Karyopharm Therapeutics

The Enhancement of Anti-Tumor Activities of Selinexor when Combined with Immune Checkpoint Inhibitors

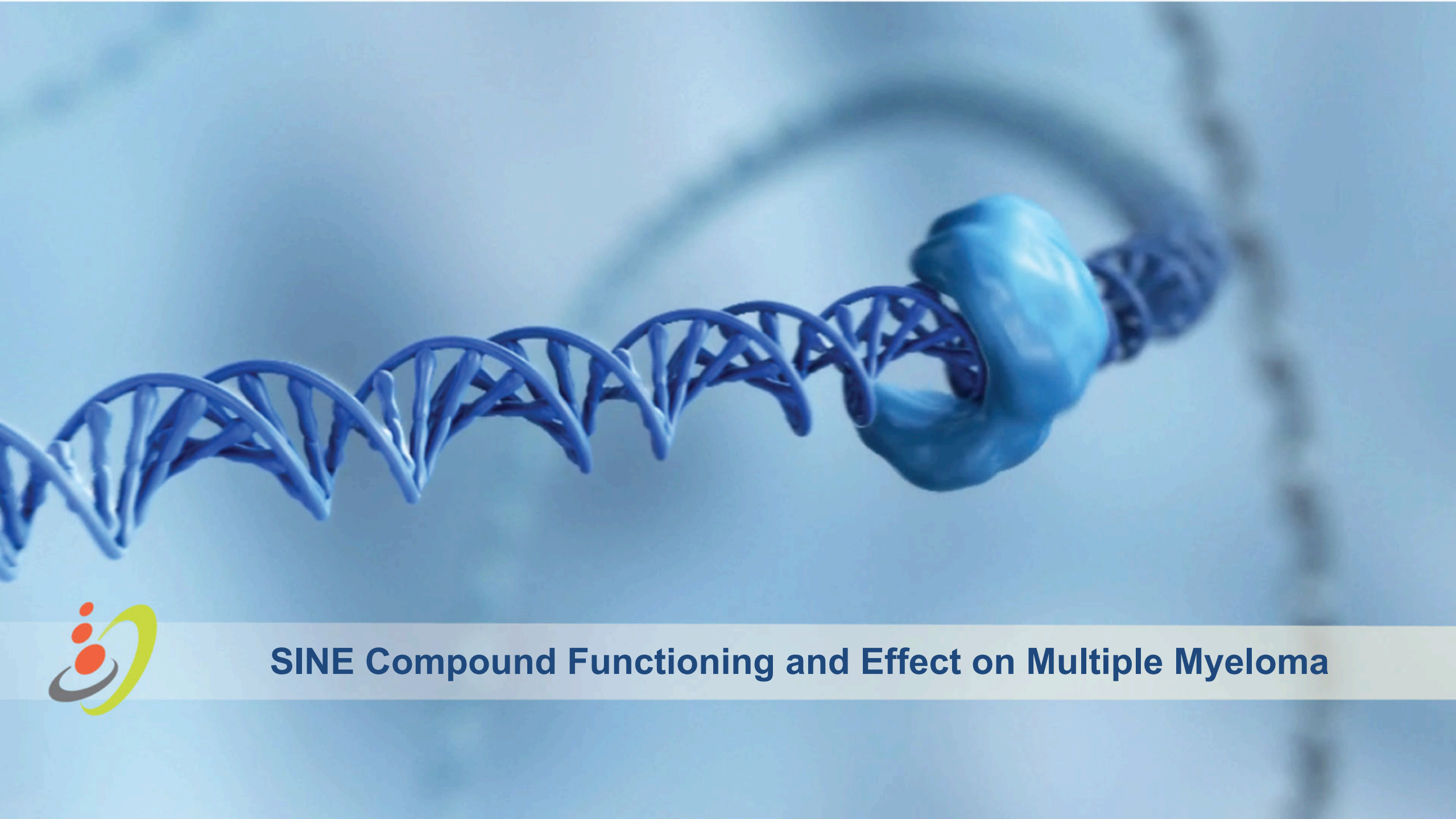
Trinayan Kashyap, Karyopharm Therapeutics

Yu-Tzu Tai and Kenneth Anderson, Dana Farber Boston

Matthew Farren and Gregory Lesinski, Emory University, Atlanta, GA

Paul Tyler, Mariah Servos, Michael Dougan and Stephanie Dougan,
Dana Farber and Mass General Hospital, Boston

