A Phase 2 Study on Efficacy, Safety and Intratumoral Pharmacokinetics of Oral Selinexor (KPT-330) in Patients with Recurrent Glioblastoma (GBM)

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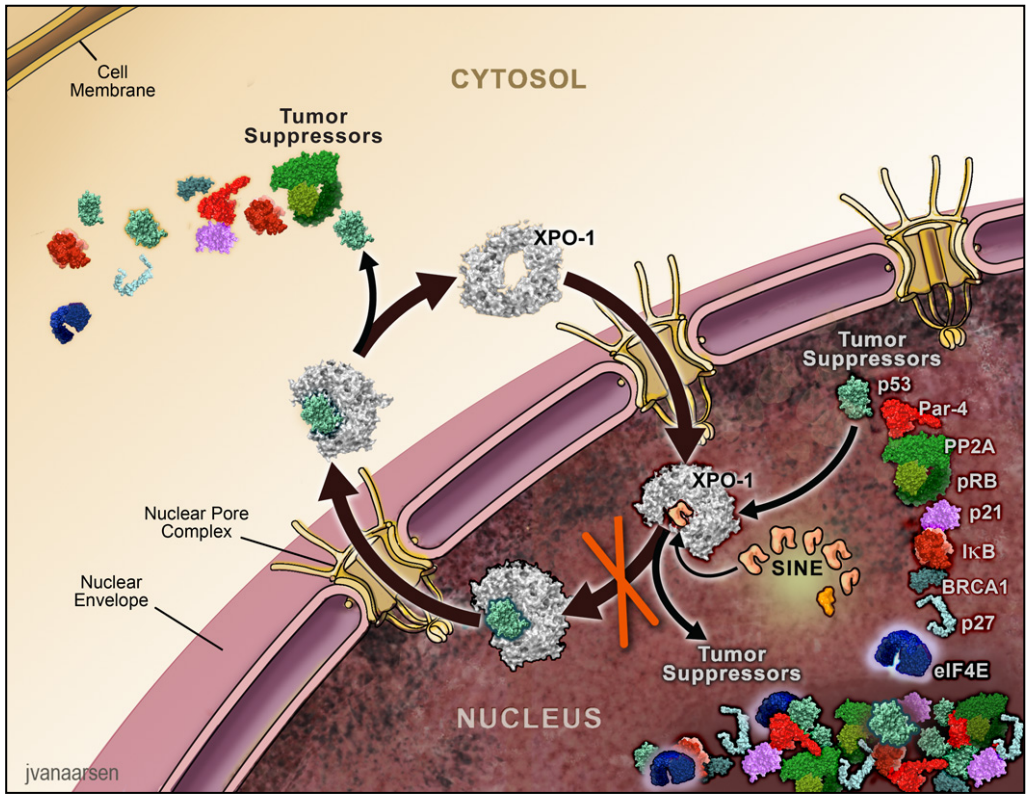
Karyopharm™ Therapeutics

