Abbreviated Title: Selinexor and Radiotherapy
NIH Protocol #: 20-C-0027
Version Date: 06/30/2025
NCT Number: NCT04216329

Title: A Phase I Clinical Trial of Selinexor (KPT-330) in Combination with Temozolomide and Radiation Therapy in Patients with Newly Diagnosed Glioblastoma

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Drug Name:	Selinexor (KPT-330)	Temozolomide
IND Number:	144383	144383
Sponsor:	CCR, NCI	CCR, NCI
Manufacturer:	KaryoPharm Therapeutics Inc.	Generic
Supplier:	KaryoPharm Therapeutics Inc.	NIH CC Pharmacy

Commercial Device: Radiation

PRÉCIS

Background:

- Although radiation has been shown to improve outcomes in patients with glioblastoma (GBM), median survival remains poor. Even with the addition of temozolomide (TMZ) to surgical resection and radiotherapy, most GBMs will recur in field or adjacent to the high dose radiation volume.
- High rates of local failure indicate that GBM cells *in situ* are relatively radioresistant and that the effectiveness of GBM radiotherapy would benefit from additional radiosensitization.
- Selinexor has recently been shown to enhance the radiosensitivity of glioma cells both *in vitro* and *in vivo.*

Objectives:

- Assess the safety, tolerability, and maximum tolerated dose of selinexor when combined with temozolomide and radiotherapy in patients with newly diagnosed glioblastoma and gliosarcoma.

Eligibility:

- Men and women greater than 18 years old
- Histologically confirmed newly diagnosed glioblastoma or gliosarcoma
- Karnofsky Performance Scale (KPS) ≥70
- Patients who have not previously been treated with chemotherapy or radiation therapy

Design:

- This is a Phase I trial to determine the safety and tolerability of selinexor in combination with external beam radiation therapy (RT) and temozolomide in patients with newly diagnosed glioblastoma or gliosarcoma using a "3 plus 3 design," and three dose escalation levels, with 3 patients per dose level (provided no DLT), a maximum of 21 patients will be enrolled.
- Patients will be treated with external beam radiation therapy in a standard manner with temozolomide given daily during radiation. Selinexor will be administered concurrent with the RT/temozolomide.
- We anticipate accrual of 21 evaluable patients which will take approximately 2 years. The accrual ceiling has been set to 24 patients.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1. INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

Assess the safety, tolerability, and maximum tolerated dose of selinexor when combined with temozolomide and radiotherapy in patients with newly diagnosed glioblastoma and gliosarcoma.

1.1.2 Secondary Objective

Define dose-limiting toxicities including effects on QOL and neurocognition of selinexor when combined with temozolomide and radiotherapy in patients with newly diagnosed glioblastoma and gliosarcoma.

1.1.3 Exploratory Objective

Determine the progression free survival and overall survival of patients with glioblastoma and gliosarcoma treated with temozolomide, radiation and selinexor.

1.2 BACKGROUND AND RATIONALE

1.2.1 High Grade Glioma

Although advances in surgical management and radiation therapy have improved survival for patients with glioblastoma, life expectancy remains poor. Median survival for patients with newly diagnosed glioblastoma is 16.1 months [1]. Most failures occur in the high-dose radiotherapy (RT) field [2]. This high rate of recurrence of GBM has highlighted the importance of optimizing local therapies, which include both surgical and radiation interventions. Multiple studies have shown a correlation between the extent of tumor resection and survival [3], [4]. Prospective, randomized trials from the Scandinavian Glioblastoma Study Group (SGSG) and the Brain Tumor Study Group have also shown a survival benefit with the addition of post-operative radiation [5], [6]. In the SGSG trial median survival increased from 5.2 months with supportive care alone to 10.8 months with the addition of post-operative radiation [6]. Attempts to improve local control with radiation have included altered fractionation schemes [7]; dose escalation with boost, stereotactic radiotherapy [8], and brachytherapy [9]. Unfortunately, these techniques have added minimal therapeutic benefit. Many of these techniques can lead to an increased incidence of necrosis and higher rates of re-operation with little or no survival advantage. This high rate of recurrence of GBM has highlighted the importance of optimizing local therapies, which include both surgical and radiation interventions.

The Stupp trial [11] represents the only significant improvement in outcomes for upfront GBM treatment in more than a decade and established the addition of temozolomide to resection and radiation as the standard of care. The trial's 5-year outcome with temozolomide demonstrated an improved overall survival (9.8% vs 1.9% with RT alone) as well as improved median survival (14.6 months vs 12.1 months with RT alone). However, in this trial temozolomide was added both concurrently with the RT and adjuvantly after the RT/temozolomide. Thus, it cannot be determined how much each phase of temozolomide contributed to the improved outcome or if temozolomide acts as a radiosensitizer.

1.2.2 XPO1 as a target for Glioma

In eukaryotic cells, RNAs are transcribed in the nucleus and exported to the cytoplasm through the nuclear pore complex (NPC). Exportin 1 (XPO1) is the major export receptor implicated in one of the two distinct RNA export pathways across the NPC [12]. This pathway is responsible for exporting ribosomal RNAs (rRNAs), small nuclear RNAs (snRNAs) and a certain subset of messenger RNAs (mRNAs) [13], [14]. Additionally, XPO1 is the sole nuclear exporter of many tumor suppressor proteins, including p53 and p27, and is overexpressed in many cancers [15]. 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 [16]. As such, XPO1 has become a protein of interest for targeting in treatment of high grade gliomas.

1.2.3 Selinexor as an inhibitor of XPO1 (Pre-clinical)

Selinexor (KPT-330) is a small molecule selective inhibitor of nuclear export (SINE) which binds to the cargo-binding portion of the XPO1 protein to prevent protein transport from the nucleus to the cytoplasm. In preclinical cancer models it has demonstrated antitumoral activity [17], [18], [19]. In the first preclinical trial that tested its efficacy against GBM cell lines, Selinexor demonstrated anti-tumor efficacy in both *in vitro* and *in vivo* models. The authors reported there was no suggestion of overt neurotoxicity, and penetration of the blood-brain barrier was excellent [15]. The suggested mechanism of action was through induction of apoptosis likely secondary to effects on both protein and mRNA export inhibition.

1.2.4 Selinexor as a radiosensitizer (Pre-clinical)

Work in our lab has shown that Selinexor enhances the radiosensitivity of glioblastoma stem-like cell (GSC) lines, NSC11 and 0923, and U251 (glioblastoma) cells in both *in vitro* and *in vivo* conditions [20]. As shown in **Figure 1** these three cell lines are sensitized to irradiation by pre-treatment with Selinexor for 1hr pre-irradiation. The dose enhancement factor (DEF) at a surviving fraction of 0.1 for NSC11 was 1.46, for 0923 was 1.39, and for U251 was 1.63. The plating efficiency of each cell line was 0.25, 0.68 and 0.27 with drug alone, respectively. These DEFs represent significant radiosensitization and show an enhancement in both GSCs and long-established cell lines.

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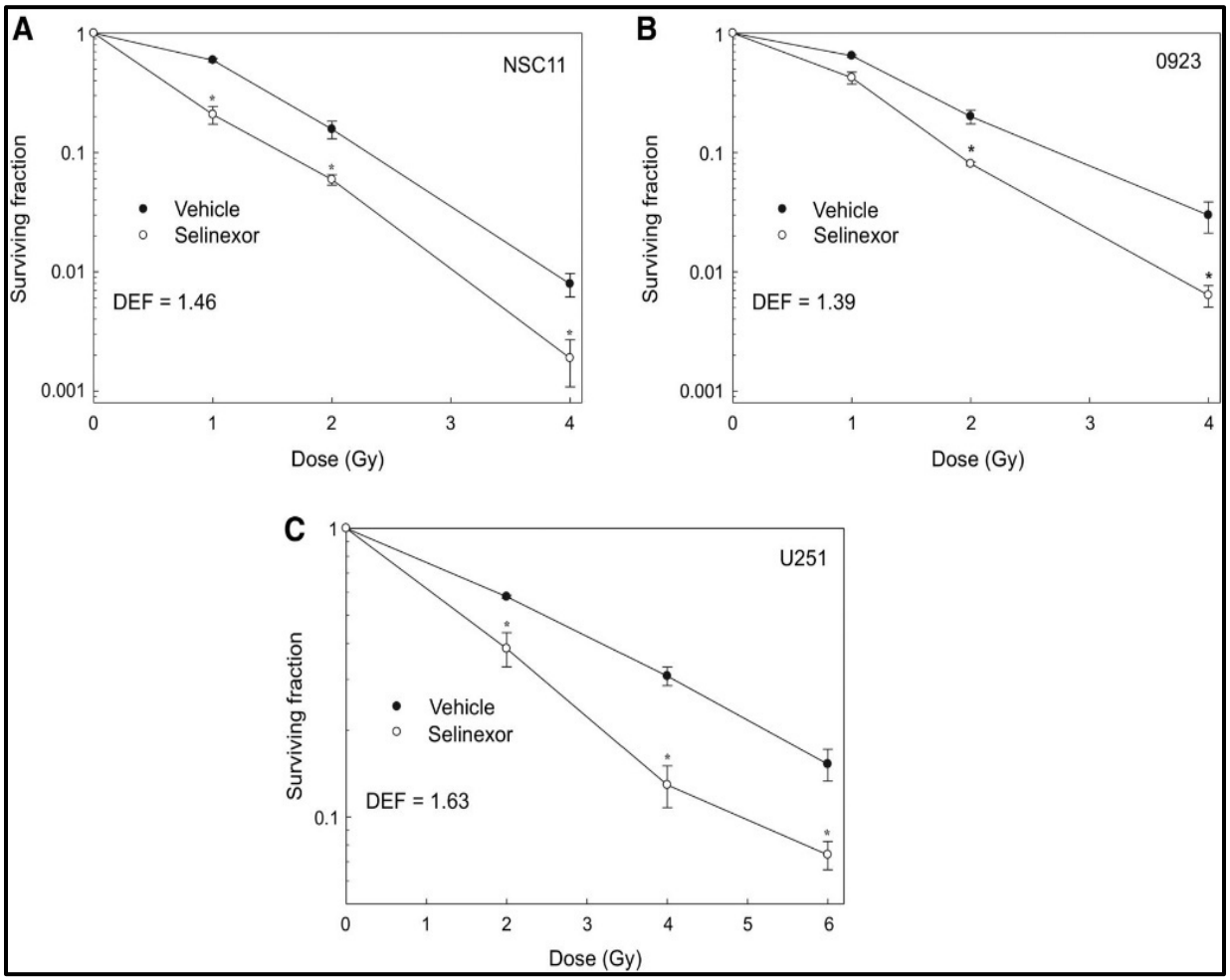


Figure 1*: Effect of Selinexor on the in vitro radiosensitivity of GBM cells. A) NSC11 B) 0923 and C) U251 cells. Selinexor (1μM) or vehicle (DMSO) were added to culture media 1h before irradiation; 24h later media was replaced with fresh, drug-free media and colonies determined after 10-14 days. Dose enhancement factors (DEFs) were calculated at a surviving fraction of 0.1 or for U251 at 0.15. Values represent the mean ± SEM of 3 independent experiments. * p < 0.05, Student's t-test (Selinexor vs. Vehicle)*

In a separate study investigating colorectal tumor cells also showed that Selinexor enhanced *in vitro* radiosensitivity. In that study, the proposed mechanism of radiosensitivity was prevention of surviving export into the cytoplasm resulting in increased in radiation-induced apoptosis [21]. However, in our investigations no increase in apoptosis was observed suggesting a separate mechanism of radiosensitivity (**Figure 2**).

