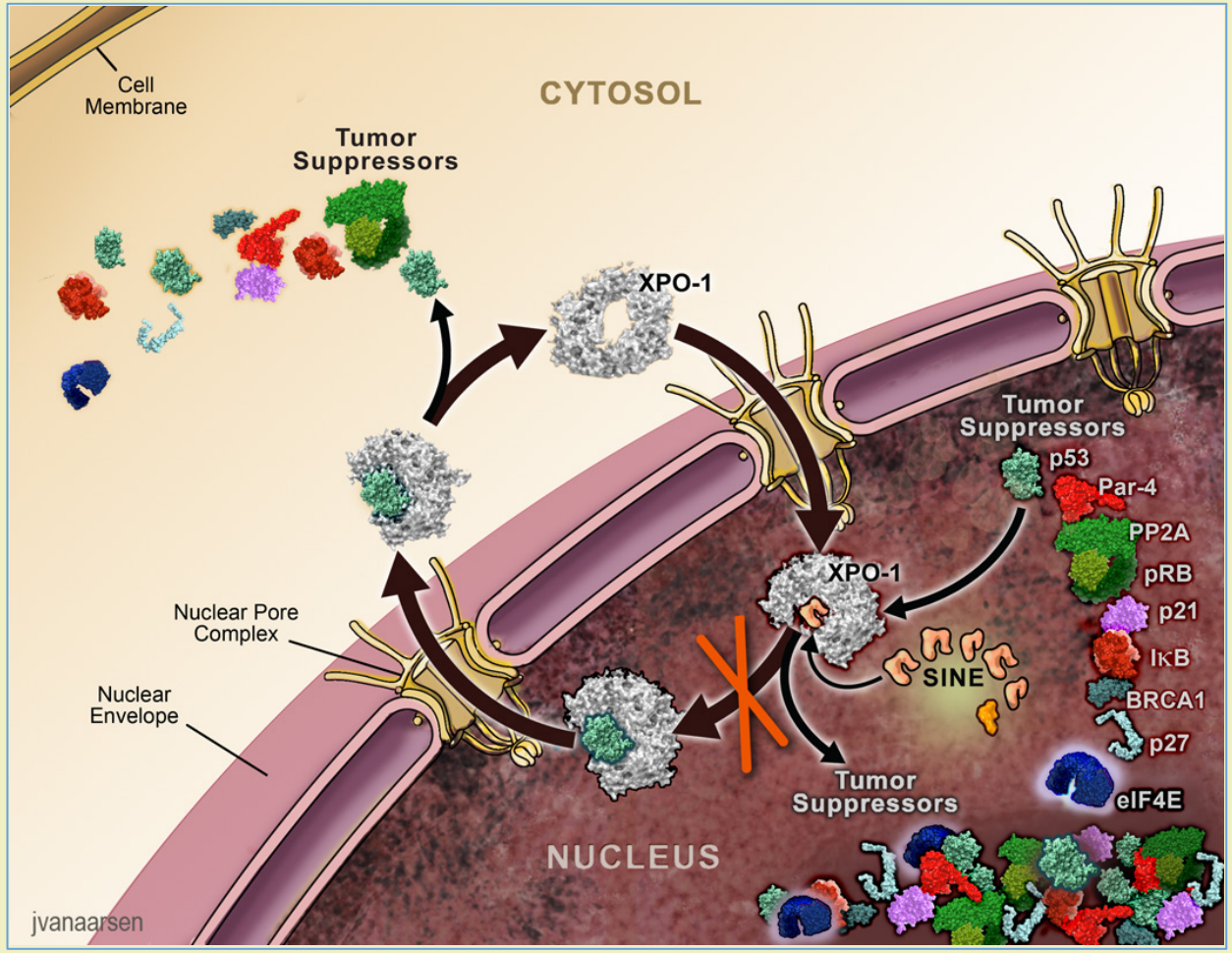
A Phase II Study on Efficacy, Safety and Intratumoral Pharmacokinetics of Oral Selinexor (KPT-330) in Patients with Recurrent Glioblastoma (GBM)

