be forwarded to Karyopharm's Pharmacovigilance Department by email or fax within 24 hours of first knowledge of its occurrence.

The pregnancy should be followed up to determine the outcome, including spontaneous or voluntary termination, details of the birth, and any birth defects, congenital abnormalities, or maternal and/or newborn complications.

All pregnancies occurring within 4 months after the patient's last dose of study drug must be reported to Karyopharm, regardless of whether the patient received selinexor or other study drugs, withdraws from the study, or the study is completed. Patients should be instructed to inform the Investigator regarding any pregnancies.

Any SAE that occurs during pregnancy must be recorded on the SAE Report Form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (described in Section 6.13.2).

A pregnancy in a female partner of a male patient must be reported to Karyopharm within 24 hours of learning of its occurrence. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

It is not known whether selinexor passes into the breast milk. Mothers should not breastfeed while being treated with selinexor-containing regimen

6.16.2. Abuse, Misuse, Medication Errors, Occupational Exposure, and Overdose

All incidences of abuse, misuse, medication errors, overdose, and occupational exposure are required to be reported to Karyopharm Pharmacovigilance on an SAE Report Form and emailed to pharmacovigilance@karyopharm.com, regardless of whether or not there is an associated AE or SAE.

6.16.2.1. Overdose

An overdose is a deliberate or accidental administration of any study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol. If an overdose occurs, the Investigator and Karyopharm should be notified immediately, and the patient should be observed closely for AEs. Resulting symptoms should be treated, as appropriate, and the incident of overdose and related AEs and/or treatment should be documented in the patient's medical record and in the eCRF. Information regarding the overdose is to be recorded on an SAE report form and sent to Karyopharm Pharmacovigilance regardless of whether or not an AE or SAE has occurred due to the overdose. If the overdose is associated with an SAE, the SAE Report Form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted as soon as possible (within 24 hours of awareness).

6.16.2.2. Abuse, Misuse, and Medication Errors

Abuse is the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.

A medication error is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

All occurrences of abuse, misuse, or medication error with any study treatment are to be recorded on an SAE Report Form and sent to Karyopharm Pharmacovigilance, regardless of whether or not an AE or SAE has occurred due to the abuse, misuse, or medication error. If the abuse, misuse, or medication error is associated with an SAE, the SAE Report Form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

6.16.2.3. Occupational Exposure

Occupational exposure is the exposure to a study treatment as a result of one's professional or nonprofessional occupation. For this protocol, please follow the instructions for preparation and administration of selinexor.

All occurrences of occupational exposure with any study treatment are to be recorded on an SAE Report Form and sent to Karyopharm Pharmacovigilance, regardless of whether or not an AE or SAE has occurred due to the occupational exposure. If the occupational exposure is associated with an SAE, the SAE Report Form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

6.17. Concomitant Medication Assessments

Concomitant medications will be documented for each patient at each scheduled visit. A detailed history of medications will be documented at the Screening Visit and C1D1 Visit. Subsequently, at each study visit, patients will be asked whether they have taken any medication other than the study medication (from Screening through EOT). All concomitant medications, as well as changes in medication, will be recorded on the eCRFs.

Necessary supportive care is allowed (Section 5.12.1).

6.18. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled and registered to a treatment arm. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. A patient would be allowed to be rescreened up to 2 times. Rescreened participants should be assigned the same participant number as for the initial screening.

6.19. Discontinuation Criteria

6.19.1. Early Termination of the Study

The study may be terminated at the sole discretion of Karyopharm for any reason, including medical or ethical reasons affecting the continued performance of the study, or

difficulties in the recruitment of patients. If this occurs, the Sponsor will notify IRBs, Investigators, and regulatory authorities.

6.19.2. Early Discontinuation of Individual Patients

A patient may withdraw from the study at any time at his/her own request, for any reason, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

The Investigator must determine the primary reason for a patient's discontinuation of study treatment/withdrawal from the study and record this information on the eCRF.