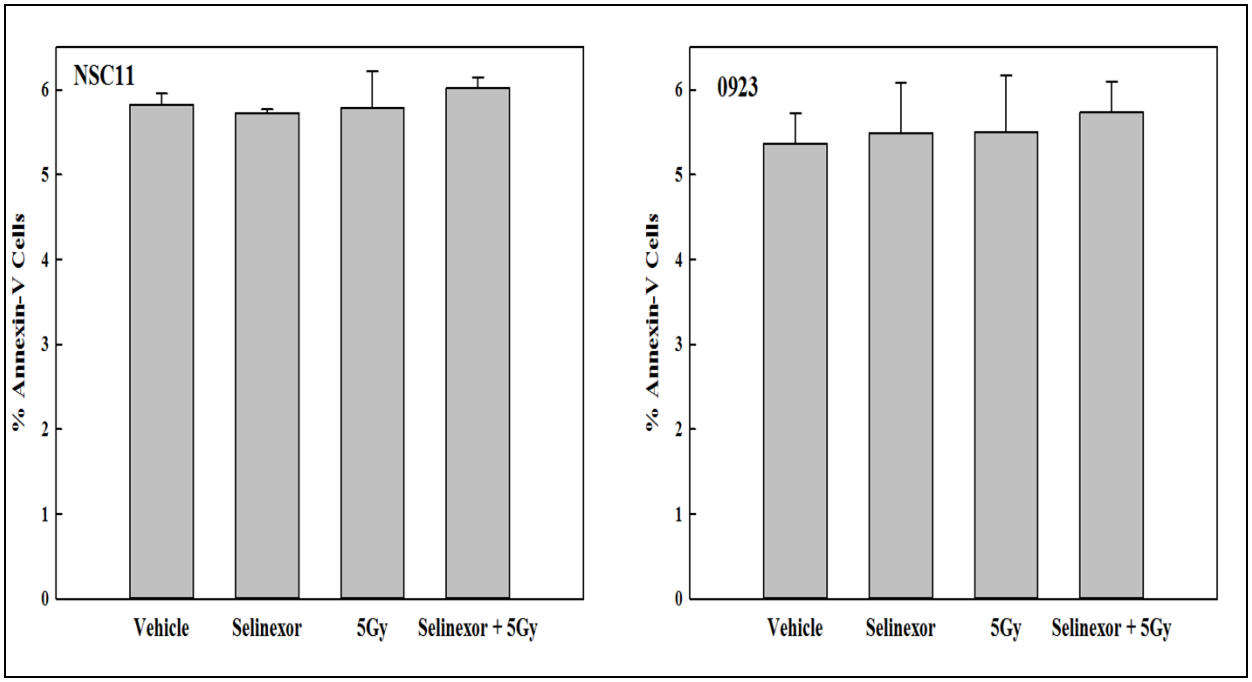


Figure 2: *Effect of Selinexor on radiation-induced apoptosis. Selinexor (l µM) or vehicle was added to NSCII (left) or 0923 (right) cultures lh prior to irradiation (5Gy) and cells collected for analysis 24h later. Cells undergoing apoptosis were quantified according to annexin V staining (Annexin V Apoptosis Detection Kit, BD Biosciences). Briefly, cells werc resuspended in 1xAnnexin V Binding Buffer and incubated with Annexin V•Cy5 antibody in the dark at room temperature for each treatment condition 1--Hoechst 33258 was added for live/dead and samples were analyzed by flow cytometry (BD LSR Fortessa). Data presented are the mean SEM Of 3 independent experiments.*

In addition to the export of a variety of proteins, XPO1 mediates the nuclear export of rRNA, suggesting that XPO1 inhibition may lead to a reduction in gene translation. Consistent with this hypothesis, Tabe et al. reported that in lymphoma cell lines the XPO1 inhibitor KPT185 reduced the nuclear export of 50 ribosomal proteins suggesting an inhibition of ribosomal biogenesis [22]. As an initial estimation of gene translation, the ratio of polysome-bound RNA to monosome-bound RNA (translational efficiency, TE) was determined from polysome profiles generated from NSC11 and 0923 GSCs as a function of time after addition of Selinexor to the culture media (**Figure 3**). Representative profiles show a reduction in the polysome fraction in both GSC lines beginning 1h after Selinexor treatment corresponding to a significant decrease in TE at 1h, which was further reduced after 24h of drug exposure. These results suggest that Selinexor disrupts gene translation. Decreased translational efficiency as well as the reduction in the polysome profile in GBM cells after Selinexor treatment, suggest reduction in translation may play a role in XPO1 inhibited radiosensitization, possibly due to reduction in ribosome biogenesis (**Figure 3**). Following the same protocol on normal lung fibroblast cell lines MRC5 and MRC9 Selinexor had no effect on the radiosensitivity of these normal lines.

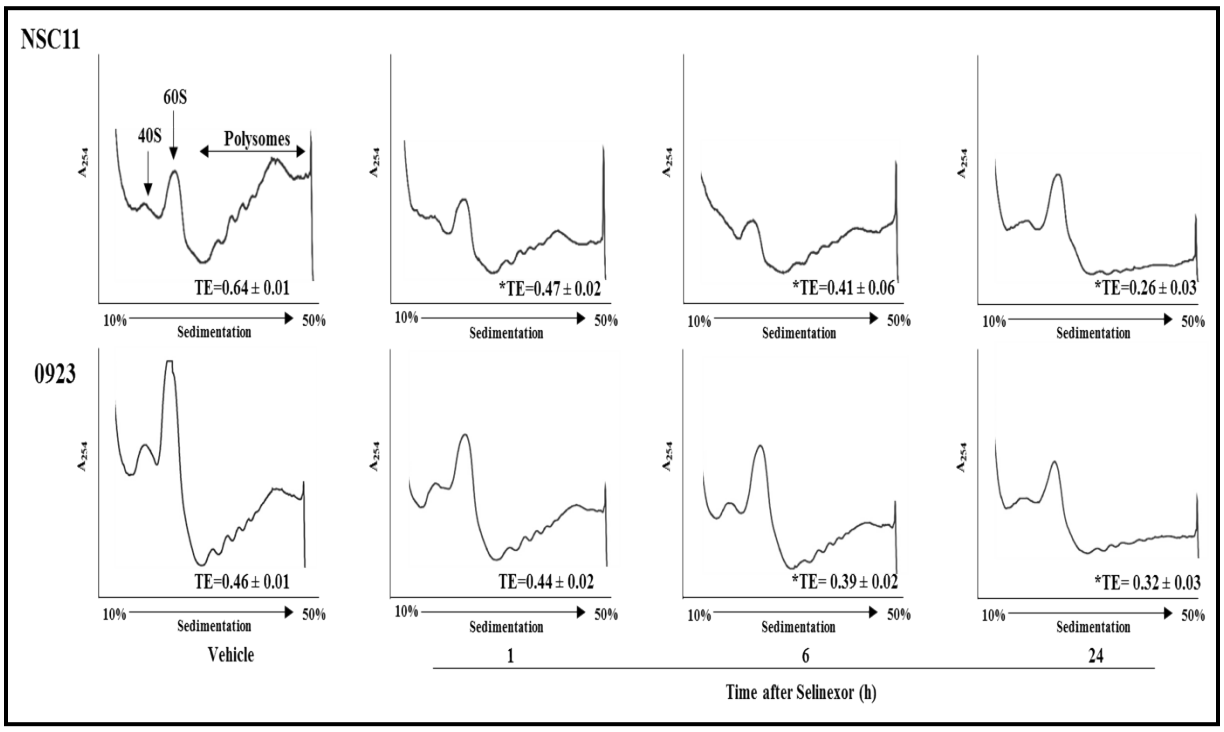


Figure 3: *Translational efficiency and protein synthesis in GBM cells treated with Selinexor. Representative polysome profiles of NSC Il (top) and 0923 (bottom) cells as a function of time after Selinexor (1µmol/L) addition to media. Translational efficiency (TE) values represent the mean ± SEM of 3 independent experiments. *p≤0.05 Student's t-test for Selinexor v. Vehicle*

To evaluate the potential of Selinexor to enhance GBM radiosensitivity under *in vivo* conditions, we used orthotopic xenografts initiated from NSC11 cells. *In vitro* results suggested that protein synthesis provides a marker of Selinexor radiosensitizing activity. Whereas it is not possible to directly measure protein synthesis in brain tumors, polysome profiles can be generated and translational efficiency (TE) determined. Towards this end, mice bearing NSC11 brain tumors (40 days post-implantation) were treated with a single dose of Selinexor (20mg/kg); tumors were collected at times out to 48h and polysome profiles generated from individual tumors. Representative profiles are shown in **Figure 4** with the listed TEs (mean ± SEM) generated from 3 mice. As reflected by the reduction in polysome fraction, TE was decreased by 1h after Selinexor administration reaching a maximum reduction by approximately 24h, which appeared to begin to recover towards untreated levels at 48h. These results indicate that Selinexor penetrates the blood-brain barrier and suggests that it targets the same processes within the tumor as detected *in vitro*.

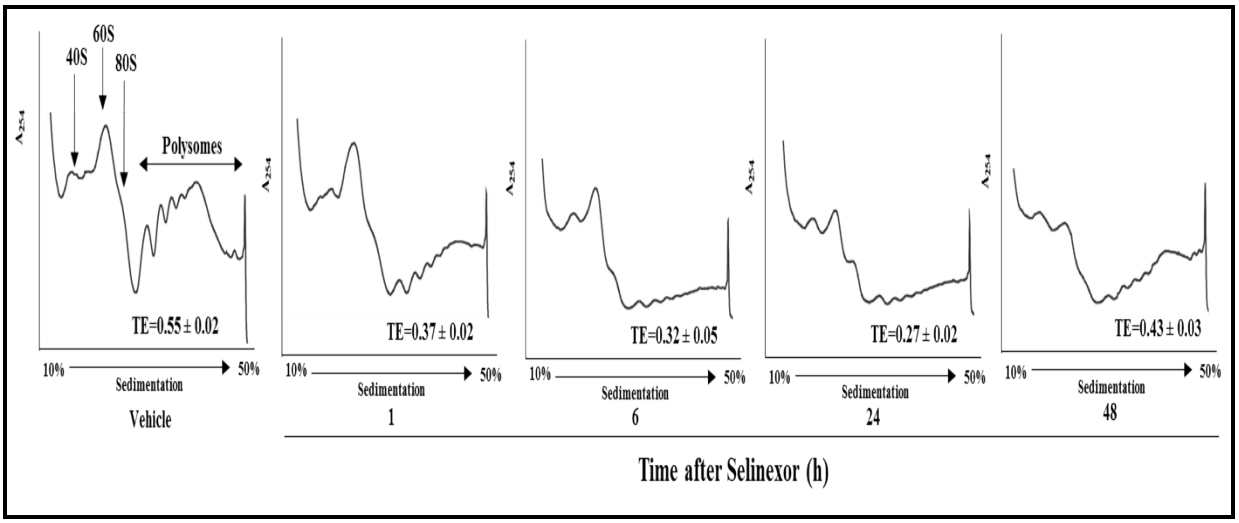


Figure 4: *The effect of Selinexor on translational efficiency and of NSC11-initiated orthotopic xenograft. Mice bearing orthotopic xenografts were treated with vehicle or Selinexor (20mg/kg) by oral gavage. Tumors were collected at the indicated timepoints and polysome profiles generated. Representative profiles from each treatment group are shown; Translational efficiency (TE) values represent the mean ± SEM of 3 mice. Student's t-test, * p≤0.05, Selinexor v. Vehicle.*

To test the antitumor effectiveness of the Selinexor/radiation combination, 24 days after intracerebral implant, mice were randomized according to BLI signal into 4 groups: vehicle (control), radiation (2Gy), Selinexor (20 mg/kg), and Selinexor plus radiation. Radiation was delivered daily for 5 days (5x2Gy) with Selinexor delivered on days 1, 3, and 5, 1h prior to local irradiation. Mice were followed until the initial onset of morbidity and survival curves generated. Selinexor treatment of mice alone had no significant effect on survival as compared to vehicle; radiation alone resulted in a significant increase in survival (**Figure 5**). The survival of mice receiving the combination protocol was significantly increased as compared with control and, importantly, as compared with radiation alone ($p<0.004$). The median survival times for the treatment groups are shown in the boxplots in **Figure 5**. Whereas the median survival after Selinexor was not significantly different from vehicle, radiation alone increased median survival by 9 days and the combination by 18 days versus vehicle, indicating that the combination protocol increased tumor radiosensitivity with an apparent DEF of 2. Thus, these data suggest that Selinexor inhibits gene translation in orthotopic brain tumors and enhances their radiosensitivity.

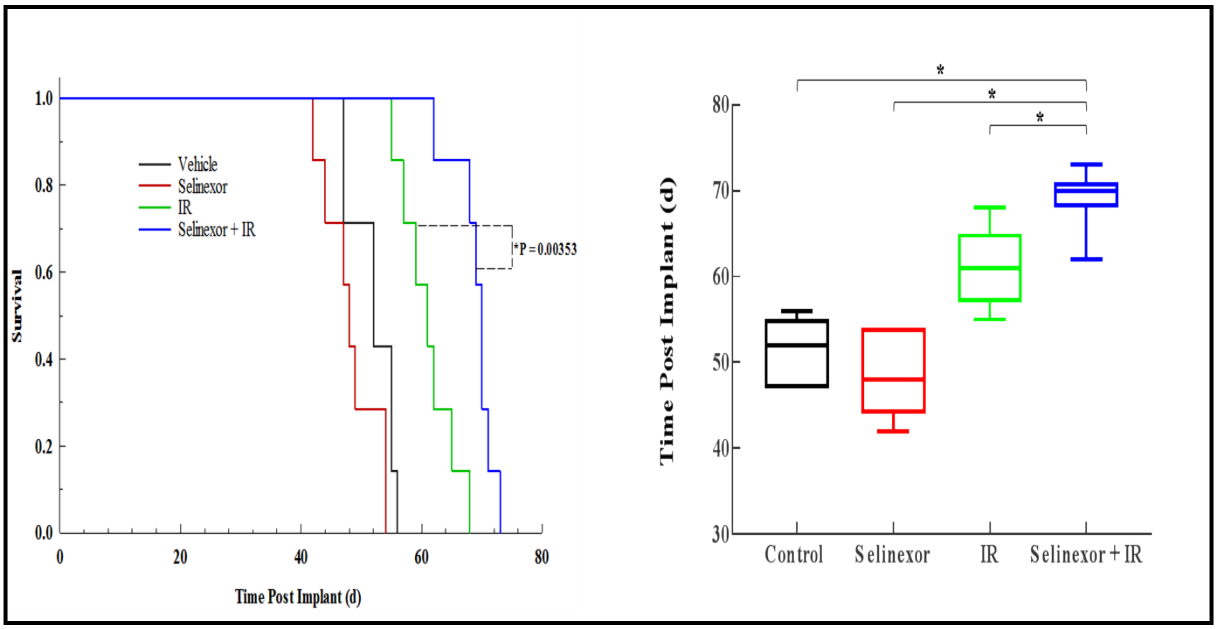


Figure 5: *The effect of Selinexor on radioresponse of NSC11-initiated orthotopic xenograft. At 24 days after orthotopic implant, mice were randomized and treatment initiated the following day as described in text (IR= 5x2Gy). Kaplan—Meier survival curves were generated with log-rank analysis for comparison. Box plot graph of median survival of each treatment group, * p < 0.05, by Dunnett's multiple comparison test.*

To test whether Selinexor was specific for tumor cells compared to normal cells, protein synthesis after selinexor treatment was compared between NSC11 and 923 and three normal cell lines MRC5, MRC9 and astrocytes. As shown in **Figure 6** at each time point measured (1-24h) there was a reduction of protein synthesis in the tumor cells which was not measured in any of the three normal cell lines. This is consistent with selinexor having a tumor specific mechanism of action.