Morten Mau-Sorensen[1], Scott Plotkin[2], Patrick Wen[3], Andrew L. Kung[6], Ulrik Lasssen[1], Jean-Richard Saint-Martin[5], Greg Wright[5], Aleksander Chudnovsky[5], Joel Ellis[5], Sharon Friedlander[5], Bert van Eijk[5], Sharon Shacham[5], Michael Kauffman[5], Andrew B. Lassman[4]

(1) Rigshospitalet, Copenhagen, Denmark (2) Massachusetts General Hospital, Boston, MA (3) Dana Farber Cancer Institute, Boston, MA (4) Department of Neurology and Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, New York (5) Karyopharm Therapeutics, Newton, Massachusetts (6) Department of Pediatrics, Columbia University Medical Center, New York, New York

XPO1, Selinexor, and Glioblastoma



- **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, oral, covalent, slowly-reversible, Selective Inhibitor of Nuclear Export (SINE) compound that inhibits XPO1
  - Selinexor forces nuclear retention and activation of p53 and p27, leading to glioblastoma apoptosis

KING Phase II Study Design

- **K**PT-330 **IN** patients with recurrent **G**liomas (**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 salvage surgery: ~20 patients
  - **ARM B** – Medical Arm for patients not eligible for surgery: ~30 patients (enrollment has stopped for ARM B to potentially improve tolerability as well as explore alternative dosing in ARMs C, D), ARM B has met the previous Simon two stage endpoint of ≥2, 6mPFS response in the first 12 patients, which allowed the study to continue
  - **ARMs C, D** – Medical Arm for patients not eligible for surgery: ~60 patients (Simon Two-Stage Design)
  - **ARMs C, D Simon Two-Stage Design** – 12 patients will be accrued to each arm. If there is ≤1, 6mPFS response in the first 12 patients per arm, no further enrollment will be allowed in that Arm
- **Primary Objective ARMs B, C, D**
  - Determine the efficacy of selinexor in recurrent GBM as determined by the 6-month (±14 days) progression-free survival rate
- **Exploratory Objective ARM A**:
  - Determine tumor concentration of selinexor and molecular effects during treatment
- **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
- **Treatment Scheme: ARMs A, B, C, D**
  - **ARM A** – Patients receive 2 doses of 50 mg/m^2 (~80–90 mg) selinexor prior to surgery. On the day of surgery, a 3rd dose is administered ~2h prior to surgery. Patient samples are collected for pharmacokinetic analysis pre-dose, 1 hr and 2 hr post dose and during resection of tumor. After recovery from surgery patients resume selinexor dosing twice weekly for the first 3 weeks of a 4 week cycle.
  - **ARM B** – Patients receive selinexor 50 mg/m^2 (~80–90 mg) twice weekly per 4 week cycle (8 doses / cycle)
  - **ARM C** – Patients receive selinexor 60 mg twice weekly per 4 week cycle (8 doses / cycle)
  - **ARM D** – Patients receive selinexor 80 mg once weekly per 4 week cycle (4 doses / cycle)

KING Patient Characteristics

Characteristic	ARM A (N=7)	ARM B (N=24)	ARM C (N=5)	ARM D (N=8)
Median Age (Range)	59 (43 – 61)	51 (29 – 69)	49 (27 – 61)	57 (42 – 64)
Male to Female	6 Males : 1 Female	19 Males : 5 Females	2 Males : 3 Females	5 Males : 3 Females
Median Prior Treatment Regimens (Range)	1 (1 – 2)	2 (1 – 3)	2 (1 – 3)	3 (1 – 3)