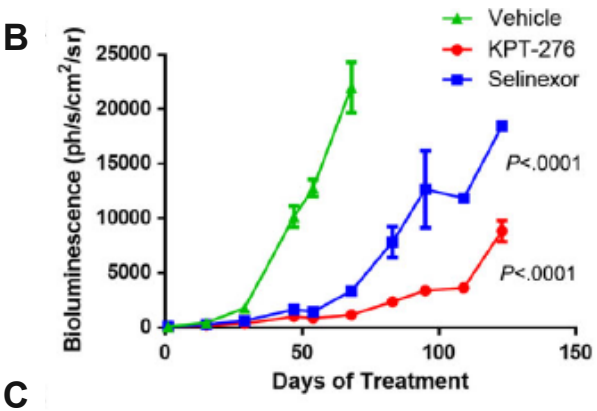


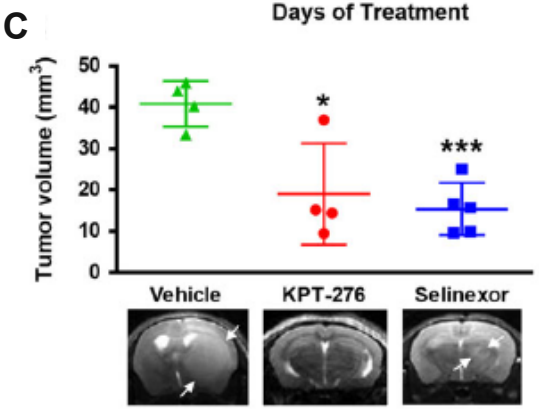
- **Exportin 1 (XPO1) is a target for glioma**
  - XPO1 overexpression in glioma correlates with higher grade and decreased overall survival
  - XPO1 is the sole nuclear exporter of the tumor suppressor proteins p53 and p27 which often drive glioblastoma tumorigenesis
- **Selinexor Inhibits XPO1**
  - Selinexor (KPT-330) is a potent, covalent, slowly-reversible, Selective Inhibitor of Nuclear Export (SINE) that inhibits XPO1
  - Selinexor forces nuclear retention and activation of p53 and p27, leading to glioblastoma apoptosis

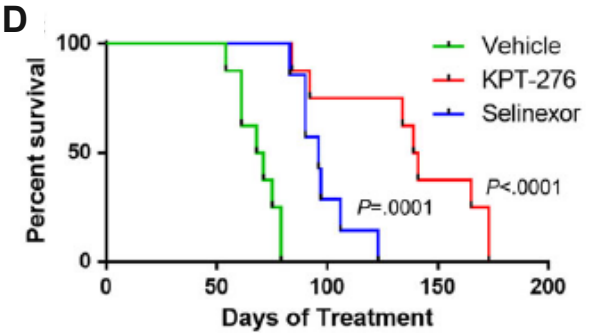
In vitro and in vivo models of patient-derived GBM

A

Selinexor in vitro cytotoxic potency in patient-derived GBM cells	
Cell Line	**IC_{50} (μM)**
BT 145	0.075
BT 159	0.148
BT 172	0.320
AGBM1	0.173
BT 245	0.114
DIPG 4	0.097
DIPG 6	0.006
Average	**0.133**







(A) Selinexor cytotoxic potency in patient-derived GBM cells grown in neurosphere culture. Average IC_{50} of 133 nM is comparable to selinexor conc. in tumors of ARM A patients at 2 hr (122 nM). **(B)-(D)** Brain orthotopic GBM patient-derived xenograft (PDX) model with BT-145 cells treated with vehicle, selinexor (20 mg/kg 3X wkly QOD) or KPT-276, a close analog of selinexor (50 mg/kg 3X wkly QOD). **(B)** Tumor growth over time based on bioluminescence. After 61 days (the last day of vehicle arm measurement), selinexor and KPT-276 induced 84% and 88% tumor growth inhibition, respectively. **(C)** Tumor volumes after 61 days with representative T2 MRIs (*p<0.05; ***p>0.001). **(D)** Kaplan–Meier curve showing increased survival with selinexor and KPT-276 of 100% and 149%, respectively.