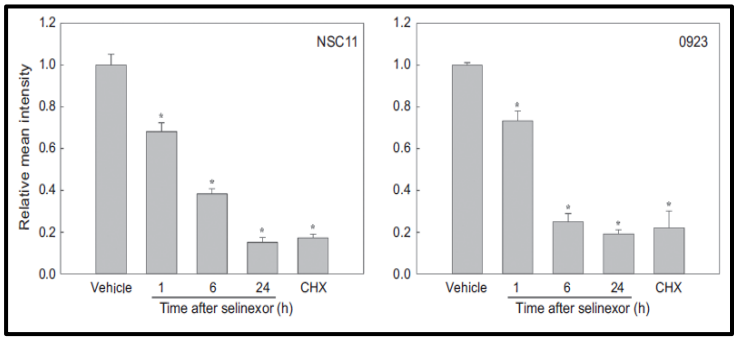
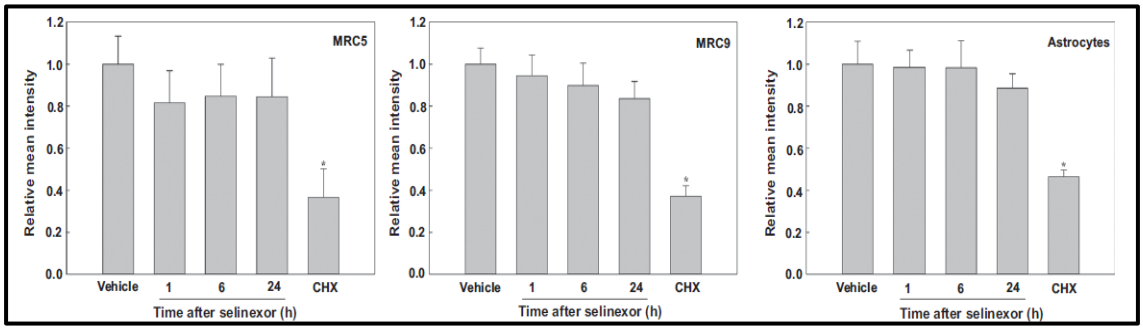


Figure* 6: Protein synthesis measured as a function of time after selinexor (umol/L) addition to media. Cyclohexamide (CHX, 0.25umol/L, 4h) was used as a positive control for protein synthesis inhibition.*



1.2.5 Selinexor with Chemotherapy (Pre-clinical)

Nu/nu mice engrafted with the breast cancer MDA-MB-231 cells were treated with vehicle, Selinexor, cisplatin, docetaxel, or Selinexor plus either of the chemotherapy drugs. The mean tumor volume for the vehicle control group (Group 1) increased from 172 mm^3 on day 1 to 665 mm^3 (287%) on day 25. Mice treated with 2.5 mg/kg Selinexor, 4 mg/kg cisplatin, and 4 mg/kg docetaxel alone showed a 68% ($p < 0.05$), 28% (not significant) or 53% ($p < 0.05$) tumor growth inhibition (TGI), respectively, when compared to vehicle control. Sequential treatment of 4 mg/kg docetaxel followed by 2.5 mg/kg Selinexor or 4 mg/kg cisplatin followed by Selinexor resulted in 93.9% ($p < 0.001$) TGI and 103.4% ($p < 0.001$) TGI (9.6% tumor regression), respectively, after 25 days (**Figure 7**A). Selinexor treatment alone or in combination with chemotherapy initially resulted in animal weight loss; however, all groups recovered and there were no statistically significant differences in body weight among the treatment groups at the end of the study, as shown in (**Figure 7**B). Significant weight loss has not been seen in the clinical trials to date. The expression of DNA damage response (DDR) proteins was examined using immunoblots in tumors from vehicle, Selinexor, cisplatin, and docetaxel-treated animals. Selinexor, even at 2.5 mg/kg, lowered DDR protein expression, while cisplatin and docetaxel had no effect on the steady-state levels of the DDR proteins (**Figure 7**C).

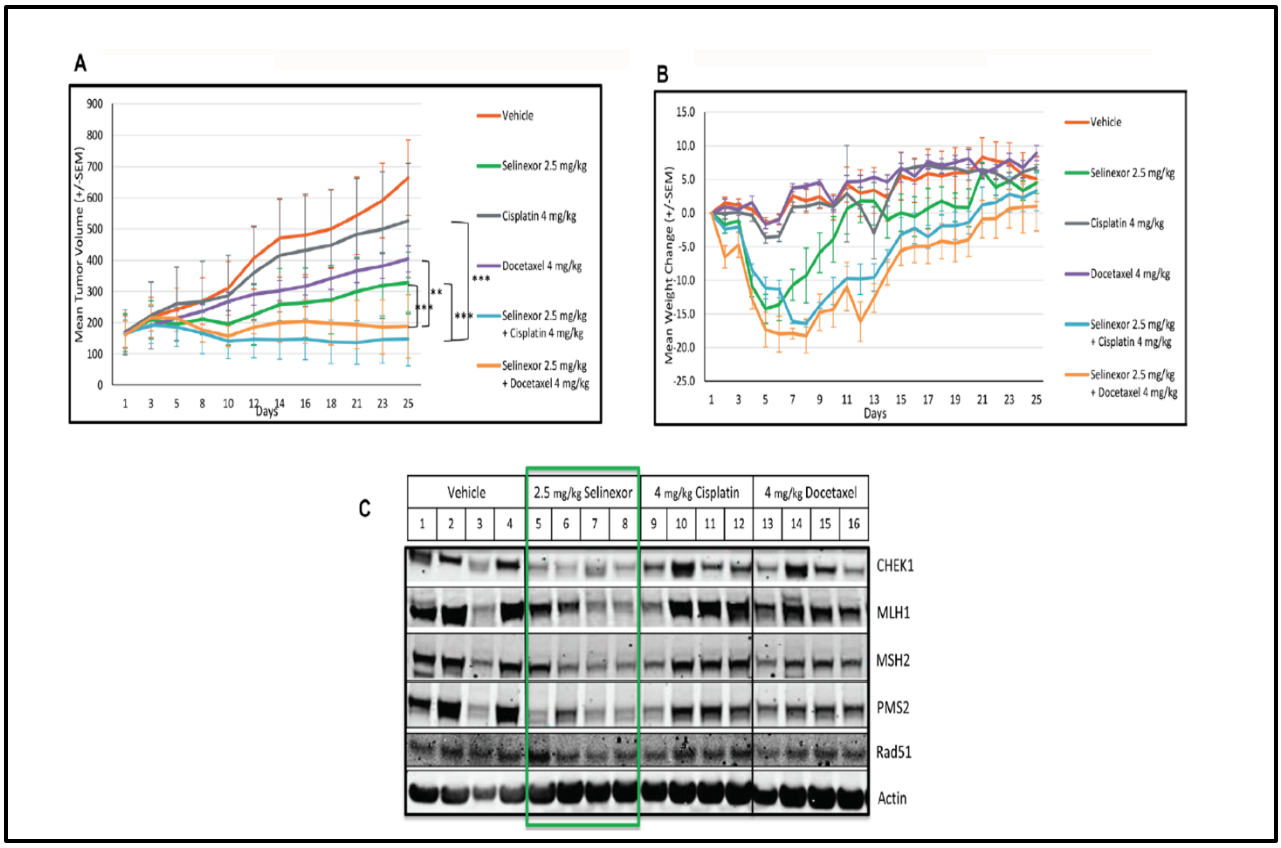


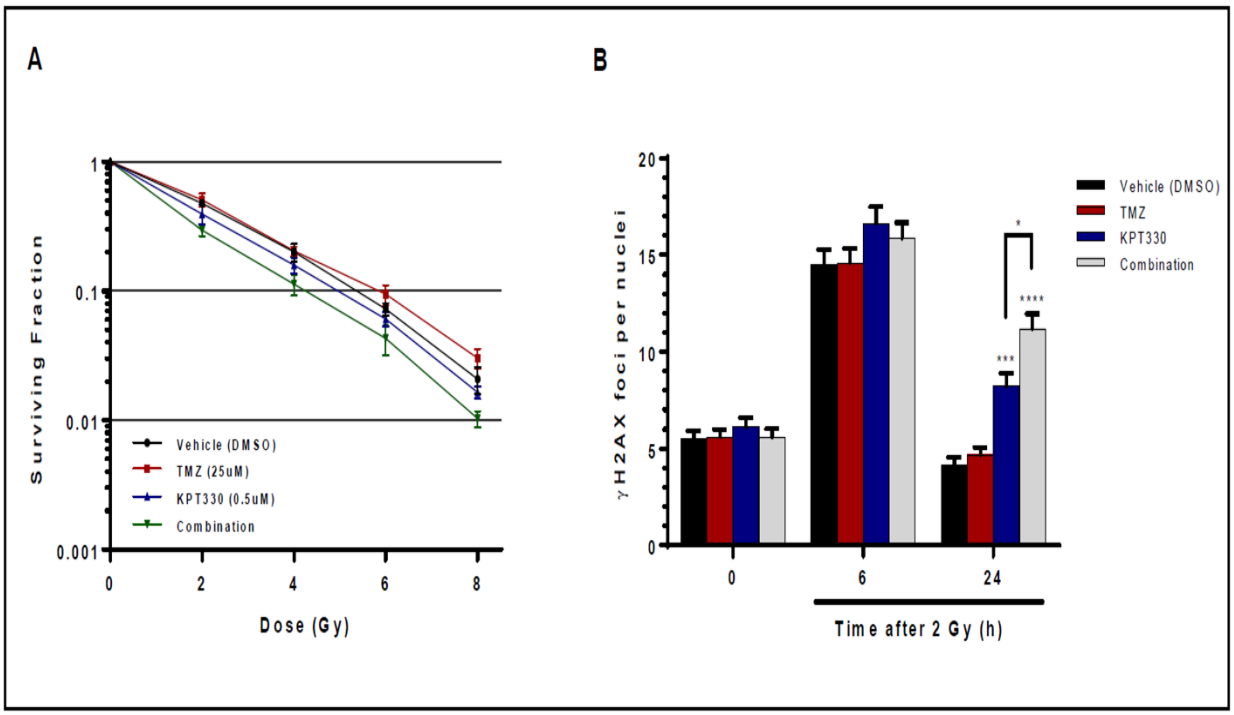
Figure 7: *Selinexor demonstrates synergistic anti-tumor effects in combination with cisplatin or docetaxel and inhibits the expression of DDR proteins in an in vivo breast cancer model: Nu/nu mice were allocated to six groups of 4 mice and treated with vehicle (1), 2.5 mg/kg Selinexor (2), 4 mg/kg cisplatin (3), 4 mg/kg docetaxel (4), Selinexor in combination with cisplatin (5) or docetaxel (6) for 25 days. For groups V and Vi, Selinexor was administered 6 hours after treatment with cisplatin and docetaxel respectively. Selinexor was administered orally, whereas cisplatin and docetaxel were administered by intraperitoneal injection. (**A**) Mean tumor volumes were calculated from the length and width measurements. Group means were calculated and are shown with error bars representing standard error of the mean (SEM) for each group. Combinatory treatments inhibited tumor growth better than each single agent. (**B**) The percent daily weight changes for each animal and the means for each treatment group were calculated. Error bars represent the SEM. There was no significant weight change among the groups at the end of the study. (**C**) At the end of the in vivo xenograft study (day 25), excised tumors from the vehicle Selinexor, cisplatin and docetaxel treated groups were assayed either by immunoblots for the expression of DDR proteins. Selinexor, but not cisplatin or docetaxel, reduced the levels of DDR proteins: CHEK1, MLH1, MSH2, PMS2, Rad51.*

1.2.6 Selinexor with temozolomide

Selinexor and TMZ were tested *in vitro* using both clonogenic survival and gamma-H2AX (a marker of DNA-DS breaks) assays. U251 cells were cultured in 6-well plates and temozolomide (25µM), selinexor (0.5µM) or both were added to the culture media 1hr prior to the delivery of 2Gy irradiation. A lower dose of Selinexor was used as the triple combination was more toxic. Colonies were counted 10-14 days later and as shown in **Figure 8**A, the triple combination had more cell kill than either of the individual drugs in combination with irradiation. The temozolomide had little effect, the selinexor had a dose enhancement of 1.06 and the triple

combination had a greater dose enhancement of 1.26. Similarly, the gamma-H2AX assay showed the greatest number of foci at 24h in the triple combination group (**Figure 8**B). These data suggest that the triple combination of Selinexor and temozolomide/RT should have a greater cell killing effect than any of the two agent combinations.