The Investigator may remove a patient from study treatment at his/her discretion for any of the following reasons:

- Disease progression defined by modified RANO (Arms A, B, and D)/ RANO (Arms C and E) (including clinical progression without radiological evidence as determined by the Investigator in consultation with the Sponsor)
- Unacceptable AE(s) that cannot be managed by supportive care or failure to tolerate the study treatment
- Any other medically appropriate reason or significant protocol violation, in the opinion of the Investigator
- Patient withdraws consent to continue study treatment
- Pregnancy

Patients may discontinue study treatment for any reason. Whenever possible, all discontinued patients should undergo the protocol-specified evaluation at the end of treatment visit. Patients who elect to discontinue study treatment should be encouraged to continue in the study survival follow-up so that follow-up information on disease progression and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the study at any time. Patients who withdraw consent must be withdrawn from the study and this information will be documented in the eCRF.

The reason for the patient's discontinuation of study drug/withdrawal from the study must be recorded in the eCRF. The reason for discontinuation must be clearly documented in the study database and include supporting data (i.e., discontinuation for PD must be accompanied by data points in the database to support PD; additionally, if the reason for discontinuation is physician decision, ample justification must be provided and linked to PD values, AEs, etc.).

Any patient who does not withdraw from the study but who stops attending study visits and does not respond to 3 documented contact attempts will be considered lost to follow up.

All patients will be followed until disease progression, withdrawal of consent, death, or loss to follow up.

6.20. End of Study

End of study will occur after the last patient to be enrolled has been followed on study treatment for at least 1 year or completed the at least 6 months of survival follow-up period.

6.20.1. Safety Follow-up Call

Study procedures will be performed 30 days (+7 days) after treatment discontinuation (last dose). Patients will be contacted by telephone or visit to obtain the following information:

- Follow-up on any AEs that were not resolved by the EoT Visit
- Information on any antineoplastic therapies utilized since discontinuation of selinexor treatment

6.20.2. Durability of Response and Survival Follow-up

After discontinuation of study treatment, patients will be followed for safety up to 30 days (Section 6.19.2). The 12-month survival follow up period starts after the EOT visit (last dose of study treatment, date of dose discontinuation, patient has died, withdrawn consent, or been lost to follow up, whichever occurs first). Patients will be followed to obtain information about disease response and/or survival:

- If a patient discontinues from the treatment due to reasons other than PD, the patient will be followed for PFS approximately every 3 months after end of treatment visit by coming to the clinic for imaging and/or clinical assessment until PD, death or initiation of the subsequent anti-GBM treatment.
- All patients will be followed for survival approximately every 3 months after EOT visit until the end of study, i.e., when the last patient in the study to be enrolled has been followed on study treatment for at least 1 year or completed at least 6 months of survival follow-up period after the last dose of study treatment, has died, has withdrawn consent, or has been lost to follow up, whichever occurs first.

6.21. Lost to Follow up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known

mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

7. PLANNED STATISTICAL METHODS

7.1. General Considerations

A statistical analysis plan (SAP) will be finalized prior to database lock. Any changes from the statistical analyses described in this document will be described in the SAP, and any deviation from the final SAP will be described in the final report.

Phase 1, a dose escalation design with 3 independent treatment arms of patients with newly diagnosed (2 arms) or rGBM (1 arm), are planned for evaluating selinexor in combination with SoC:

- Arm A: nGBM patients with uMGMT
- Arm B: nGBM patients with mMGMT
- Arm C: rGBM patients regardless of MGMT status
- Arm D: rGBM patients regardless of MGMT status
- Arm E: rGBM patients regardless of MGMT status

A standard 3 + 3 dose escalation of selinexor will be performed in each treatment arm until the MTD and/or RP2D for that arm is reached, with flexibility to expand any dose level to better understand safety, efficacy and PK/PDn of that dose.