KING Patient Pharmacokinetics

[selinexor] (nM)				
Patient	**Tumor (~2 h)**	**Plasma (1 h)**	**Plasma (2 h)**	**Tumor/Plasma**
001-007	142	2071	1620	0.08
001-008	69	1033	722	0.08
001-009	40	311	645	0.08
001-010	291	NA	1529	0.19
001-015	64	986	835	0.07
301-002	211	593	562	0.37
301-020*	39	19	859	0.09
Average	**122**	**836**	**967**	**0.14**

Patient Pharmacokinetics: Selinexor tumor and plasma concentrations in GBM tumors from patients in **ARM A.** Average selinexor concentration of 122 nM in GBM tumors is equivalent to the average in vitro selinexor IC_{50} of 133 nM in patient-derived GBM cells. *(Green et al. Neuro-Oncology 2014)*

Related Adverse Events ARMs B, C, D

AE Term	ARM B – 50 mg/m^2 (~80–90 mg fixed dose) *Twice* Weekly Dosing (N=24)					ARM C – 60 mg (fixed dose) *Twice* Weekly Dosing (N=5)				ARM D – 80 mg (fixed dose) *Once* Weekly Dosing (N=8)			
Gastrointestinal	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**	**Grade 1**	**Grade 2**	**Grade 3**	**Total**	**Grade 1**	**Grade 2**	**Grade 3**	**Total**
Anorexia	5 (20.8%)	6 (25.0%)	--	--	**11 (45.8%)**	1 (20.0%)	1 (20.0%)	--	**2 (40.0%)**	2 (25.0%)	--	--	**2 (25.0%)**
Nausea	7 (29.2%)	2 (8.3%)	1 (4.2%)	--	**10 (41.7%)**	2 (40.0%)	--	--	**2 (40.0%)**	3 (37.5%)	2 (25.0%)	--	**5 (62.5%)**
Vomiting	7 (29.2%)	--	--	--	**7 (29.2%)**	3 (60.0%)	--	--	**3 (60.0%)**	--	1 (12.5%)	--	**1 (12.5%)**
Dysgeusia	6 (25.0%)	1 (4.2%)	--	--	**7 (29.2%)**	1 (20.0%)	--	--	**1 (20.0%)**	1 (12.5%)	1 (12.5%)	--	**2 (25.0%)**
Diarrhea	2 (8.3%)	1 (4.2%)	--	--	**3 (12.5%)**	--	--	--	**--**	1 (12.5%)	--	--	**1 (12.5%)**
Constitutional													
Fatigue	6 (25.0%)	5 (20.8%)	5 (20.8%)	--	**16 (66.7%)**	1 (20.0%)	1 (20.0%)	1 (20.0%)	**3 (60.0%)**	2 (25.0%)	1 (12.5%)	--	**3 (37.5%)**
Weight loss	2 (8.3%)	2 (8.3%)	--	--	**4 (16.7%)**	1 (20.0%)	--	--	**1 (20.0%)**	--	--	--	**--**
Metabolic													
Hyponatremia	9 (37.5%)	--	1 (4.2%)	--	**10 (41.7%)**	--	--	--	**--**	--	--	--	**--**
Hypophosphatemia	--	1 (4.2%)	2 (8.3%)	1 (4.2%)	**4 (16.7%)**	--	--	--	**--**	--	--	--	**--**
Blood													
Thrombocytopenia	8 (33.3%)	6 (25.0%)	2 (8.3%)	--	**16 (66.7%)**	--	1 (20.0%)	--	**1 (20.0%)**	--	1 (12.5%)	--	**1 (12.5%)**
Neutropenia	--	5 (20.8%)	2 (8.3%)	--	**7 (29.2%)**	--	--	1 (20.0%)	**1 (20.0%)**	1 (12.5%)	--	1 (12.5%)	**2 (25.0%)**
Anemia	4 (16.7%)	2 (8.3%)	--	--	**6 (25.0%)**	1 (20.0%)	--		**1 (20.0%)**	--	1 (12.5%)	--	**1 (12.5%)**
Leukopenia	1 (4.2%)	4 (16.7%)	--	--	**5 (20.8%)**	--	--	1 (20.0%)	**1 (20.0%)**	--	2 (25.0%)	--	**2 (25.0%)**
Other													
Blurred vision	5 (20.8%)	1 (4.2%)	--	--	**6 (25.0%)**	1 (20.0%)	--	--	**1 (20.0%)**	--	1 (12.5%)	--	**1 (12.5%)**