Figure 8: *Influence of TMZ (25 µM), KPT330 (0.5 µM) and their combination on **A)** clonogenic*



*cell survival in U251 cells and **B)** gamma-H2AX foci repair. **A)** Cells were exposed to treatments for 1 h before irradiation. 24 h after irradiation the drug containing media was removed and cells were fed fresh, drug-free media. Colonies were counted 10-14 days thereafter and the dose enhancement factor (DEF) for each group was calculated at a surviving fraction (SF) of 0.1. The DEFs for TMZ, KPT330, and combination treatments were 0.94, 1.06, and 1.26 respectively. Values are represented as the mean ± SEM of 3 independent experiments. **B)** Cells were exposed to treatments for 1 h, irradiated with 2 Gy, and collected at the indicated timepoints to evaluate DNA repair. Foci were evaluated in 50 nuclei per treatment per experiment. (* p<0.05; ** p<0.01, *** p<0.001; ****p<0.0001)*

1.2.7 Selinexor in Clinical Studies

1.2.7.1 Phase I Studies:

1.2.7.1.1 PK of Selinexor in Phase 1 Studies KCP-330-001 and KCP-330-002

Plasma Selinexor PK parameters were determined following oral administration of Selinexor in patients with hematologic and solid malignancies (KCP-330-001 and KCP-330-002). Based on unaudited results, Selinexor exhibited dose-proportional PK and moderate- to moderately-high inter-patient variability following repeated oral dosing in 8-to-10 dose/28-day cycle dose regimens over a dose range of 3 to 65 mg/m2 (0.08 to 1.76 mg/kg). The median time to peak plasma levels (t_{max}) of Selinexor was ~2 to 4 hours after administration. The apparent volume of distribution after non-intravenous administration (Vd/F) was 1.5 to 2.5 L/kg, indicating good distribution to tissues beyond the central (vascular) compartment. The $t_{½}$ was ~5 to 8 hours,

dose-independent, and similar across patients with different tumors. Sex or age did not appear to affect Selinexor PK. As a part of Study KCP-330-002, 8 patients were given 20, 28, or 39 mg/m^2 Selinexor along with 500 or 1000 mg of acetaminophen; there were no clinically significant laboratory abnormalities or symptoms associated with the co-administration. Preliminary unaudited PK analysis was conducted, and the results indicated there was no difference in Selinexor plasma exposure in these patients when compared with equivalently-dosed patients with Selinexor alone. Given the theoretical potential for GSH depletion, the total dose of acetaminophen should be ≤1 gram per day on days of Selinexor dosing.

1.2.7.2 PK Rationale for Flat Dosing Regimen: Studies KCP-330-001 and KCP-330-002

PK analyses support the use of fixed, rather than body surface area (BSA)-based, dosing for Selinexor. The 5th and 95th percentile for BSA values (n = 331 patients) in the Phase 1 Studies KCP-330-001 and KCP-330-002 are 1.5 and 2.3 m^2, respectively. PK values (C_{max} and $AUC_{0-\infty}$) for Selinexor doses 3 to 85 mg/m^2 BSA (females) and 12 to 85 mg/m^2 BSA (males) were similar across this typical BSA range, indicating that exposure is not strongly correlated with BSA and justifying the use of fixed milligram doses for Selinexor in the clinic.

1.2.7.3 Phase II Studies:

KCP-330-004: (KING: KPT-330 in Glioblastoma): A Phase 2 Study Evaluating the Efficacy and Safety of Selinexor (KPT-330) in Patients with Recurrent Gliomas

1.2.7.3.1 KCP-330-004 Study Design

This is a multicenter, Phase 2, open-label study to evaluate the safety and efficacy of Selinexor in approximately 57 patients with recurrent WHO Grade 4 glioma (glioblastoma, glioblastoma multiforme [GBM], and subvariants) (NCT01986348). Patients in Arms A and B receive Selinexor 50 mg/m2 (80-90mg/dose) for 4 weeks per 4-week cycle. Patients in Surgical Arm A receive an additional 3 doses of Selinexor prior to surgery and resume Selinexor after recovery. Patients in Arm C receive Selinexor 60 mg bi-weekly (BIW) and patients in Arm D receive 80 mg weekly for 4 weeks per 4-week cycle. Primary end point was 6-months PFS rate.

This study has been re-activated to add 12 patients. Study enrollment will close when 75 patients are enrolled.

1.2.7.3.2 KCP-330-004 Efficacy Results

Selinexor had reasonable brain penetration as shown by significant intra-tumoral selinexor concentrations in surgical specimens (Arm A) [23]. The average tumor concentration was 136nM compared to a plasma concentration of 836nM for a tumor/plasma ratio of 0.14 (N=6).

In the most recent efficacy analysis, the overall response rate (ORR) was 13% in Arm B, 0% in Arm C, and 8 % in Arm D [24]. The 6 months PFS rate was 17% in Arm B, 8% in Arm C, and ~20% in Arm D [24]. The toxicity profile for Arm B 50mg/m^2 (80-90mg/dose) twice a week was high and thus two additional arms C and D were added with bi-weekly dosing of 60mg for Arm C, and once weekly dosing of 80mg for Arm D. Arm C (60mg BIW) had one grade 3 DLT of fatigue and Arm D (80mg QW) had one grade 3 DLT of lymphopenia. No grade 4 or 5 DLT were seen with the once weekly dosing schedule.

1.2.8 Studies with Selinexor and Radiation

There are no clinical studies with Selinexor and radiation.

1.2.9 Updated Clinical and Efficacy Results (IB version 10, dated 9/21/2020)

Results from ongoing and completed clinical studies have shown that selinexor induces durable antitumor responses across a broad range of relapsed or refractory (RR) hematologic and solid tumor cancers, which is consistent with its proposed mechanism of action. In general, these effects appear to be independent of tumor type or prior treatment(s).

As of 31 March 2020, 3419 patients with hematologic or solid-tumor malignancies had received at least 1 dose of selinexor; in addition, 301 patients received at least 1 dose of selinexor or blinded study treatment (i.e., selinexor or placebo) for a total of 3720 patients. These 3720 patients include 2310 patients from Company-sponsored trials (CSTs; 2009 who received selinexor and 301 who received blinded study treatment), 1201 active patients from Investigator-Sponsored Trials (ISTs) who received selinexor, and 161 patients from the selinexor Expanded Access Program (EAP) who received selinexor; and 9 and 39 patients who received selinexor through clinical trials sponsored by Ono Pharmaceutical Co., Ltd and Antengene, respectively.

The most commonly reported treatment-emergent adverse events (TEAEs) for selinexor in CSTs were nausea (66.1%), fatigue (56.7%), anorexia (includes MedDRA “decreased appetite”; 51.1%), thrombocytopenia (51.0%), anemia (43.5%), vomiting (38.7%), and diarrhea (36.6%), that were generally low-grade and reversible. The TEAEs of thrombocytopenia and anemia, which can be higher grade, were reported primarily in patients with hematologic malignancies.

1.2.9.1 KCP330012/STORM

Based on activity observed for selinexor in combination with dexamethasone in RRMM in Part 2 of the Study KCP330012/STORM (hereafter referred to as STORM), selinexor received accelerated US Food and Drug Administration (FDA) approval in July 2019 for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies and whose disease is refractory to at least 2 PIs, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody. The objective response rate (ORR) was 26.2%, with a quick median time to first response of 4.1 weeks (range: 1 to 14 weeks). The median progression-free survival (PFS) was 3.7 months and median overall survival (OS) was 8.4 months.

1.2.9.2 KCP330-023/ BOSTON

Study KCP330-023/ BOSTON (hereafter referred to as BOSTON) evaluating selinexor plus bortezomib plus lowdose dexamethasone (SVd) vs bortezomib and dexamethasone alone (Vd) in RRMM in which the SVd arm showed a clinically and statistically significant improvement for PFS compared to the Vd arm (median PFS 13.93 months vs 9.46 months) serves as a confirmatory study of the accelerated approval asserting that the responses observed in the STORM study are highly likely to confer clinical benefit. A supplemental new drug application (sNDA) was submitted to the FDA in May 2020 seeking full approval for selinexor as a treatment for patients with MM after at least 1 prior line of therapy.

1.2.9.3 KCP-330-009/SADAL

Selinexor has shown activity in diffuse large B-cell lymphoma (DLBCL) in Study KCP-330-009/SADAL (hereafter referred to as SADAL), a multi-center, single-arm Phase 2b study. Based on the results of this study, selinexor received approval from FDA in June 2020 for the treatment of adult patients with RR DLBCL, not otherwise specified, including DLBCL arising from

follicular lymphoma, after at least 2 lines of systemic therapy. In this study, the ORR was 28.3%, median duration of response (DOR) was 9.3 months and median OS was 9.1 months.

Study XPORT-DLBCL-030 was agreed as the confirmatory trial for evaluating selinexor in DLBCL. This trial will assess the effect of selinexor or placebo added to a standard backbone immunochemotherapy of rituximab-gemcitabine-dexamethasone-platinum (R-GDP) in patients with 1 to 3 prior treatments for DLBCL.

1.2.10 Rationale for Dose Level 2 and 3 Modification (amendment version date: 03/26/2021)

We are using Selinexor as a radiation sensitizer. In theory, it would be more effective if we gave it more frequently as radiation is given 5-days per week. However, we did not have sufficient clinical data to support multi-dosing per week when the trial was originally written. We now have that data and are thus requesting the change. The once-a-week dosing was supported by the FDA approval of Selinexor in the treatment of multiple myeloma (80mg weekly). The new data supporting the twice a week dosing (BIW) is from ARM C of the recently reported KING trial [23]. The KING trial is a Phase 2 study of Selinexor monotherapy in recurrent glioblastoma multiforme. In that trial 14 patients were treated with 60mg BIW with a similar side effect profile to the 80mg once per week given in ARM D. Additionally, in the pre-surgical ARM A of the KING study 6 patients were dosed with 50mg/$m^{2,}$ 2-3 hours prior to surgical resection. 136nM of Selinexor was measured within the tumor and is consistent with the desired CNS dose in animal models. Thus, 60mg BIW should give adequate penetration of the CNS, allowing additional fractions of radiation to be sensitized with an equivalent side effect profile. The company has additional unpublished data from a trial in patients with lymphoma with twice weekly dosing (60mg BIW) which has recently received FDA approval.

Thus, we havechanged dose levels 2 and 3 in our trial from once-a-week dosing to twice a week dosing.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Histological diagnosis

- Pathologically confirmed glioblastoma or gliosarcoma (including astrocytoma, grade IV)

2.1.1.2 Patients must be eligible for definitive external beam radiotherapy and temozolomide.

2.1.1.3 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of Selinexor in combination with temozolomide in patients <18 years of age, children are excluded from this study.

2.1.1.4 Patients should have a KPS greater than or equal to 70 (see **Appendix A**).

2.1.1.5 Absolute neutrophil count (ANC) >1.5x10^9/L; platelet count >100x10^9/L; and hemoglobin (Hb) >9.0 g/dL. Note: the use of transfusion or other intervention prior to cycle 1 day 1 to achieve Hb >9.0 g/dL is acceptable.

2.1.1.6 Ability of subject or Legally Authorized Representative (LAR) to understand and the willingness to sign a written informed consent document.

2.1.1.7 The effects of Selinexor on the developing human fetus are unknown. For this reason and because Selinexor agents as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study treatment and for one month after treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

2.1.1.8 Patients must have had surgery and/or biopsy not greater than 8 weeks prior to initial evaluation to be eligible for this study.

2.1.2 Exclusion Criteria

2.1.2.1 Patients who are receiving any other investigational agents and have had prior therapy including:

- Patents who have previously received radiation therapy (RT) to the brain.
- Patients who received chemotherapy for the treatment of their glioma
- Patients who are being treated with implanted gliadel wafers
- Patients who are being treated with tumor treating fields

2.1.2.2 History of allergic reactions attributed to compounds of similar chemical or biologic composition to selinexor or temozolomide used in study.

2.1.2.3 Patients with coagulation problems and medically significant bleeding in the month prior to start of treatment (peptic ulcers, epistaxis, spontaneous bleeding). Prior history of DVT or PE is not exclusionary

2.1.2.4 Patients with active uncontrolled or suspected infections

2.1.2.5 Patients with severe liver dysfunction defined as:

- Total bilirubin > 1.5 x upper limit of normal (ULN) Note: Subjects with Gilberts syndrome should not be excluded as long as total bilirubin is < 3.0 x ULN and documentation to support diagnosis is available.
- Serum glutamate pyruvate transaminase (SGPT) or called as Alanine aminotransferase (ALT) ≥3 x ULN = 135 U/L; for the purpose of this study, the ULN for SGPT is 45 U/L
- Serum glutamic oxaloacetic transaminase (SGOT) or called as Aspartate aminotransferase (AST) ≥3 x ULN = 150 U/L; for the purpose of this study, the ULN for SGOT is 50 U/L
- Serum albumin ≥ 2 x ULN

2.1.2.6 Known active hepatitis A, B, or C infection

2.1.2.7 HIV patients are not eligible because of their immunocompromised status and overlap of side effects between HAART therapy and radiation therapy.