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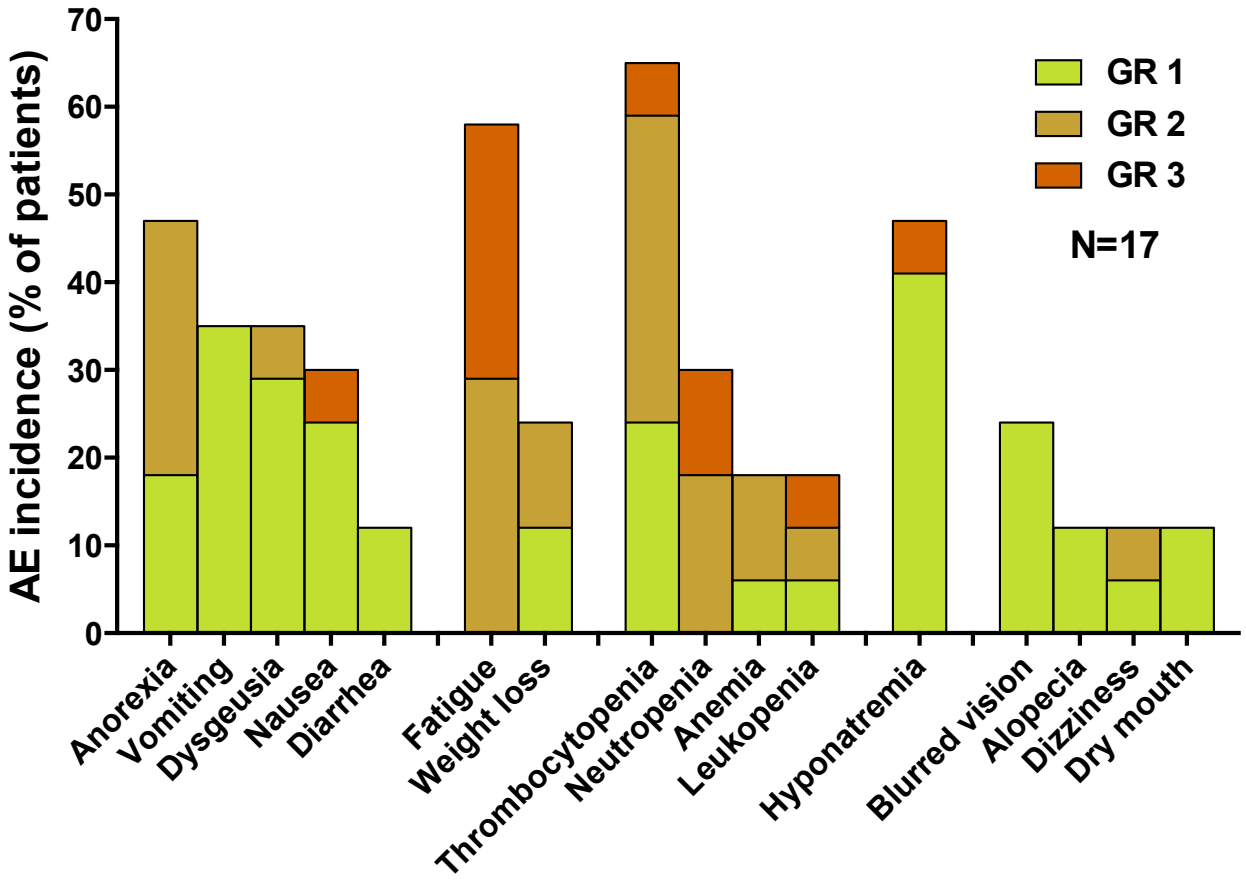
KING Phase II Study Design – NCT01986348

- **K**PT-330 **IN** patients with recurrent **G**lioblastomas (**KING**) is an open label Phase II study in patients with recurrent gliomas after failure of radiation and temozolomide
  - **ARM A** – Surgical Arm for patients who require cytoreductive surgery: ~20 patients
  - **ARM B** – Medical Arm for patients not eligible for surgery: ~30 patients
- **Main Inclusion Criteria**:
  - Patients ≥18 years must have received treatment with prior radiation and temozolomide
  - Measurable disease according to RANO guidelines, Karnofsky Perfomance Status ≥60
  - Prior bevacizumab was not allowed
- **Primary Objective ARM B**
  - Determine efficacy of selinexor based upon fraction of patients to achieve 6 months PFS
- **Exploratory Objective ARM A**:
  - Determine tumor concentration of selinexor and molecular effects during treatment
  - Evaluate efficacy of selinexor for patients undergoing cytoreductive surgery
- **Treatment Scheme**: ARM A & ARM B
  - **ARM A** – Patients received 2 doses of 50 mg/m^2 selinexor QOD prior to surgery. On the day of surgery, a 3rd dose was administered ~2 prior to surgery. Patient samples were collected for pharmacokinetic analysis pre-dose, 1 hr and 2 hr post dose and during resection of tumor. After recovery from surgery patients resumed selinexor dosing twice weekly for the first 3 wks of a 4 week cycle.
  - **ARM B** – Patients receive selinexor 50 mg/m^2 twice weekly per 4 week cycle (8 doses per cycle)