Adverse Events ARMs B, C, D: All patients (N=37) were evaluable for safety. The adverse event profile is comparable to that seen in patients with other solid tumors in Phase 1 trials. The most common adverse events across all Arms B, C, D include: anorexia, nausea, fatigue, and thrombocytopenia. Several patients on Arm B had dose reductions due to fatigue. Therefore, to improve tolerability, Arms C and D were added. Fatigue rates are lower in Arm D, and other common side effects were markedly reduced in both Arms C & D.

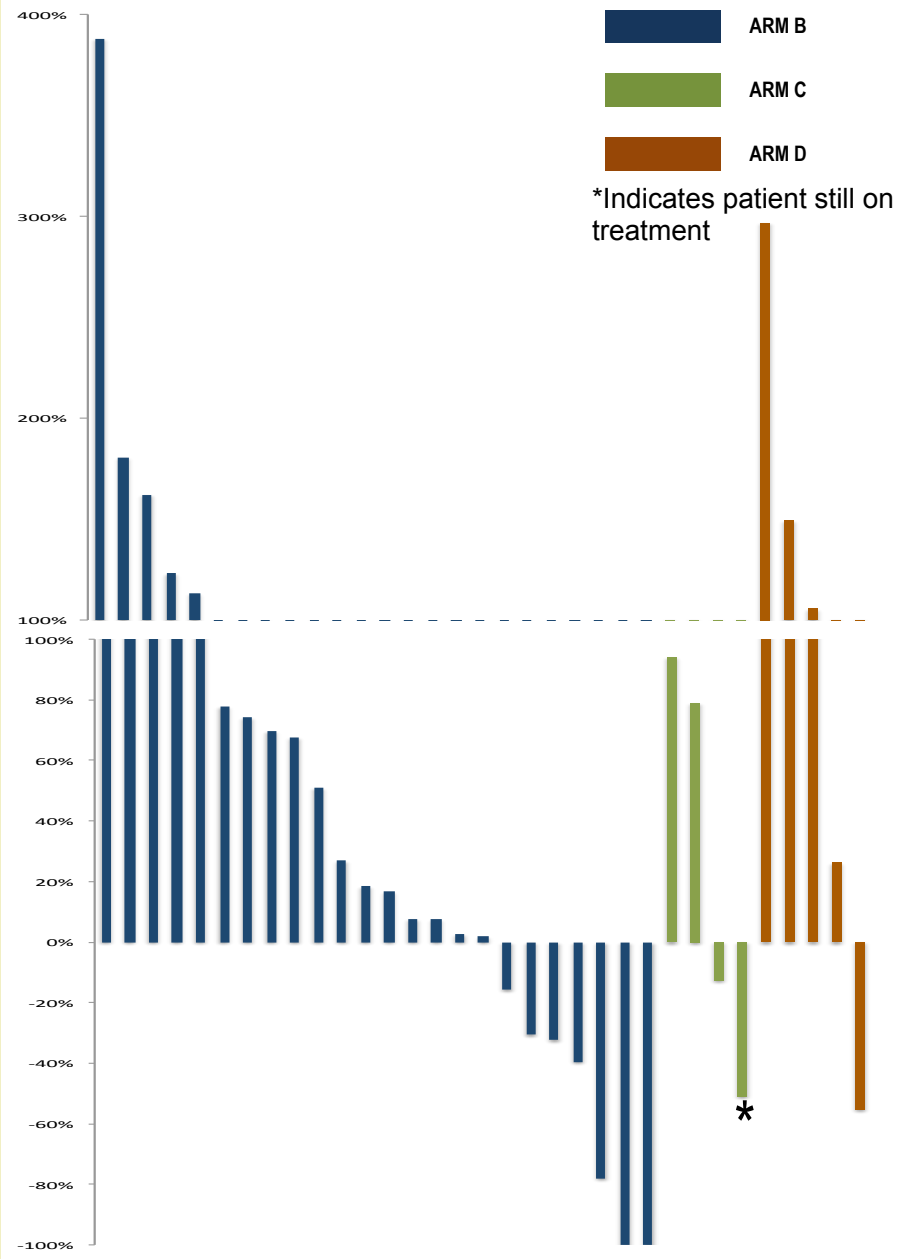
Efficacy: ARMs B, C, D

Best Responses* Arms B, C, D as of 23-May-2016						
Treatment Arm	**N**	**PR (%)**	**SD (%)**	**SD >3 Months (%)**	**PD (%)**	**DCR (%)**