2.1.2.8 Patients must not have significantly diseased or obstructed gastrointestinal tract malabsorption, uncontrolled vomiting or diarrhea, or inability to swallow oral medication

2.1.2.9 Pregnant women are excluded from this study because Selinexor could have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother

with Selinexor, breastfeeding should be discontinued if the mother is treated with Selinexor. These potential risks may also apply to temozolomide used in this study.

2.1.2.10 Patients with pre-existing known or suspected radiation sensitivity syndromes will be excluded due to potential confounding effect on outcome.

2.1.3 Recruitment Strategies

Both men and women and members of all races and ethnic groups are eligible for this trial. This study will be listed on NIH websites and www.clinicaltrials.gov. Participants will be recruited from the current patient population as well as referrals at NIH. Social media platforms managed by NIH/NCI may also be used to publicize the study. This protocol may be abstracted into a plain language announcement posted on NIH websites and on NIH social media platforms.

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the consent for study # 01C0129 (Eligibility Screening and Tissue Procurement for the NIH Intramural Research Program Clinical Protocols). Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a patient has signed the consent.

- All tumors will undergo central pathology review at NIH prior to study including molecular CNS panel whenever possible. Archival samples from surgery will be used for pathology review.
- Clinical Evaluations (within 7 days prior to enrollment):
    - Complete history and physical exam completed by principal or associate investigator, including thorough documentation of signs and symptoms caused by the tumor, determination of Karnofsky performance scale (KPS), neurological function and mental status.
    - Vital signs: including height and weight
- Laboratory Evaluations: Pre-treatment blood tests should be performed within 14 days prior to enrollment
    - Hematology: complete blood count (CBC) with differential, PT/INR, PTT

- Chemistries: bilirubin (total and direct), AST, ALT, LDH, BUN, alkaline phosphatase, albumin, serum creatinine, serum electrolytes, calcium, magnesium, phosphorus, uric acid , amylase and lipase
- Hepatitis A, B and C serologies
- HIV antibody test screening.
- Urinalysis
- Serum/urine pregnancy test: required for females of childbearing potential

- Conventional MRI (if needed based upon PI discretion)

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g. when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at: https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit.

2.3.1 Treatment Assignment Procedures

Cohorts

Number	Name	Description
1	Cohort 1	Patients with newly diagnosed glioblastoma or gliosarcoma

Arms

Number	Name	Description
1	Experimental therapy	Selinexor with temozolomide and radiation

Arm assignment

Patients in cohort 1 will be directly assigned to arm 1. No randomization and stratification will be performed on this study.

2.4 BASELINE EVALUATION

Baseline assessments will be performed per **Study Calendar**. Tests done at screening do not need to be repeated on baseline (C1D1) if performed within 7 days prior to enrollment except for physical exam, KPS, vital signs, neurological exam, performance and mental status, and urine pregnancy test. Screening laboratory evaluations do not need to be repeated if performed within 14 days prior to enrollment. Please refer to section **2.2** for screening details.

- Thyroid function tests: total T3, freeT4 and TSH+
- Treatment planning CT/MRI scans: All patients will have radiation therapy treatment planning CT and MRI scans (as explained below). Treatment planning CT scans will be obtained with immobilization mask in place.

- Conventional MRI: Conventional MRI including T1, T2, T2 FLAIR and postcontrast T1 as well as diffusion weighted (DWI) MRI (NOB Procedure DCE MRI) of the brain to occur within 2 weeks prior to study entry. If scans were obtained from another institution copies should be produced and maintained on file with the PI for future comparison, the patient however must receive MRI imaging as per above. MRI of the brain obtained within 2 weeks prior to enrollment can be used as baseline staging evaluations to be done at the NIH.
- If initial imaging evaluation was greater than 3 weeks prior to referral, a diagnostic quality contrast enhanced MRI will be obtained for baseline staging evaluation.

- Baseline quality of life (QOL) will be collected as per the MD Anderson Symptom Inventory for Brain Tumors (MDASI-BT) (**Appendix D**), PROMIS Depression, PROMIS Anxiety, and NeuroQoL assessments (**Appendix E**), PRO-CTCAE (**Appendix F**) within 1 week of study entry.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

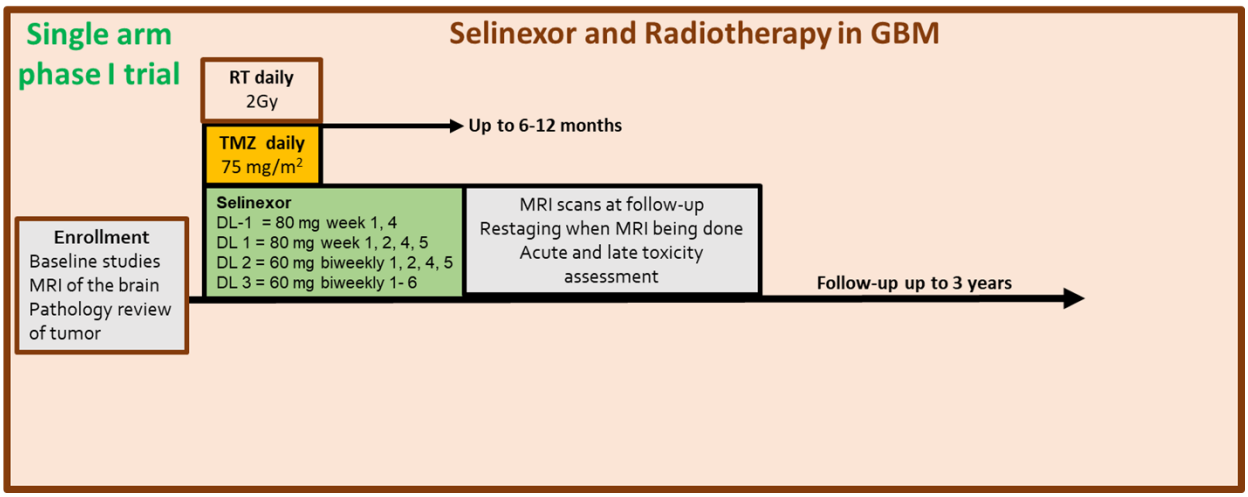
3.1.1 Concurrent Therapy

- Radiation therapy (RT) will be administered daily (Monday to Friday) in the Radiation Oncology Branch (ROB), NCI, unless the treatment schedule requires change in the event of inclement weather or federal holidays.
- Oral temozolomide will be taken as described in section **3.2.1**.
- Selinexor will be given during radiationas determined by dose level. Please refer to section **3.1.5** for details. All the protocol related follow-up appointments will occur at NCI ROB.

3.1.2 Adjuvant Therapy

- Post RT, temozolomide will be given per standard of care. It could be given under this study or by patient's primary oncologist.

3.1.3 Study Schema



3.1.4 Dose Limiting Toxicity

A dose-limiting toxicity (DLT) is defined as a clinically significant adverse event assessed as unrelated to tumor progression, intercurrent illness or concomitant medications and meets any of the criteria below. Any DLT must be a toxicity considered at least possibly related to selinexor and the acute effects thereof.

- Any grade 3 or 4 toxicity as per CTCAE Criteria Version 5.0 during treatment and within 30 days after completion of RT
- Any grade 3 or 4 toxicity as per Section **14.1.2.** RTOG acute morbidity during treatment and within 30 days after completion of RT
- Any toxicity at least possibly related to selinexor that causes a patient to miss consecutive radiation or temozolomide doses for 5 days.

3.1.5 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 within 1 month of completion of treatment, and the dose below that at which at least 2 (of ≤6) patients have DLT as a result of selinexor/RT/temozolomide. If a patient did not experience DLT and did not finish treatment, he or she will not be evaluable for toxicity and will be replaced in the dose level. Enrollment to a dose level would stop if 2 or more patients had a DLT.

The number of patients may be increased to 9 total patients at the MTD (provided no DLT) with a maximum of 21 evaluable patients enrolled and the minimum evaluable patients required will be 15. The once weekly dosing schedule was based on the results of the KCP-330-004 study Arm D. The twice weekly dose of 60mg is from KCP-330-004 Arm C.

Dose Escalation Schedule of Selinexor	
Dose Level	
Level -1	80 mg on weeks 1, 4
Level 1	80 mg on weeks 1, 2, 4, 5
Level 2	60 mg twice a week on weeks 1, 2, 4, 5
Level 3	60 mg twice a week, weeks 1-6

All patients will receive 2Gy daily RT plus 75mg/m^2 temozolomide.

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 dose level
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to three (3) additional patients will be entered at the next lowest 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 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 lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is the MTD and is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

3.1.6 Study Stopping Rule

Accrual will be halted if there are ≥2 patients who miss consecutive doses of RT or temozolomide for 5 days that are possibly attributable to the selinexor treatment.

Prior to resumption of the study, PI will evaluate these events and determine the next course of action.

3.2 DRUG ADMINISTRATION

3.2.1 Selinexor

At dose level 1, Selinexor will be administered orally at an initial dose of 80 mg. The first dose will be given on day 2 of radiation and will thereafter be administered weekly on the second day of weekly radiation on weeks 1, 2, 4, and 5. If dose level 1 is tolerated, the Selinexor dose will be escalated to 60 mg twice a week on weeks 1, 2, 4, 5 given on Monday and Thursday. The third and final dose level will be 60 mg administered twice a week (on Monday and Thursday of radiation) for 6 weeks.

Prophylactic concomitant treatments with a 5-HT3 antagonist and olanzapine may be administered per section **4**.

3.2.2 Temozolomide

Temozolomide will begin on the first day or evening prior of radiation and be administered orally daily at a dose of 75 mg/m^2 during the radiation treatment. Temozolomide will continue until the completion of radiation and then will be stopped.

Beginning 1-month post-RT, the adjuvant temozolomide will be given per standard of care.

3.2.2.1 CCR self – administered study drugs policy

All oral self-administered study drug will be properly accounted for, handled, and disposed in accordance with existing federal regulations and principles of Good Clinical Practice. All oral study drugs will be recorded in the patient diary found in **Appendix H** or **Appendix I.** This will be used as a memory aide for subjects. The clinical research team will maintain the primary source record. Subjects should be asked to bring the diary as well as unused study drug and empty containers with them at each study visit. If a subject goes off study while at home, the research nurse will ensure and document the return of the unused oral study drug from the participant. Unused study drug will be disposed and destroyed per CC pharmacy SOPs.

3.3 DOSE MODIFICATIONS

3.3.1 Radiation Therapy

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.

3.3.2 Concurrent Systemic Agents

3.3.2.1 Selinexor

Supportive Care and Selinexor Dose Adjustment Guidelines for AEs related to Selinexor [a,b]

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
Fatigue	
Grade 1 or Grade 2 lasting ≤7 days	Maintain dose. Rule out other causes. If found to be anemic and symptomatic, consider transfusions for hemoglobin >8 g/dL (Grade <3).
Grade 2 lasting >7 days or Grade ≥3	Rule out other causes. If found to be anemic and symptomatic, consider transfusions for hemoglobin >8 g/dL (Grade <3); transfusions usually indicated for hemoglobin <8 g/dL (Grade ≥3). Stop Selinexor.
Anorexia or Weight Loss	
Grade 1 weight loss or Grade 2 anorexia and weight loss	Maintain dose. Rule out other causes. Consider nutritional consultation and utilize nutritional supplements. Should consider olanzapine 2.5 mg to 5 mg once a day if the weight loss is rapid.
Grade 2 weight loss or Grade ≥3 anorexia and weight loss	Rule out other causes. Consider nutritional consultation and utilize nutritional supplements or consider appetite stimulants including olanzapine 2.5 mg to 5mg once a day. Stop Selinexor.
Nausea, Acute	
Grade 1 or 2 (If intolerable or persistent Grade 2 not responsive to supportive care follow guidelines for Grade 3)	Maintain dose. Rule out other causes. Utilize any additional anti-nausea needs to supplement breakthrough nausea
Grade 3	Rule out other causes. Utilize additional anti-nausea meds to supplement the breakthrough nausea

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
	Stop Selinexor.
Hyponatremia	
Grade 1 (sodium levels <Normal to 130 mmol/L)	Maintain dose. Rule out other causes including drug (e.g. diuretics) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose >150mg/dL). Treat hyponatremia per institutional guidelines including dietary review. Consider addition of salt tablets to patient's diet.
Grade 3 with sodium levels <130-120 mmol/L without symptoms	Rule out other causes including drug (e.g. diuretics) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose >150mg/dL). If (corrected) sodium is Grade ≤3 and continues to be asymptomatic then patient may continue current dosing without interruption provided that IV saline and/or salt tablets are provided and patient is followed closely. Stop Selinexor.
Grade 3 with sodium levels <130-120 mmol/L with symptoms or Grade 4 (<120 mmol/L)	Rule out other causes including drug (e.g. diuretics) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose >150mg/dL). Stop Selinexor.
Diarrhea	
Grade 1	Maintain dose. Rule out other causes including drug effects. Treat per institutional guidelines.
Grade 2	Rule out other causes including drug effects. Treat per institutional guidelines with anti-diarrheals. Interrupt Selinexor dosing until resolved to Grade 1 or baseline.