Patient Characteristics

ARM A (N=7)	
Median Age (Range)	59 (43 – 61)
Male to Female	6 Males : 1 Female
Median Prior Treatment Regimens (Range)	1 (1 – 2)

ARM B (N=17)	
Median Age (Range)	57 (43 – 61)
Male to Female	12 Males : 5 Females
Median Prior Treatment Regimens (Range)	1 (1 – 2)



ARM B: All patients (N=17) were evaluable for safety. The adverse event profile is comparable to that seen in solid and hematological tumor patients studied in Phase 1 trials. Approximately half of the patients (N=8) required dose reductions to 35 mg/m^2 primarily due to fatigue. To improve tolerability, all ongoing and newly enrolled patients will move to a 60 mg (~35 mg/m^2) flat dose twice weekly or 80 mg (~50 mg/m^2) flat dose once weekly.

Selinexor penetrates GBM tumors

A

[selinexor] (nM)				
Patient	**Tumor (~2 h)**	**Plasma (1 h)**	**Plasma (2 h)**	**Tumor/Plasma**
001007	142	2071	1620	0.08
001008	69	1033	722	0.08
001009	40	311	645	0.08
001010	291	NA	1529	0.19
001015	64	986	835	0.07
301002	211	593	562	0.37
301020*	39	19	859	0.09
Average	**122**	**836**	**967**	**0.14**

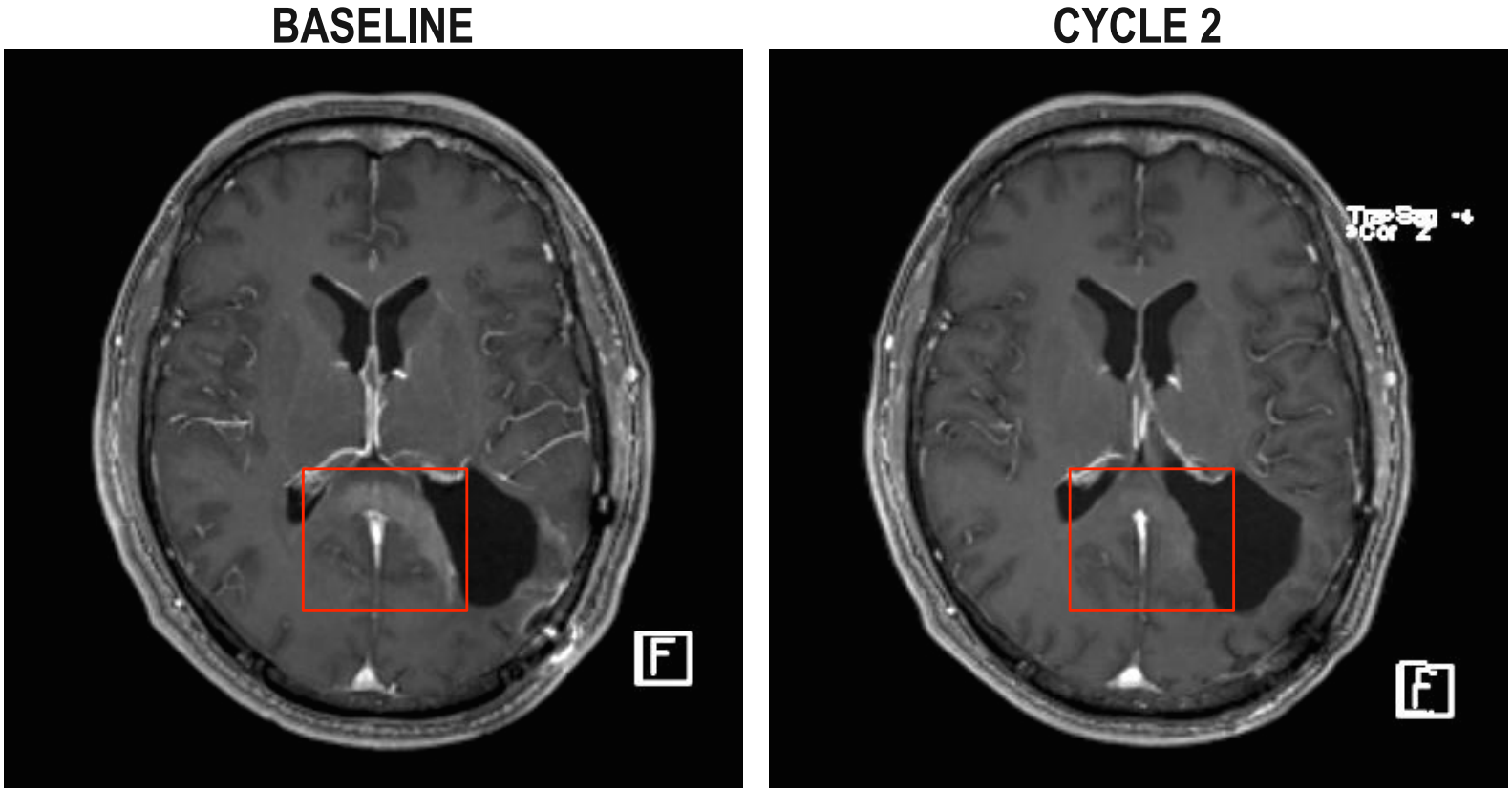
*tumor specimen was collected ~6 hours after selinexor administration