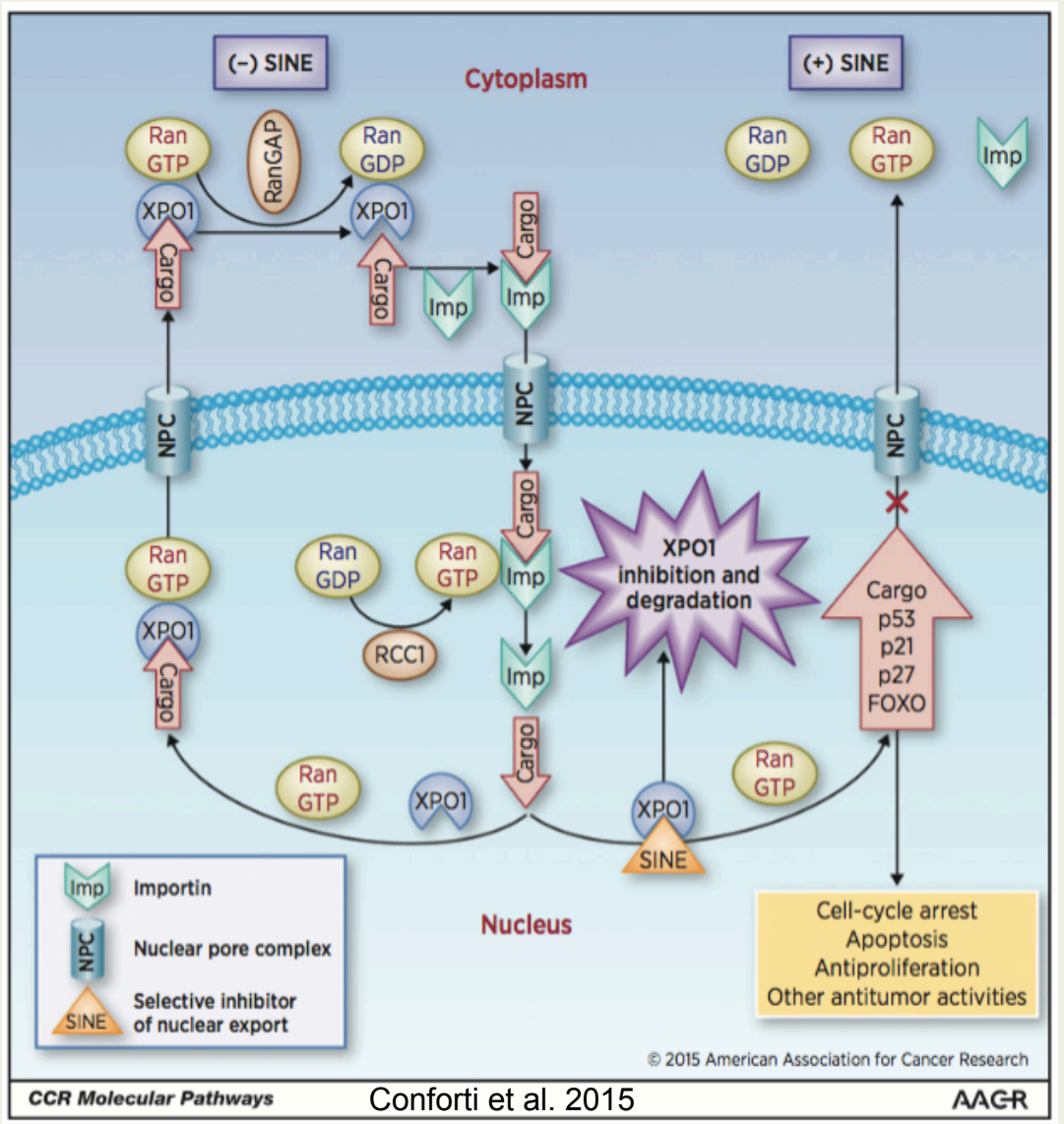
Targeting Disease at the Nuclear Pore



SINE Compound Functioning and Effect on Multiple Myeloma

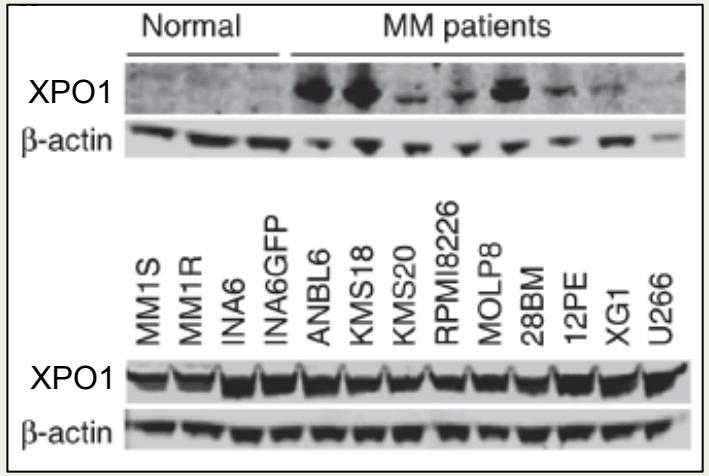
Nucleocytoplasmic Shuttling & XPO1 Inhibition by SINE Compounds

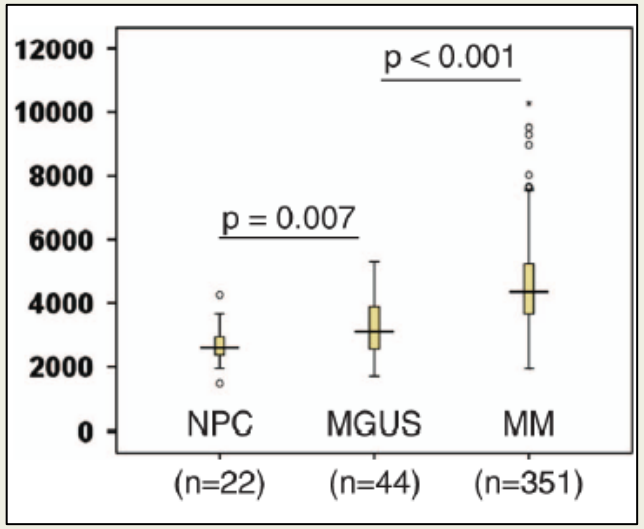
- Movement of large (>40kD) proteins between the cytoplasm and the nucleus through the nuclear pore complex is dependent on importin and exportin transport proteins as well as on energy from Ran GTP.
- SINE™ compounds such as selinexor covalently bind XPO1 and inhibit it's nuclear export function