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
	For first occurrence, restart Selinexor at current dose. For ≥ second occurrence, reduce Selinexor by 1 dose level.
Grade 3 or 4	Rule out other causes including drug effects. Treat per institutional guidelines with anti-diarrheals. Stop Selinexor.
Thrombocytopenia	
See below section **3.3.2.1.1**	
Neutropenia	
See below section **3.3.2.1.1**	
Anemia	
Treat per institutional guidelines including blood transfusions and/or erythropoietins. Consider transfusing for symptoms with hemoglobin >8g/dL (Grade <3) or for any Grade 3 (hemoglobin <8 g/dL). If possible, maintain Selinexor dose as long as patient is clinically stable, but if a dose reduction or interruption is desired, consult with the Principal Investigator.	
Other Selinexor-related adverse events	
Grade 1 or 2	Rule out other causes. Maintain dose. Initiate treatment and/or standard supportive care per institutional guidelines.
Grade 3 or 4	Rule out other causes. Isolated values of Grade ≥3 alkaline phosphatase does not require dose interruption. Determination of liver versus bone etiology should be made and evaluation of gamma-glutamyl transferase, 5'-nucleotidase, or other liver enzymes should be performed. Stop Selinexor.

[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.

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.

3.3.2.1.1 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. 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.

3.3.2.1.2 Renal Insufficiency

Baseline renal insufficiency does not appear to affect tolerability of Selinexor and renal dysfunction should not preclude continued dosing with Selinexor, even for patients on dialysis. If a patient is undergoing dialysis, Selinexor should be given after dialysis procedure because the effect of dialysis on Selinexor plasma levels has not yet been studied. Selinexor can lead to increased creatinine and the majority of these cases are associated with hypovolemic conditions (e.g., represent "pre-renal" azotemia). Dose modifications or interruptions and appropriate hydration typically reverse the increased creatinine.

3.3.2.1.3 Conditions not requiring Selinexor dose reduction

The following conditions are exceptions to the dose-modification guidelines. Selinexor does not need to be held for alopecia of any grade, or for electrolytes or serum analyte (e.g., urate) abnormalities that are reversible with standard interventions.

3.3.2.2 Temozolomide (TMZ)

3.3.2.2.1 During concomitant radiotherapy

A complete blood count should be obtained weekly. Adjustments to the dose of Temozolomide and Selinexor will be made at the direction of the PI or study chairperson.

Toxicity and Intensity	**Supportive Care and Dose Adjustment Guidelines**
Platelets	
>75k	Continue both drugs.
Grade 2, >50-75k	Hold TMZ Hold Selinexor Continue RT. Recheck CBC, when platelets >75k restart TMZ and selinexor

Grade 3, 25-50k	Hold TMZ. Discontinue Selinexor. Continue RT. Recheck CBC, when platelets >75k restart TMZ
Grade 4, <25k	Hold TMZ Discontinue Selinexor Hold RT Recheck CBC, when platelets >50k restart RT When platelets >75 k restart TMZ
ANC	
>1.5	Continue both drugs
Grade 2, >1-1.5	Hold TMZ Hold Selinexor Continue RT Recheck CBC when ANC 1.5 restart TMZ and selinexor
Grade 3, 0.5-1	Hold TMZ Discontinue Selinexor Continue RT Recheck CBC, when ANC >1.5 restart TMZ
Grade 4, <0.5	Hold TMZ Discontinue Selinexor Continue RT Recheck CBC, when ANC >1,5 restart TMZ,

3.3.2.2.2 Following the completion of chemoradiation

Beginning 1-month post-RT, the adjuvant temozolomide will be given per standard of care.

3.4 QUESTIONNAIRES (FOR ENGLISH SPEAKING PATIENTS ONLY)

MD Anderson Symptom Inventory for Brain Tumors (MDASI-BT) (**Appendix D**) will be performed at baseline, at completion of radiation and at all subsequent follow-up visits.

PROMIS Depression, PROMIS Anxiety, and NeuroQoL assessments (**Appendix E** and **Appendix F**) will be performed at baseline, at completion of radiation and at all subsequent follow-up visits.

PRO-CTCAE (**Appendix G**): Patients will complete a baseline PRO-CTCAE before starting treatment, at completion of radiation and at all subsequent follow-up visits if the patient is able. It takes 5-10 minutes to complete each questionnaire. It will only be completed by the patient, unless changes in vision or weakness make this difficult. If this occurs, then the caregiver may read the questions to the patient or assist with marking the answers as described by the patient. A patient caregiver may complete the questionnaires as a patient-preference proxy if the patient's deficits preclude self-report.

All questionnaires are allowed to be completed within +/-7 days from the scheduled dates.

Every attempt will be made to collect this data from every patient at each time point. If the patient is a non-English speaker the data will not be collected.

3.5 STUDY CALENDAR

Procedure	Screening	Baseline[1]	Radiation[2] (every day up to 6 weeks)	Follow-up (Total 3 yrs) [8, 10]		
				1 month	Every 2 months for 2 yrs	Every 3 months for 3rd yr
History & PE	X	X		X	X	X
Karnofsky Performance	X	X		X	X	X
Neurological function & Mental Status	X	X		X	X	X
Vital signs incl Weight	X	X	X	X	X	X
Height	X					
Pathology review incl molecular CNS panel	X					
Treatment						
On treatment visit (OTV) evaluation once per week			X			
Temozolomide (Daily)[3]			X			
Selinexor [4]			X			
Toxicity assessment[5, 9]			X	X	X	X
Labs (Please refer section 2.2.2 for details)						
Hematology[6a]	X	X	X	X	X	X
Chemistries[6b]	X	X	X	X	X	X
Thyroid function tests		X				
Pregnancy Test (urine/serum)	X	X				
Hepatitis A, B and C testing	X					
HIV testing	X					
Radiographic (Please refer section 2.4 for details)						
MRI	X	X		X	X	X
CT scans		X				
Questionnaires (Please refer section 3.4 for details)						
QoL questionnaires per MDASI-BT (**Appendix D**)[7]		X	X	X	X	X
PROMIS Depression, PROMIS Anxiety, and NeuroQoL (**Appendix E**) [7]		X	X	X	X	X
PRO-CTCAE (**Appendix F**) [7]		X	X	X	X	X

[1] Tests done at screening do not need to be repeated on baseline (C1D1) if performed within 7 days prior to enrollment except physical exam, KPS, vital signs, neurological exam, performance and mental status, and urine pregnancy test. Screening laboratory evaluations do not need to be repeated if done within 14 days prior to enrollment.

[2] Patients will be treated with 2Gy daily RT plus 75mg/m^2 temozolomide for six weeks with Selinexor given once or twice a week depending on dose level.

[3] Regarding temozolomide dosing details, please refer to section **3.2.2**.

[4] Administered per section **3.1.5**.

[5] Assessment of acute toxicity (CTCAE Version 5.0 and RTOG Acute Morbidity score. (see **Appendix B** and **Appendix C**)

[6] Laboratory evaluation weekly during radiation.

a. Complete blood count with differential and platelets, PT/INR, PTT
b. Serum chemistries: LDH, AST, ALT, alkaline phosphatases, bilirubin (total and direct), BUN, serum creatinine, serum electrolytes, glucose, calcium, magnesium, phosphorous, uric acid, albumin, amylase, lipase

[7] QOL assessment will be performed at baseline, at completion of radiation and at all subsequent follow-up visits. The questionnaires are allowed to be completed within +/-7 days from the scheduled dates.

[8] May be completed by remote visit with a member of the study team (e.g., if the patient is not able to return to the NIH CC). A patient may be referred to their local provider or asked to come to the NIH CC for an in-person assessment, if clinically indicated, and at the discretion of the PI. In the case of any visits with participants' local providers, records will be obtained. Follow-up evaluations should occur at one month after the completion of therapy, followed by at least every 2-month intervals for the first 2 year(s), and then at least every 6 months thereafter for a total of 3 years following completion of radiation/ Temozolomide/ Selinexor.

[9] Toxicity assessment, vital signs and weight measurement may be done weekly during the on treatment visit and as needed.

[10] All follow-up appointments will take place within +/- 7 days of the designated timepoint.

3.6 RADIATION THERAPY GUIDELINES

3.6.1 Scheduling

Radiation therapy will be administered daily Monday-Friday at NCI ROB unless the treatment schedule requires amendment in the event of inclement weather or federal holidays. All the protocol related follow-up appointments will occur at NCI ROB at the NIH Clinical Center.

3.6.2 Technique

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. 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:

<table>
<tr><th>EORTC treatment volumes (single phase)</th><th>RTOG treatment volumes (two phases)</th></tr>
<tr><td>Single Phase (Treated to 60 Gy in 30 fractions)</td><td>Phase I (Treated to 46 Gy in 23 fractions)</td></tr>
<tr><td rowspan="3">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</td><td>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 tumor plus 2.5 cm.
PTV1: CTV plus a margin of 3-5 mm</td></tr>
<tr><td>Phase II (Treated to 14 Gy in 7 fractions)</td></tr>
<tr><td>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</td></tr>
</table>

3.6.3 Target coverage and dose limits

The volume of 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 ICRU criteria, the max point dose shall not exceed 107% of the prescribed dose.

3.6.4 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 below:

OAR	Objective
Brainstem	Dmax≤60 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

3.7 COST AND COMPENSATION

3.7.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by an insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.7.2 Compensation

There will not be any compensation as part of the study.

3.7.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.8 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

3.8.1 Criteria for removal from protocol therapy

- Completion of 6 weeks of RT
- Progressive disease as defined in **6.3.1**
- Participant requests to be withdrawn from active therapy
- Unacceptable Toxicity as defined in section **3.3**
- Investigator discretion
- Positive pregnancy test

3.8.2 Off-Study Criteria

- Completed study follow-up period
- Participant requests to be withdrawn from study
- Death
- Investigator discretion
- Non-compliance with follow-up visits or protocol mandated procedures
- Participant lost to follow up
- Investigator decision to end the study

3.8.3 Lost to Follow-up

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

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

- The site will attempt to contact the participant and reschedule the missed visit within two weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

- Prophylactic concomitant treatments with a 5-HT3 antagonist and olanzapine 5 mg for men and 2.5 mg for women must be provided 3 days prior to and during treatment with each dose of selinexor. Olanzapine may be administered as needed on days 6 and 7 during week of selinexor treatment.
- PJP prophylaxis should be given during the concurrent chemoradiation phase of treatment. Acceptable forms of treatment include oral trimethoprim-sulfamethoxazole and aerosol pentamidine as is left to the discretion of the treating physician.
- Other cancer chemotherapy, immunotherapy, or investigational agents may NOT be administered to patients in the active course of treatment on this study.
- Patients will receive corticosteroids as needed for symptoms of cerebral edema as clinically indicated. Attempts to wean patients from steroids should be made as indicated by improvement or stabilization of neurologic symptoms. Any initiation of steroids or increase in dose thereof will be documented.
- All patients with a seizure history will be maintained on their existing anticonvulsant medication.

- Radiation therapy side effects include fatigue, nausea and vomiting and possible worsening of preexisting neurological symptoms. These will be managed using general best supportive care and corticosteroids may be initiated at the discretion of the treating radiation oncologists and taper as needed depending on clinical status once irradiation has been completed.
- The ROB staff physician, nurse practitioner and research nurse will frame the support infrastructure required to assist with the patient`s care in the event of serious treatment toxicity. The pain and palliative team, will be consulted as needed to address end of life issues and disposition as has been standard procedure for all ROB patients to date.

5 CORRELATIVE STUDIES FOR RESEARCH

None.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCRand ensuring data accuracy, consistency and timeliness. An enrollment log will be maintained in the regulatory binder/file which is the only location of personal identifiers with unique subject identification number. Imaging will be digitally archived and processed using computer software in the Radiology department of the Clinical Center, NIH, and the Radiation Oncology Branch, NCI. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Document AEs from the first study intervention, Study Day 1, through 30 days after the subject received the last study drug administration.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization
- Is judged by the Principal Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient’s outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

- Coded, linked data in an NIH-funded or approved public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center)
- Identified or coded, linked data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository. Such as: clinical trial.gov
- BTRIS (automatic for activities in the Clinical Center)
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

When will the data be shared?

- Before publication.
- At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

NIH Genomic Data Sharing Policy will not apply for this protocol as no genetic/genomic testing is performed.

6.3 RESPONSE CRITERIA

6.3.1 Modified RANO Response Criteria

Response will be assessed by Modified RANO criteria and as such, the first imaging following completion of radiation will be considered the baseline for response assessment as per Ellingson et al. Neurotherapeutics 2017[25].

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). 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 observe 2. No new lesion. 3. Steroid dose should be the same or lower compared with baseline scan. 4. Stable or improved clinical assessments.

Response	**Modified RANO response Criteria**
Progressive Disease (PD)	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)	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.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. RTOG morbidity score will be used for radiation related toxicity

(**Appendix B** and **Appendix C**). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7 NIH REPORTING REQUIREMENTS/DATA SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements. Note: Only IND Safety Reports that meet the definition of an unanticipated problem or present new information that might affect the willingness of participants to enroll or remain on the study will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2)).

8.1.2 Treatment-emergent adverse event (TEAE)

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

8.1.3 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see **8.1.4**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience 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.

8.1.4 Life-threatening

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. (21CFR312.32).

8.1.5 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.0.

8.1.6 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor with the exception of any listed in section **8.4**.

8.3 Reporting of Serious Adverse Events

Any AE that meets a protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. Any exceptions to the expedited reporting requirements are found in section **8.4**.