Phase 1b, a dose expansion phase with non-inferiority design for 5 independent treatment arms in Phase 1a, are planned for continuing to evaluate the safety of MTD/RP2D dose found in Phase 1a and to explore the efficacy of selinexor in combination with SoC/other therapies:

- Arm A: nGBM patients with uMGMT
- Arm B: nGBM patients with mMGMT
- Arm C: rGBM patients regardless of MGMT status
- Arm D: rGBM patients regardless of MGMT status
- Arm E: rGBM patients regardless of MGMT status

Phase 2 is an open-label randomized study, independently conducted in patients with newly diagnosed or rGBM:

- Arm A (nGBM with uMGMT): RT + TMZ vs. RT+ selinexor
- Arm B (nGBM with mMGMT): RT + TMZ vs. RT + TMZ + selinexor
- Arm C (rGBM regardless of MGMT status): lomustine/carmustine only vs. lomustine/carmustine + selinexor

There is no multiplicity issue that needs to control in either Phase 1 or Phase 2 of this study in this protocol.

Tabulations will be produced for appropriate disposition, 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. For continuous variables, the number of patients,

mean, median, standard deviation, minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology with median event time and associated 2-sided 95% confidence intervals, as well as number and percentage of patients with events and censored patients.

Data for the analysis of the primary endpoint in Phase 2 will be generated by the local and central laboratory and reviewed by the IRC. The IRC's assessments of time of progression or disease response will be used as the basis for the evaluation of the primary endpoint.

7.2. Stratification in Randomization of Arm C in Phase 2

An interactive Response Technology system will be used to perform treatment randomization. Patients will be randomized to treatment arm in a block of randomization codes that have been assigned to patient's stratum.

Randomization will be performed prior to dosing.

Randomization will be stratified based on the following stratification factors and will maintain the 1:1 allocation between treatment and control arms within each of the stratification categories:

- Number of prior lines of anti-GBM regimens (1 versus >1)

It is planned to randomize patients in a 1:1 allocation to treatment and control arm.


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7.4. Analysis Populations

7.4.1. Phase 1

7.4.1.1. Dose Escalation Population (per Arm in Phase 1a)

The dose escalation population will consist of all patients in the Dose Escalation Phase 1a who have either had a DLT prior to completion of 1 cycle of therapy, or who have completed a cycle of therapy.

7.4.1.2. Dose Expansion Population (per Arm in Phase 1a/b)

The dose expansion population will consist of all patients in the Dose Expansion Phase 1b and those in Phase 1a receiving MTD/RP2D dose who are assigned to study therapy and receive at least 1 dose of study treatment. This population will include patients who have discontinued therapy due to toxicity or disease progression and patients who have died from any cause, including those related to study drug or disease. This population will be used for primary analyses of efficacy for Phase 1b.

7.4.1.3. Safety Population (per Arm in Phase 1a/b)

The safety population will consist of patients in Phase 1a and Phase 1b who have been assigned to study intervention and who have received ≥1 dose of study drug. Participants will be analyzed according to the intervention actually received.

7.4.2. Phase 2

7.4.2.1. Intent-to-Treat Population (Arm A to C in Phase 2)

The intent-to-treat (ITT) population will consist of all patients who are randomized to study treatment in Phase 2. This population will be used for primary analyses of efficacy. Patients will be analyzed in the treatment arm to which they were randomized.

7.4.2.2. Per Protocol Population (Arm A to C in Phase 2)

The per-protocol (PP) population will consist of all patients in the ITT population who have no major protocol violations, including mis-randomizations, that would compromise the assessment of efficacy; this would include receipt of sufficient study treatment (80% compliance or more). Major violations will be determined independently of the knowledge of response to study treatment. This population will be used for supportive inferences concerning efficacy. Patients will be analyzed according to treatment received.

7.4.2.3. Safety Population (Arm A to C in Phase 2)

The safety population will consist of patients in Phase 2 who have been assigned to study intervention and who have received ≥1 dose of study drug. Participants will be analyzed according to the intervention actually received.