ARM B[1]	24	2 (8%)	6 (25%)	4 (17%)	16 (67%)	8 (33%)
ARM C	4	1 (25%)	1 (25%)	--	2 (50%)	2 (50%)
ARM D	5	1 (20%)	--	--	4 (80%)	1 (20%)
All ARMs	**33**	**4 (12%)**	**7 (21%)**	**4 (12%)**	**22 (67%)**	**11 (33%)**

*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. PR=partial response, SD=stable disease, PD=progressive disease, DCR=disease control rate (PR+SD) One patient in ARM C and 3 patients in ARM D were not as of yet evaluable for response

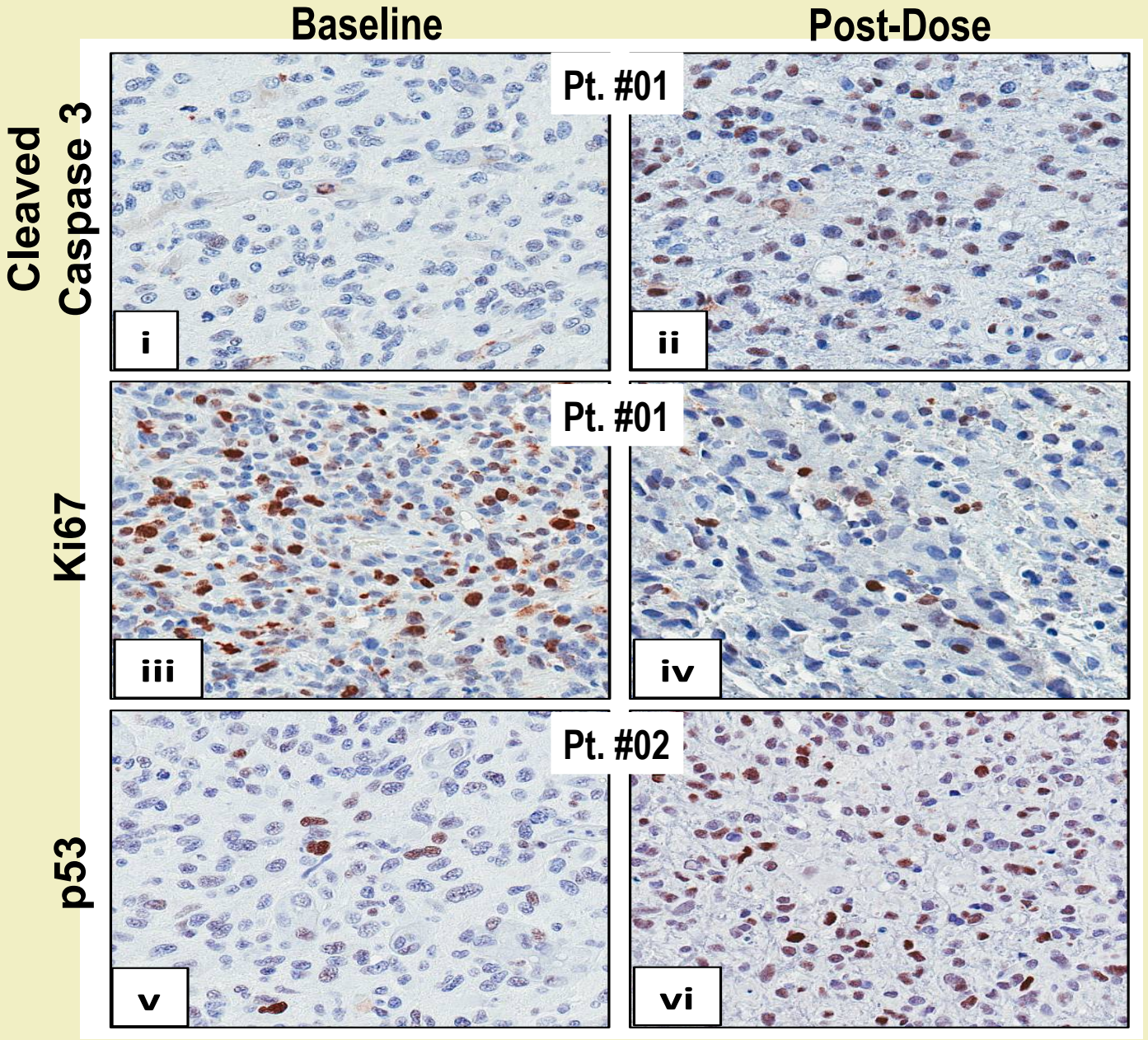
Selinexor shows anti-tumor activity in GBM. ARMs B, C, and D patients were evaluable for efficacy. Best responses as of 23-May-2016 and disease control rate (DCR) for patients in ARMs B, C, and D. [1]Two patients in ARM B have met the 6 month progression free survival endpoint.