All SAE reporting must include the elements described in **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://nih.sharepoint.com/:u:/r/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=uWBXtI

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 Waiver of Expedited Reporting to CCR

Progression of the malignancy disease (including fatal outcomes) should NOT be reported as an SAE during the study or within the safety reporting period. Any 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.

8.5 Safety Reporting Criteria to the Pharmaceutical Collaborators

Reporting will be per the collaborative agreement.

8.6 Reporting Pregnancy

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here: https://nih.sharepoint.com/:u:/r/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=uWBXtI

8.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy become known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (section **8.1.3**) should be reported as SAEs.

The outcome of all pregnancies should be followed up and documented.

8.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for one month after the last dose of temozolomide.

Pregnancy of the patient's partner is not considered to be an AE. The outcome of all pregnancies occurring from the date of the first dose until one month after last dose of temozolomide should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.8 SPONSOR DEVIATION REPORTING

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documentsGCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitorin the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements. In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and,
- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site(s). Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, coordinating center (if applicable), and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESIS

10.1.1 Primary Endpoint

Define the maximum tolerated dose (MTD) of Selinexor given concurrently with radiation and temozolomide. Assessment of toxicities for dose escalation will occur for 30 days following the completion of RT.

10.1.2 Secondary Endpoint

Define the dose-limiting toxicities including effects on QOL and neurocognition in the setting of the addition of Selinexor to concurrent radiation therapy and temozolomide.

10.2 SAMPLE SIZE DETERMINATION

The primary objective of this trial is to determine the safety, toxicity profile, DLT and maximum tolerated dose (MTD) of Selinexor given concurrently alongside temozolomide and radiation in patients with newly diagnosed glioblastoma patients. There are 3 planned dose levels for this trial that will enroll 1 to 6 patients each using the 3+3 design to define the MTD. The MTD will be based on the assessment of DLT within one month following the irradiation, and will be defined as the dose level at which less than one-third of patients (0/3 or 0-1/6 patients) treated at that dose level experience a DLT, with the next higher dose level demonstrating a one-third or greater number of patients ($\geq$ 2/3 or $\geq$ 2/6 patients) having DLT. If a patient did not experience DLT and did not finish therapy, he or she will not be evaluable for determination of the MTD

and will be replaced in the dose level. An additional 3 to 6 patients will be enrolled at the MTD, so that a total of 9 patients will be treated at this dose to better characterize the clinical activity of this combination in this patient population. Thus, if all 3 dose levels are evaluated (6 patients per dose level with 9 total patients at the MTD or maximum administered dose), a maximum of 21 evaluable patients will be enrolled. Similarly, if all dose levels are evaluated, the minimum number of evaluable patients required will be 15. To compensate for inevaluable patients, an additional 3 patients may be enrolled. Thus, a maximal of 24 patients are targeted for this study. It is expected that accrual can be completed in 24 months.

Using this dose escalation scheme, the probability of escalating to the next dose level, based on the true rate of DLT at the current dose, is given by the following table (each group will be considered independently of the other):

True rate of DLT at a given dose	10%	20%	30%	40%	50%	60%
Probability of escalating	.91	.71	.49	.31	.17	.08

10.3 POPULATIONS FOR ANALYSES

10.3.1 Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with Selinexor.

10.3.2 Evaluable for response

Only those patients who have completed radiation treatment will be considered evaluable for response.

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

This is a phase I single arm dose escalation study of Selinexor in combination of radiation and temozolomide for patients with newly diagnosed Glioblastoma. Cohorts of 3-6 patients are evaluated at each dose level. The dose level on which 2 patients experience unacceptable toxicity is considered to have exceeded the MTD. The next lower dose level on which no more than 1/6 patients experience unacceptable toxicity is considered the MTD for this study.

10.4.2 Analysis of the Primary Endpoints

The primary endpoint will be to define the MTD of this approach.

10.4.3 Analysis of the Secondary and Exploratory Endpoint(s)

- Define the dose-limiting toxicities of Selinexor in combination with external beam radiation therapy (RT) and temozolomide in patients with newly diagnosed with glioblastoma or gliosarcoma. DLT's will be reported descriptively.
- Determine progression-free survival and overall survival. Time to progression will be determined by the interval from initiation of treatment on protocol to progression as per RANO criteria or death due to disease progression. For patients without progression, time to progression will be censored at last assessment date per RANO criteria. Survival duration will be determined by the interval from initiation of

treatment on protocol to date of death due to any cause. For patients alive as of last follow-up, time to death will be censored at last contact date.

10.4.4 Safety Analyses

Adverse events will be coded as per the CTCAE v5.0. Each AE will be coded once for each patient based on the maximum severity during the assessment period. The relationship of AEs to study intervention will be recorded in addition to the onset date, end date, severity, expectedness, and outcome.

10.4.5 Planned Interim Analyses

The primary endpoint will be defined for the entire cohort and no planned interim analyses will be performed.

10.4.6 Sub-Group Analyses

The primary endpoint is based on toxicity at a dose level. Only 3-6 patients will be included per dose level except for the expansion cohort. Thus, it is not feasible to include sub-group analyses.

10.4.7 Tabulation of Individual Participant Data

Individual participant data will not be tabulated.

10.4.8 Exploratory Analyses

- QOL scores will be summarized at baseline and for each visit. This summarization will include the mean, standard deviation, standard error of measurement, effect size, median, minimum, and maximum. Changes from baseline of health-related quality of life questionnaire mean scores will be evaluated. Total and domain mean scores of patients will be compared by the response. Analyses to explore clinically meaningful change of QOL scores may be performed.
- PFS and OS will be informally compared with historical outcomes.

11 COLLABORATIVE AGREEMENTS

11.1 CLINICAL TRIAL AGREEMENT (CTA)

A Clinical Trial Agreement between Karyopharm Therapeutics Inc. and the National Cancer Institute for the clinical development of Selinexor (KPT-330) has been executed (CTA # 01119-18).

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

Subjects of both sex and from all racial and ethnic groups are eligible if they meet eligibility criteria. To date, there is no information that suggests that differences in radiation or disease response would be expected in one group compared with another. Efforts will be made to extend accrual to a representative population, but in this preliminary study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on one hand and the need to explore ethnic aspects of clinical research on the other hand. If differences in outcome that correlate with ethnic identity

are noted, accrual may be expanded or a follow-up study may be written to investigate those differences more fully.

12.2 Participation of Children

The biology of gliomas in children is very different than the biology of adult gliomas. As such most children are treated in children oncology protocols (COG) protocols through Children's Hospital. This protocol should not compete with the excellent work being done at Children's Hospital and is thus aimed at treating adult patients.

12.3 Participation of Subjects Unable to Give Consent

Adults unable to give consent are eligible to enroll in and remain on the protocol should capacity be lost during the study as the incidence of cognitive incapacitation in the glioma population is high. Excluding them would significantly impact enrollment and our ability to meet study objectives. All subjects able to provide consent at the time of enrollment will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate.

Please see section **12.5.1** for consent procedure.

12.4 Risk/Benefit Assessment

12.4.1 Known Potential Risks

12.4.1.1 Risks from Selinexor

The primary risk from this study is increased toxicity from selinexor (**14.1.2**).

12.4.1.2 Risks of Temozolomide

Refer to package insert.

12.4.1.3 Risks from Radiation

During participation in this research study, patients will be exposed to 60 Gy from radiation therapy and a much smaller amount of radiation from a CT scan used for treatment planning.

12.4.1.4 Risks from CT Imaging Contrast Agent

Itching, hives or headaches are possible risks associated with contrast agents that may be used during CT imaging. Symptoms of a more serious allergic reaction include shortness of breath and swelling of the throat or other parts of the body. Very rarely, the contrast agents used in CT can cause kidney problems for certain patients, such as those with impaired kidney function.

12.4.1.5 Risk from MRI scans

Participants are at risk for injury from the MRI magnet if they have metal in their body. There is a possibility that participants may experience claustrophobia. There are risks of back discomfort related to lying in the scanner.

12.4.1.6 Risks from MRI Gadolinium Based Contrast Agent (GBCAs)

The most common side effects from MRI contrast (gadolinium) include injection site pain, nausea, itching, rash, headaches and dizziness. Serious but rare side effects such as gadolinium toxicity and nephrogenic systemic fibrosis, or NSF, are most often seen in patients with severe kidney problems.

12.4.1.7 Risks of Blood draws

Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop. Up to 31 mL will be drawn during screening and/or baseline and up to 10 mL during follow-up.

12.4.1.8 Risks of Questionnaires

Questionnaires may contain questions that are sensitive in nature. The patients are asked to only answer questions they are comfortable with.

12.4.2 Known Potential Benefits

The potential benefits from this therapy are disease stabilization and delay or reduction of symptoms caused by the cancer, predominantly neurological impairment.

12.4.3 Assessment of Potential Risks and Benefits

A number of clinically appropriate strategies to minimize risks to patients have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, and management guidelines. The protocol provides for detailed and careful monitoring of all patients to assess toxicity. The potential benefit to a patient that participates in this study is better control of their tumor growth which may or may not have a favorable impact on symptoms and/or survival.

Overall, the potential benefit of the study drug combination and radiation in subjects with newly diagnosed glioblastoma and gliosarcoma outweigh the risks. This assessment applies for subjects able and unable to provide consent.

12.5 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant or consent designee as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with

policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location, but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at: https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit.

12.5.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation

For participants addressed in section **12.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section 12.5.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping

- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

13.2 Quality Assurance and Quality Control

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIH has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL AND DEVICE INFORMATION

14.1 SELINEXOR (KPT-330) (IND # 144383)

14.1.1 Source/Acquisition and Accountability

Selinexor will be supplied by Karyopharm Therapeutics and delivered directly to the NIH pharmacy. Selinexor (KPT-330) is a small molecule, oral, first-in-class, potent selective inhibitor of nuclear export (SINE) compound. The NIH pharmacy will be in charge of storing, dispensing and disposing/returning the study drug.

14.1.2 Toxicity

14.1.2.1 Very common side effects (≥10%)

In 100 people receiving selinexor more than 10 people may have:

- Nausea
- Vomiting
- Diarrhea
- Weight loss
- Decreased appetite
- Low sodium which may increase the risk of seizures

- Dehydration
- Abdominal pain
- Blurred vision
- Low platelets in the blood (thrombocytopenia) – which may increase the risk of bleeding
- Decrease in red blood cells (anemia) causing fatigue
- Decrease in neutrophils (a type of white blood cell that helps fight infections)
- Decrease in white blood cells (leukopenia), which may increase the risk of infection
- Dysgeusia – change in taste
- Dizziness
- Constipation
- Shortness of breath
- Fatigue and asthenia -- loss of energy; weakness
- Cough
- Fever
- Headache
- Difficulty falling asleep
- Pneumonia
- Low potassium which may cause weakness, muscle cramps and spasms
- Peripheral edema - swelling in the extremities due to accumulation of fluid, usually in the legs
- High blood sugar which may cause fatigue, increased thirst/hunger, frequent urination, weight loss, numbness and tingling in the hands and feet.

14.1.2.2 Common side effects (≥1-10%)

In 100 people receiving selinexor about 1 to 10 people may have:

- Rash
- Eye disorders including cataract (new or worsened), dry eye, visual impairment, seeing flashes of light.
- Night sweats
- Dry mouth
- Stomatitis – a condition that causes painful swelling and sores inside the mouth
- Dyspepsia – indigestion
- Chills
- Hypotension – low blood pressure
- Hypertension
- Tachycardia – fast heart rate
- Nosebleed
- Contusion (bruise due to body injuries such as fall)
- Electrolyte disturbances including:
- Low phosphate which may cause muscle weakness and fatigue
- Low magnesium which may cause muscle twitches and cramps
- Low calcium which may cause numbness and tingling in the hands/feet/face, muscle stiffness and cramps

- High potassium which may cause muscle weakness, palpitations, or irregular heartbeats and chest pain.
- Low albumin-a specific type of protein in blood (which may cause swelling especially of the hands/feet, weakness, or exhaustion)
- Peripheral neuropathy - weakness, numbness and pain from never damage, usually in the hands and feet
- Decrease in lymphocytes – a specific type of white blood cell that are part of your immune system
- Increase of creatinine in the blood due to a reduction in kidney function, often related to dehydration
- Elevated liver enzymes, which indicates destruction of the liver cells, including alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased.
- Elevated pancreatic enzymes including high amylase and high lipase
- Muscle weakness
- Febrile neutropenia – fever in the absence of a normal white blood cell response that may mean you have an infection
- Urinary tract infection
- Pain in the joints and muscles
- Malaise (a general feeling of being ill or bodily weakness)
- Muscle spasms
- Gait disturbance
- Hair loss
- Itching
- Depression
- Syncope – fainting
- Sepsis (including septic shock) – potentially life-threatening complication of an infection
- Cognitive disorder- brain disorder in which thinking abilities are impaired.
- Mental status changes including confusion

14.1.2.3 Uncommon side effects (>0.1-1%)

In 1,000 people receiving selinexor about 1 to 10 people may have:

- Tumor lysis syndrome – potentially a life-threatening side effect caused by the rapid breakdown of tumor cells and may cause irregular heartbeat, kidney failure or abnormal blood test results which included elevated uric acid level, elevated serum potassium and phosphorous levels, and a decreased calcium level.
- Gastroenteritis (stomach flu)