(A) Selinexor tumor and plasma concentrations in GBM tumors from patients in **ARM A.** Lower GBM tumor/plasma compared to brain/plasma ratios in animals may be due to later T_{max} in patients (~4 hours). GBM tumors have comparable selinexor plasma concentrations at 2 hours to that of other cancer patients. Average selinexor concentration of 122 nM in GBM tumors is equivalent to the average in vitro selinexor IC_{50} of 114 nM in patient-derived GBM cells (see bottom of first panel).

B

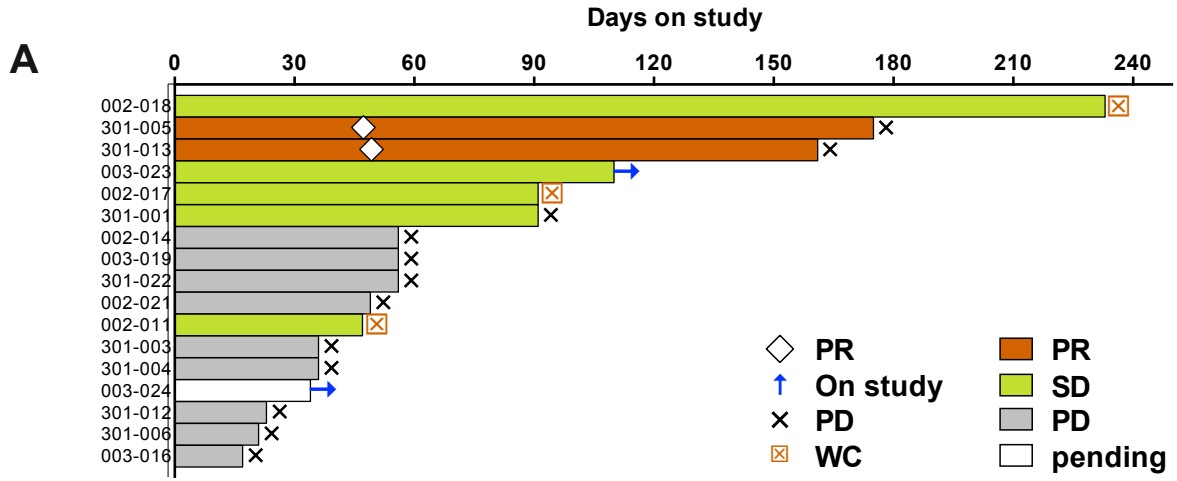
Species	[selinexor] - 2 h (nM)		Brain/ Plasma	Plasma T_{max} (h)
	Plasma (nM)	Brain (nM)		
Mouse	3970	2920	0.71	0.5-1
Rat	3770	2730	0.72	0.5-1
Monkey	5750	3530	0.60	1-3