Efficacy: ARMs B, C, D



Selinexor shows anti-tumor activity in GBM. ARMs B, C, and D patients were evaluable for efficacy. Waterfall plot for patients with quantified tumor burden

KING Patients Translational Research



Biopsies from patients on ARM A obtained before and 8 days after selinexor treatment initiation were subjected to comparative Immunohistochemical analysis for the apoptosis marker cleaved caspase 3 (i, ii), the proliferation marker Ki67 (iii, iv), and the tumor suppressor protein p53 (v, vi).

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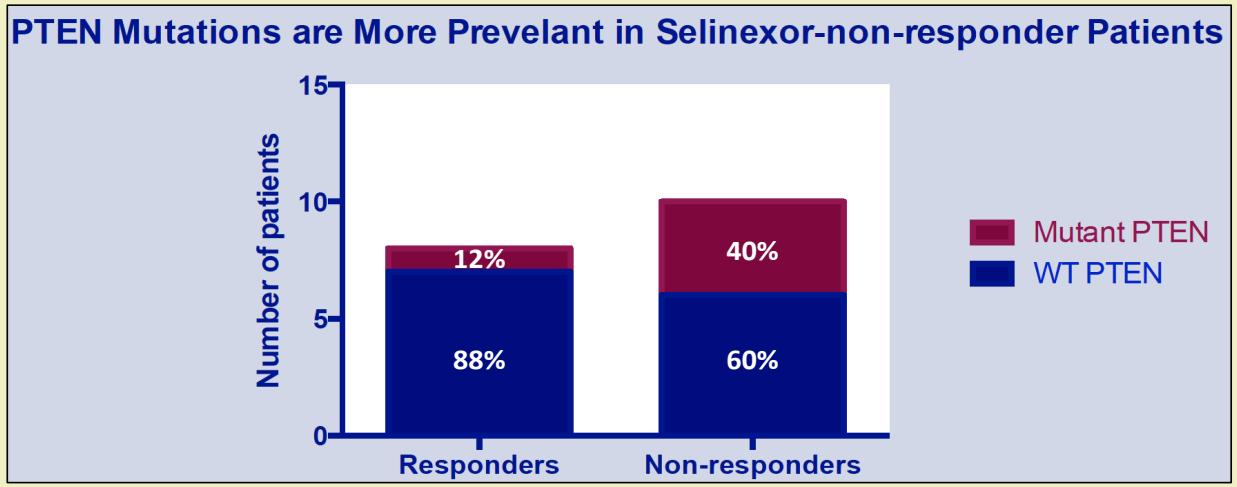
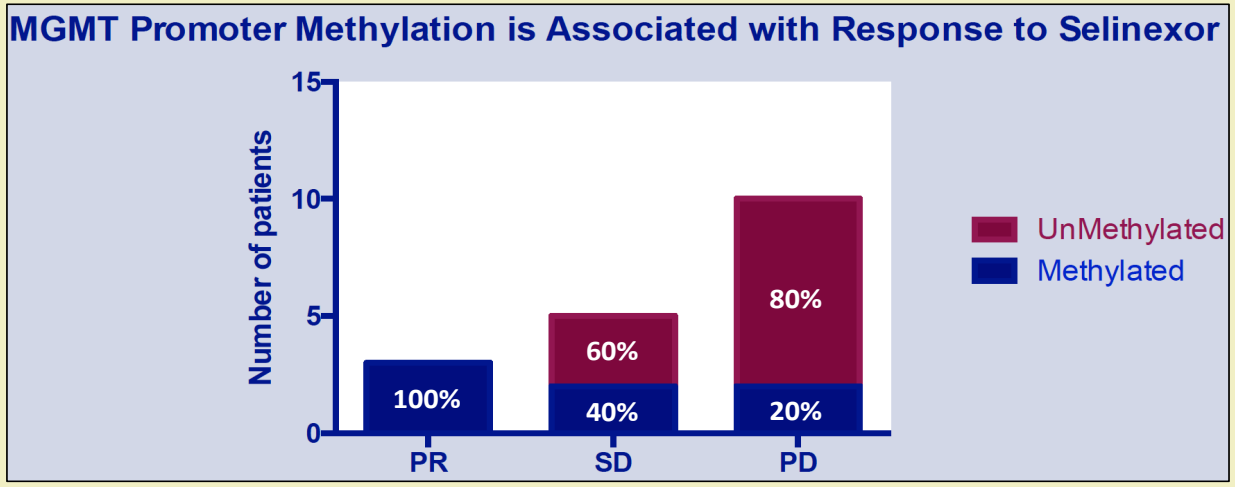
A



B



(A) Biopsy samples from patients who have not progressed and patients who have progressed were subjected to next generation sequencing using the Columbia Combined Cancer Panel (CCCP) of 467 unique genes. Mutations in the tumor suppressor gene PTEN were unequally distributed among responder and non-responder patients suggesting a potential predictive value for this gene. **(B)** Pre-treated biopsy samples from patients were subjected to Methylguanine-DNA Methyltransferase (MGMT) promoter methylation detection by real-time PCR. MGMT promoter methylation appears to be associated with PR or SD.

Conclusions

- Selinexor reaches anti-tumor concentrations in GBM tissues from patients
- The most common AEs related to oral selinexor are thrombocytopenia, fatigue, anorexia, and nausea
- Because of dose reductions due to Grade 2/3 fatigue in ARM B (~80–90mg twice weekly), the trial was amended to include ARMs C (60mg twice weekly) and D (80mg once weekly). AEs were lower with improved tolerability in ARMS C & D.
- Two patients in ARM B have met the 6 month progression free survival endpoint
- Single agent selinexor shows anti-tumor activity with 12% ORR (PRs) and 33% DCR (PR + SD) in patients with relapsed or refractory (after temozolomide and radiation) GBM