7.5. Demographics and Baseline Characteristics

The demographic characteristic 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 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.

7.6. Efficacy Analysis

Objective disease response assessment will be made according to modified RANO in Arms A, B, D or RANO in Arms C and E. The data used for Phase 2 primary statistical analysis will be provided by the IRC.

- Progression is defined as the first occurrence of PD per RANO/modified RANO including both radiological PD and clinical deterioration.
- Clinical disease progression should be radiographically confirmed whenever possible and must be comprehensively documented by the treating physician.

Patients who have clinical disease progression in the absence of radiographical confirmation will be still counted as PD. Serial scans should utilize the same type of scanner and techniques as closely as possible as prior scans.

- PFS is defined as the duration of time from randomization (Phase 2)/first dose of study treatment (Phase 1a/b) until progression or death due to any cause.
- 3-month progression-free survival (PFS3) rate (progression of disease defined according to the RANO/modified RANO criteria).
- OS is defined as the duration of time from randomization (Phase 2)/first dose of study treatment (Phase 1a/b) until death due to any cause.
- TTP is defined as the duration of time from first dose of study treatment (Phase 1) until progression or death due to progression.
- ORR is defined as PR+CR
- DOR is defined as the duration of time from first occurrence of CR or PR until the first date that disease progression is objectively documented
- DCR is defined as the proportion of patients who achieve CR, PR, or SD, following randomization/first dose of study treatment (i.e., ORR+SD)

7.6.1. Primary Endpoint

7.6.1.1. Phase 1a

- MTD/RP2D: once the MTD has been determined for each arm, the SRC will use the results to inform their determination of the RP2D (by arm) for Phase 2.
- The occurrence of Grade ≥3 AEs, all SAEs, and all AEs leading to treatment discontinuation.

Outcomes will be summarized using tables and listings.

7.6.1.2. Phase 1b

- PFS3 defined as the progression free survival rate at 3 months.
- OS, defined as the time from initiation of treatment until death due to any cause.

7.6.1.3. Phase 2

- Progression-free survival for patients in Arms A and Arm B will be calculated from the date of randomization to the date of disease progression, or date of death due to any cause should progression not have occurred per IRC assessment. The log-rank test will be used to compare the PFS distributions, and Cox proportional hazards regression models will be used to estimate a HR for the risk of progression in the experimental arm vs the control arm treated with SoC regimen. Patients who remain progression-free (whether they drop out prior to study end or reach their maximum follow-up) will be censored at

the last available assessment date at which no evidence of disease was observed.

- OS in Arm C will be calculated from the date of randomization to the date of death due to any cause. The stratified log-rank test will be used to compare the OS distributions between treatment arms for primary efficacy assessment; the strata will be those used for stratified randomization. A stratified Cox proportional hazards regression models will be used to estimate a HR for the risk of survival in the experimental arm vs the control arm with treatments as the only factor, the strata will be those used for stratified randomization. Patients who remain alive (whether they drop out prior to study end or reach their maximum follow-up) will be censored at the last available assessment date at which no evidence of disease was observed.

7.6.2. Secondary Endpoints

7.6.2.1. Phase 1a/b

Phase 1a

- OS will be calculated from the start of selinexor treatment to the date of death due to any cause.

Phase 1a/b

- TTP will be calculated from the start of selinexor treatment to the date of disease progression, or date of death due to disease progression.
- .
- PFS will be calculated from the start of selinexor treatment to the date of disease progression, or date of death due to any cause should progression have not occurred.
- The analysis of time-to-event endpoints will be based on Kaplan-Meier method for estimation of summary statistics and include the median event times and associated 95% CIs, as well as the number and percentage of censored patients.
- To characterize selinexor PK when co-administered with radiation therapy and temozolomide or lomustine/carmustine, or bevacizumab, or TTField.