(B) Brain availability in mice, rats and monkeys. Selinexor was also found to have brain penetration in animal models. Plasma and brain concentration are shown 2 hours post administration of 10 mg/kg selinexor.

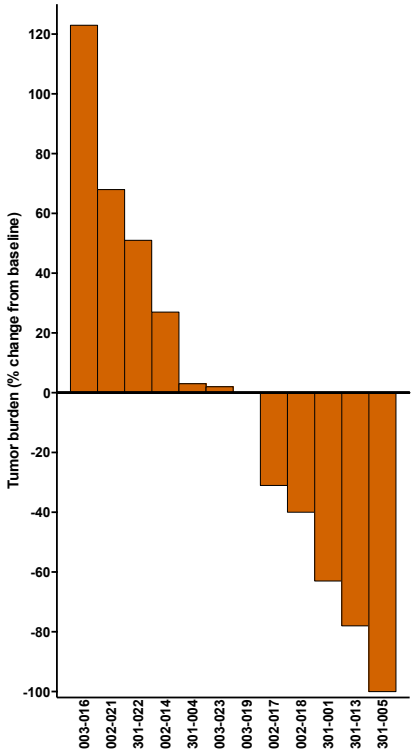


MRI brain scans of patient 301-005 from ARM B. 45-year old male diagnosed with stage IV glioblastoma multiform in July 2013. Selinexor was preceded by separate regimens of temozolomide, radiation, and surgery. Selinexor monotherapy began in April 2014, leading to a partial response in Cycle 2 with a 100% reduction in tumor burden (non-target lesions still present). This patient remained on study 175 days before progressing.

ARM B: Efficacy and Patient Duration of Study



PR=partial response, SD=stable disease, PD=progressive disease, WC=withdrew consent



C

Best Responses* (ARM B)				
N	PR	SD	PD	DCR
16	2 (13%)	4 (25%)	10 (62%)	6 (38%)

* Responses were allocated by Investigators according to Response Assessment in Neuro-Oncology (RANO) lab based on interim unaudited data and and will be independently verified by a central lab. DCR=disease control rate (PR+SD).

Selinexor shows evidence of efficacy in GBM (as of 10-May-2015). ARM B patients were evaluable for efficacy. **(A)** Swimmer plot depicting time to response, time on study and reasons for going off study. **(B)** Waterfall plot for patients with quantified tumor burden. PD designation not shown was based on clinical symptoms. **(C)** Best responses and disease control rate (DCR) in ARM B patients.

Summary & Conclusions

- Selinexor is highly active against patient-derived GBM cells in culture, while sparing normal neuronal and glial cells
- Oral selinexor is active in brain orthotopic xenografts
- Selinexor reaches concentrations in GBM tumors that are active in vitro against patient-derived GBM cells
- The most common selinexor-related AEs are thrombocytopenia, fatigue, anorexia, and hyponatremia
- Due to high incidence of dose reduction due to Grade 2/3 fatigue, the trial will be amended with two arms with reduced doses
  - ARM C: 60 mg flat dose of selinexor, twice weekly
  - ARM D: 80 mg flat dose of selinexor, once weekly
- One patient in twelve evaluable patients on ARM B has reached 6 months PFS endpoint
- Selinexor shows anti-tumor activity with 13% ORR and 38% DCR in patients with pretreated (temozolomide and radiation) GBM