14.1.2.4 Rare side effects (>0.01-0.1%)

In 10,000 people receiving selinexor about 1 to 10 people may have:

- Acute cerebellar syndrome – symptoms can include a sudden loss of coordination, balance, or slurred speech

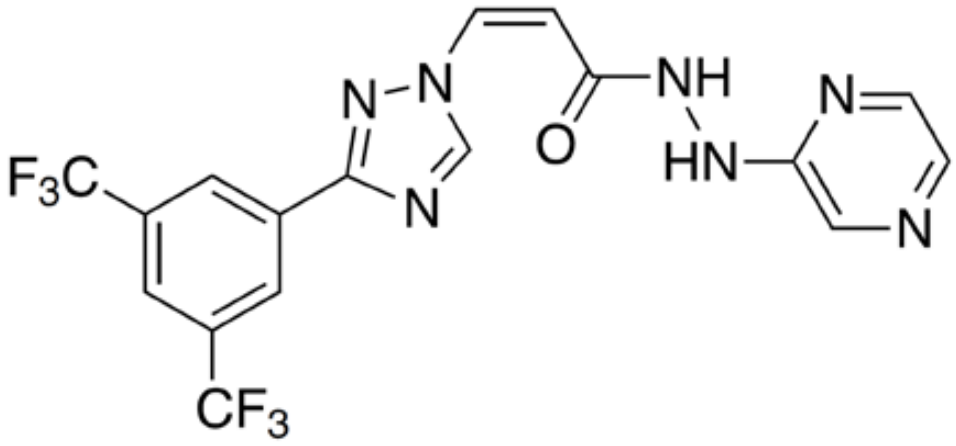
14.1.2.5 Serious adverse effects (≥3 cases reported as related by the Principal Investigator)

- Cardiac failure
- Multiple organ dysfunction syndrome
- Lung infection
- Bronchitis – infection of the tubes that carry air to and from lungs
- Acute kidney injury
- Bacteremia – bacterial infection in the blood
- Delirium – state of acute confusion
- Encephalopathy – brain disease, damage, or malfunction, which can present different symptoms that range from mild, such as memory loss or subtle personality changes, to severe, such as dementia, seizures, or coma.
- General physical health deterioration
- Pulmonary embolism – pulmonary embolism occurs when a clump of material, most often a blood clot, gets wedged into an artery in your lungs.
- Hypoxia – an absence of oxygen supply at the tissue level

14.1.3 Formulation and preparation

The Selinexor drug substance has a molecular formula of C17H11F6N7O and a molecular weight of 443.31. Selinexor is supplied as 20 mg tablets.

14.1.3.1 Chemical Structure of Selinexor



14.1.4 Stability and Storage

Selinexor will be supplied in clear blister strips composed of either: PVC/PE/PCTFE clear film blister with an aluminum foil lidding, or aluminum foil paper lidding . Shipping temperature will be 2-30ºC.

- Do not store Selinexor above 30°C.
- Do not freeze Selinexor.

14.1.5 Administration procedures

Route of administration is oral.

14.1.6 Incompatibilities: None known

14.2 TEMOZOLOMIDE (IND # 144383)

Refer to the package insert for toxicities, formulation and preparation, stability and storage and incompatibility information.

14.2.1 Source

Commercial temozolomide will be purchased by NIH CC Pharmacy.

14.2.2 Administration procedures

Please refer to section **3.2.2** for details.

14.3 RADIATION

14.3.1 Source

The radiation device is an FDA cleared commercial device located in the NIH Clinical Center. The device will be used/investigated in accordance with labeling and therefore will be IDE exempt under 812.2 (c) – category 1.

14.3.2 Toxicity to brain

This list represents the effects of radiation that have been noted for patients to this area of the body. Each person may have different reactions. It is not possible, therefore, to predict any individual's exact side effects.

Reactions can occur during shortly after, or long after the treatment courses and may include, but are not necessarily limited to the following:

DURING OR SHORTLY AFTER TREATMENT COURSE	AFTER TREATMENT COURSE (MONTHS TO YEARS)
COMMON	**COMMON**
Skin redness and irritation in area treated	Scalp discoloration and thickening
Hair loss in area treated, including eyebrows	Mild decrease in memory or ability to think
Tiredness	Permanent thinning or loss of hair in treated area including eyebrows
Worsening of neurologic symptoms present prior to radiation	
UNCOMMON	**UNCOMMON**
Tiredness, headache, weakness, numbness, or other neurologic deficit which may require steroid treatment	Permanent loss (death) of brain cells
	Development of seizures
	Severe memory loss
Nausea, vomiting, weight loss	Cataracts in eyes
Increase in seizure activity if already present	Hearing loss
Dry eyes	Dry eyes
RARE	**RARE**
Decreased blood cell count	Death of brain cells causing swelling in the brain and requiring long term steroid treatment, hospitalization, or/or surgery
Excessive need of sleep	
OTHER	Loss or decrease of vision
	Change in hormone levels from the pituitary
	EXTREMELY RARE
	Development of new tumors in scalp, skull or brain
	Difficulty with control of water balance, thirst, loss of salts from body
	Loss of function specific to the area affected such as: vision, sensation, memory, judgement, motor skills
	Damage to retina causing blindness
	Damage to blood vessels leading to stroke or may be fatal.

14.3.3 Administration Procedures

Refer to section **3.6**.

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16 APPENDICES

16.1 APPENDIX A: 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.

16.2 APPENDIX B: RTOG RADIATION MORBIDITY SCORING CRITERIA

Name _____MR# _____

	BRAIN/CNS	SKIN
Grade 0	No change over baseline	No change over baseline
Grade 1	Fully functional status (i.e., able to work) with minor neurologic findings, no medication needed	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating
Grade 2	Neurologic findings present sufficient to require home case/ nursing assistance may be required/ medications including steroids/anti-seizure agents may be required	Tender or bright erythema, patchy moist desquamation/ moderate edema
Grade 3	Neurologic findings requiring hospitalization for initial management	Confluent, moist desquamation other than skin folds, pitting edema
Grade 4	Serious neurologic impairment which includes paralysis, coma or seizures>3 per week despite medication/hospitalization required	Ulceration, hemorrhage, necrosis

	EYE	EAR
Grade 0	No change over baseline	No change over baseline
Grade 1	Mild conjunctivitis with or without scleral injection/ increased tearing	Mild external otitis with erythema, pruritis, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline
Grade 2	Moderate conjunctivitis with or without keratitis requiring steroids &/or antibiotics/ dry eye requiring artificial tears/ iritis with photophobia	Moderate external otitis requiring topical medication/ serious otitis medius/ hypoacusis on testing only
Grade 3	Severe keratitis with corneal ulceration/ objective decrease in visual acuity or in visual fields/ acute glaucoma/ panopthalmitis	Severe external otitis with dischange or moist desquamation/ symptomatic hypoacusis/tinnitus, not drug related
Grade 4	Loss of vision (unilateral or bilateral)	Deafness

PHYSICIAN _____ DATE _____

16.3 APPENDIX C: RTOG LATE RADIATION MORBIDITY SCORING CRITERIA

Name _____MR# _____

	BRAIN/CNS	SKIN
Grade 0	None	None
Grade 1	Mild headache Slight lethargy	Slight atrophy Pigmentation change Some hair loss
Grade 2	Moderate headache Great lethargy	Patch atrophy; Moderate telangiectasia; Total hair loss
Grade 3	Severe headaches Severe CNS dysfunction (partial loss of power or dyskinesia)	Marked atrophy; Gross telangiectasia
Grade 4	Seizures or paralysis Coma	Ulceration

	EYE
Grade 0	None
Grade 1	Asymptomatic cataract Minor corneal ulceration or keratitis
Grade 2	Symptomatic cataract Moderate corneal ulceration Minor retinopathy or glaucoma
Grade 3	Severe keratitis Severe retinopathy or detachment Severe glaucoma
Grade 4	Panopthalmitis/ Blindness

PHYSICIAN _____ DATE _____

16.4 APPENDIX D: MD ANDERSON SYMPTOM INVENTORY FOR BRAIN TUMORS (MDASI-BT)

Date: _____ Institution: _____

Participant Initials: _____ Hospital Chart #: _____

Participant Number: _____

MD Anderson Symptom Inventory - Brain Tumor (MDASI - BT)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been *in the last 24 hours.* Please select a number from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **speaking (finding the words)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

MDASI-BT - 2006

Date: _____ Institution: _____

Participant Initials: _____ Hospital Chart #: _____

Participant Number: _____

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your **seizures** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty concentrating at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your vision at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in appearance at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in bowel pattern (diarrhea or constipation) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your irritability at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items ***in the last 24 hours***? Please select a number from 0 (symptoms have not interfered) to 10 (symptoms interfered completely) for each item.

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. General activity?	○	○	○	○	○	○	○	○	○	○	○
24. Mood?	○	○	○	○	○	○	○	○	○	○	○
25. Work (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
26. Relations with other people?	○	○	○	○	○	○	○	○	○	○	○
27. Walking?	○	○	○	○	○	○	○	○	○	○	○
28. Enjoyment of life?	○	○	○	○	○	○	○	○	○	○	○

MDASI-BT - 2006

16.5 APPENDIX E: NEURO-QOL ITEM BANK V2.0

Cognition Function– Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely (once)	Sometimes (2-3 times)	Often (once a day)	Very often (several times a day)
NQCOG64r1	I had to read something several times to understand it……..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG75r1	My thinking was slow……	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG77r1	I had to work really hard to pay attention or I would make a mistake…….	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG80r1	I had trouble concentrating…….	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

	How much DIFFICULTY do you currently have…	None	A little	Somewhat	A lot	Cannot do
NQCOG22r1	reading and following complex instructions (e.g., directions for a new medication)?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG24r1	planning for and keeping appointments that are not part of your weekly routine, (e.g., a therapy or doctor appointment, or a social gathering with friends and family)?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG25r1	managing your time to do most of your daily activities?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG40r1	learning new tasks or instructions?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

English
September 8, 2014

Page **1** of **1**

16.6 APPENDIX F: EMOTIONAL DISTRESS -DEPRESSION-SHORT FORM 8A

Emotional Distress – Anxiety – Short Form 8a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX46	I felt nervous	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX07	I felt like I needed help for my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX05	I felt anxious	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX54	I felt tense	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2 June 2016
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Emotional Distress – Depression – Short Form 8a

Please respond to each question or statement by marking one box per row.

	In the past 7 days...	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP22	I felt like a failure	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP36	I felt unhappy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP05	I felt that I had nothing to look forward to	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP09	I felt that nothing could cheer me up	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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16.7 APPENDIX G: PRO-CTCAE

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 19 March 2019

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days…

1.	In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

3.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

4.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

5.	In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

6.	In the last 7 days, did you have any RASH?	
	○ Yes	○ No

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 19 March 2019

7.	In the last 7 days, did you have any HAIR LOSS?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

8.	In the last 7 days, what was the SEVERITY of your SKIN BURNS FROM RADIATION at their WORST?					
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe	○ Not applicable

9.	In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

10.	In the last 7 days, what was the SEVERITY of your BLURRY VISION at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did BLURRY VISION INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

11.	In the last 7 days, what was the SEVERITY of your INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

12.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 19 March 2019

Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

16.8 APPENDIX H: ORAL MEDICATION DIARY FOR SELINEXOR – WEEKLY

Today's Date _____ _____

Patient Name_____ (*initials acceptable for patient's name)*

Patient Study ID _____

Please bring your pill bottle and this form to your physician when you go for your next appointment. ***This is required for study compliance.***

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle (14 days).

2. You will take selinexor tablets on the second day of radiation and by mouth once a week. Please ask your doctor what dose you will be getting and how often you will get it.

3. Record the date, the number of tablets you took, and when you took them.

4. If you have any comments or notice any side effects, please record them in the Comments column.

Date	**Week/Day**	**Selinexor**	**Comments**
	W1 D2		
	W2 D2		
	W3 D2		
	W4 D2		
	W5 D2		

Patient's Signature: _____ Date: _____

Study Team will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study _____
3. Patient's planned daily dose_____
4. Total number of pills taken this month _____

Physician/Nurse Practitioner/Nurse's Signature: _____

16.9 APPENDIX I: ORAL MEDICATION DIARY FOR SELINEXOR – TWICE WEEKLY

Today's Date _____ _____

Patient Name_____ (*initials acceptable for patient's name)*

Patient Study ID _____

Please bring your pill bottle and this form to your physician when you go for your next appointment. ***This is required for study compliance.***

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle (14 days).

2. You will take selinexor tablets on the first and fourth day of radiation. Please ask your doctor what dose you will be getting and how often you will get it.

3. Record the date, the number of tablets you took, and when you took them.

4. If you have any comments or notice any side effects, please record them in the Comments column.

Date	Week/Day	Selinexor	Comments
	W1 D1		
	W1 D4		
	W2 D1		
	W2 D4		
	W3 D1		
	W3 D4		
	W4 D1		
	W4 D4		
	W5 D1		
	W5 D4		
	W6 D1		(only take if you are in the third group of the study)
	W6 D4		(only take if you are in the third group of the study)

Patient's Signature: _____ Date: _____

Study Team will complete this section:

5. Date patient started protocol treatment_____
6. Date patient was removed from study _____
7. Patient's planned daily dose_____
8. Total number of pills taken this month _____

Physician/Nurse Practitioner/Nurse's Signature: _____