Arm C, D and E only:

- ORR will be estimated for each arm separately, by calculating the percentage of patients in that arm who have a response of PR or CR, as assessed by RANO/modified RANO criteria.
- DCR will be calculated as the proportion of patients in whom the best overall response is determined as CR, PR or SD, as assessed by RANO/modified RANO criteria.
- DOR will be analyzed by Kaplan-Meier descriptive statistics for patients who have achieved overall response, with DOR calculated as the time from the date of first evidence of objective response until progression

7.6.2.2. Phase 2

- Comparison of ORR and DCR (for Arm C only), PFS6, OS1, and OS2 between control and experimental arms will be performed. The estimate of the odds ratio and its 95% CI will be reported.
- For time-to-event endpoints of DOR (For Arm C only), PFS and OS, the median event time will be estimated with a 95% CI for each treatment arm using the Kaplan-Meier method.
- For endpoints such as ORR, DCR, and DOR (For Arm C only), PFS and PFS6, both analyses per Investigator assessment and per IRC will be performed.
- Safety analyses will be performed on the Safety Population which consists of all patients who received at least 1 dose of study treatment and will be presented by actual treatment arm (see Section 7.8). Details of the analyses will be described in the Statistical Analysis Plan.

7.7. Pharmacokinetic Analysis

Plasma samples will be analyzed via a validated high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS) method for quantification of plasma selinexor concentrations. Selinexor PK parameters may include, but are not limited to, estimations of C_{max}, area under the concentration-time curve from time zero to the last non-zero concentration (AUC_{0-t}), area under the concentration-time curve from time zero to infinity (extrapolated) (AUC_{0-inf}) and apparent clearance. Selinexor PK may be assessed using a population PK modeling approach and subsequent exposure-response analyses would be performed if deemed necessary. The details of the PK analysis will be outlined in a separate Data Analysis Plan.

Results of PK analyses may be presented in a separate report from, or appendix to, the primary CSR for this study.

7.8. Safety Analysis

All safety analyses will be made on the Safety Population. Details of the analyses will be described in the SAP.

7.8.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and displayed in tables and listings using MedDRA system organ class (SOC) and preferred term (PT).

In those instances, in which the AEs only has a partial date is recorded, the AE will be assessed using the available date information to determine if it is treatment emergent. For AEs in which the date is completely missing, the AE will be assumed to be treatment emergent. No formal hypothesis-testing of AE incidence rates will be performed.

Adverse events will be summarized by frequency counts at patient level; therefore, in any tabulation, a patient contributes only once to the count for a given AE (by PT). The number and percentage of patients with any TEAE will be summarized for each dose level, classified by SOC and PT. The number and percentage of patients with TEAEs assessed by the Investigator as related to treatment will also be tabulated. The number and percentage of patients with any Grade ≥3 TEAE will be tabulated in the same manner.

SAEs will be summarized in the same manner as TEAEs.

All AEs (treatment emergent and post-treatment) will be listed in by-patient data listings, classified by dose level, patient, and day on study. In addition, separate by patient listings will be provided for the following: patient deaths; serious AEs; and AEs leading to withdrawal.

7.8.2. Laboratory Data

Clinical laboratory values will be expressed using conventional SI units.

For each dose level, the actual value and change from baseline (Day 1, prior to the first administration of study drug) 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. If Day 1 data is unavailable for a given patient/parameter, the screening value or the value from the latest unscheduled visit before Day 1 will substitute as the baseline value.

Severity of select clinical lab measures will be determined using CTCAE criteria (e.g., those measures that have a corresponding CTCAE grade classification). Shift tables that present changes from baseline to worst on-study and baseline to last on-study values relative to CTCAE classification ranges will be produced.

7.8.3. Vital Signs and Physical Examinations

The actual value and change from baseline (Day 1, prior to the first administration of study treatment) to each on study evaluation will be summarized for vital signs.

Abnormal physical examination results at Screening, and abnormal physical examination results (AEs) during the study, will be summarized.

7.9. Interim Analyses

No interim analyses are planned.

7.10. IRC and DSMB

7.10.1. Independent Review Committee

An IRC will be organized to review the radiological and clinical assessments during the Phase 2 portion of the study. The data used for Phase 2 primary statistical analysis will be provided by the IRC. The IRC will develop and follow a data monitoring charter. The IRC will be composed of a minimum of 1 neuro-oncologist, and 3 radiologists. The IRC Charter will specify that this committee is charged with review and confirmation of radiologic PD and clinical PD per modified criteria for Phase 2.

The IRC will not be involved in the efficacy data review for Phase 1.

7.10.2. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be established and will review the safety of study treatment and any SAEs that occur during the study. Details on how the DSMB will review safety and response data are provided in the *DSMB Charter*.

The DSMB will be comprised of a minimum of two oncologists (at least one of whom specializes in Neuro-Oncology) and a statistician. Following their initial meeting during the Phase 2 portion of the study, the DSMB will meet approximately every 6 months to review clinical data and provide recommendations to the Sponsor on whether the study should continue. The DSMB may also meet more frequently, if needed.

8. ADMINISTRATIVE MATTERS

8.1. Regulatory and Ethical Compliance

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

8.2. Institutional Review Boards/Ethics Committees/Research Ethics Boards

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB/IEC/REB before study start. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the Sponsor, Quality Assurance representatives, designated agents of the Sponsor, IRBs/IECs/REBs and regulatory authorities as required.

8.3. Regulatory Authority Approval

Before implementing this study, the protocol must be approved by relevant, competent regulatory authorities.

8.4. Protocol Adherence

Investigators attest they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the CSR per ICH E3 guidelines. A significant protocol deviation is defined as any change to the execution of the protocol, that affects the scientific integrity or design of the study, or the rights, safety or welfare of study patients.

8.5. Amendments to the Protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be provided by the Sponsor, and approved by Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the Sponsor should be notified of this action and the IRB/IEC/REB at the study site should be informed according to local regulations but not later than 10 working days.

8.6. Informed Consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e., all procedures described in this protocol except for standard of care). The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's informed consent was actually obtained will be recorded in their eCRFs.

The Sponsor will provide to Investigators, in a separate document, a proposed ICF that is appropriate for this study and complies with the ICH GCP guidelines and regulatory requirements. The Sponsor or its designee must agree to any Investigator-suggested changes to this ICF *before* their submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Sponsor or its designee after IRB/IEC/REB approval.

Additionally, in the ICF, specific assent will be requested for: (1) The Sponsor to obtain, and retain for up to 15 years, samples of peripheral blood and/or tumor tissue, including DNA and RNA from same, for future pharmacogenomic biomarker studies on GBM, selinexor, patient response to treatment, and AE. Note: Given the rapid changes in this field, future tests cannot be specified at this time: (2) Portions of blood and tumor biopsy to be used for research correlative studies (not clinical standard of care).

8.7. Patient Confidentiality and Disclosure

The Investigator must ensure anonymity of all patients; patients must not be identified by names in any documents submitted to Sponsor or its designee. Signed ICFs and patient enrollment logs must be kept strictly confidential to enable patient identification at the site.

8.8. Collection, Auditing Study Documentation, and Data Storage

8.8.1. Study Documentation, Record Keeping and Retention of Documents

Each participating site will maintain appropriate medical and research records for this study, in compliance with Section 4.9 of ICH E6 GCP, and according to the regulatory and institutional requirements for the protection of confidentiality of patients. Each site will permit authorized representatives of the Sponsor and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data include all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical study.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site Investigator. The study eCRF is the primary data collection instrument for the study. The Investigator should ensure the accuracy, completeness, and

timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRFs, which are derived from source documents, should be consistent with the source documents, or the discrepancies should be explained in the eCRF or in a manner agreed upon in writing, in advance, with the Sponsor. All data requested on the eCRF must be recorded. Any missing data must be explained. An audit trail will be maintained by the eCRF system, in compliance with 21 CFR Part 11.

The Investigator/institution should maintain study documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents. The destruction of essential documents is prohibited unless specifically discussed with the Sponsor.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Study unless the Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

8.8.2. Auditing Procedure

In addition to the routine monitoring procedures, the Sponsor or the Regulatory Authority may conduct an audit or an inspection (during the study or after its completion) to evaluate compliance with the protocol and with the principles of GCP. The Investigator will ensure that the Sponsor's auditors have access to the clinical study-related information and documents, required for them to perform the audit.

The Investigator agrees that representatives of the Sponsor and Regulatory Authorities will have direct access, both during and after the course of this study, to audit and review all study-relevant medical records.

In the event that a major compliance or regulatory issues arises, the Sponsor may conduct an audit without prior notice.

8.9. Disclosure of Information

All information provided to the Investigator by the Sponsor, or its designee, will be kept strictly confidential. No disclosure shall be made except in accordance with a right of publication granted to the Investigator in the Clinical Trial Agreement.

No information about this study or its progress will be provided to anyone not involved in the study other than to the Sponsor, or its authorized representatives, or in confidence to the IRB, or similar committee, except if required by law.

8.9.1. Discontinuation of the Study

It is agreed that, for reasonable cause, either the Investigator or the Sponsor, may terminate the Investigator's participation in this study after submission of a written notice. The Sponsor may terminate the study at any time upon immediate notice for any reason including the Sponsor's belief that discontinuation of the study is necessary for patient safety.

8.10. Study Report and Publication Policy

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

- Reported to appropriate, competent regulatory authorities in full compliance with ICH E3: Structure and Content of Clinical Study Reports. A primary CSR may be written based on all available patient efficacy and safety data for the primary analysis; a final CSR may be submitted when all evaluable patients have completed the long-term follow up period, died, progressed, withdrawn consent or been lost to follow up.
- Submitted for publication and/or posted in a publicly accessible database of clinical study results.
- The results of PK/PDn studies may be reported and/or published separately from the clinical study results.

9. REFERENCES

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APPENDIX 1. KARNOFSKY PERFORMANCE STATUS

Performance Status Criteria

Karnofsky Performance Scale	
Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

APPENDIX 2. DESCRIPTION OF SELINEXOR (KPT-330)

Selinexor is a Selective Inhibitor of Nuclear Export (SINE) compound. Selinexor specifically blocks nuclear export by binding to the nuclear export protein XPO1.

The chemical name is: (*Z*)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-*N*′-(pyrazin-2-yl)acrylohydrazide

The *molecular formula* is: $C_{17}H_{11}F_6N_7O$.

The *molecular weight* is: 443.31.

Form

Selinexor will be supplied and administered as coated, immediate-release 20 mg oral tablets in wallet-sized blister packs.

Storage and Stability

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

Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Selinexor tablets are coated for ease of use and handling. Tablets should not be divided, broken or crushed due to increased risk of dermal exposure and/or toxicities. Inadvertently, broken tablets should be handled with gloves. Reference the pharmacy manual for additional handling instruction.

Availability

Selinexor is an investigational agent and will be supplied free-of-charge from Karyopharm Therapeutics Inc.

Preparation

No special preparation required.

NOTE: Tablets of selinexor should not be crushed because of increased risk of dermatologic toxicity if powder comes in contact with skin.

Administration

Selinexor tablets should be taken orally with at least 120 mL (4 ounces) of water. Selinexor can be taken with or without food.

Ordering

Resupply of selinexor will be managed by an IRT.

Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (see the Cancer Therapy Evaluation Program [CTEP] website at http://ctep.cancer.gov/ protocol development for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form).

Destruction and Return

At the end of the study, unused supplies of selinexor should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.