- Inhibition of XPO1 leads to nuclear accumulation of XPO1 cargo proteins such as the tumor suppressor proteins (TSPs) p53, pRb, APC, p21, p27, IκB and FOXOs.
- Inhibition of XPO1 also blocks the transport of Eukaryotic Translation Initiation Factor eIF4E, a carrier of several oncoprotein mRNAs such as c-Myc, cyclins and Pim1, thereby limiting oncoprotein translation in the cytoplasm.
- Accumulation of TSPs in the nucleus and the inhibition of oncoprotein translation leads to cell-cycle arrest and cell death.

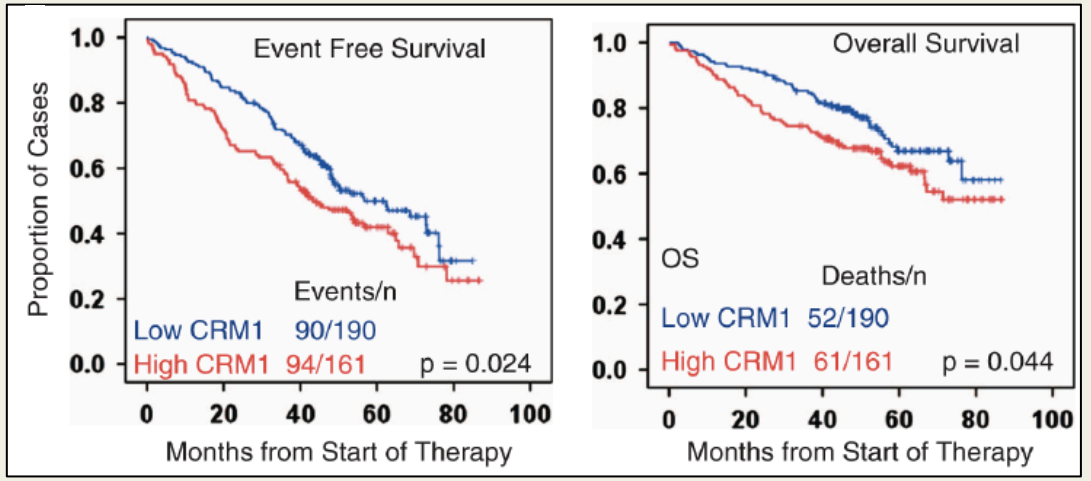


Conforti et al. 2015

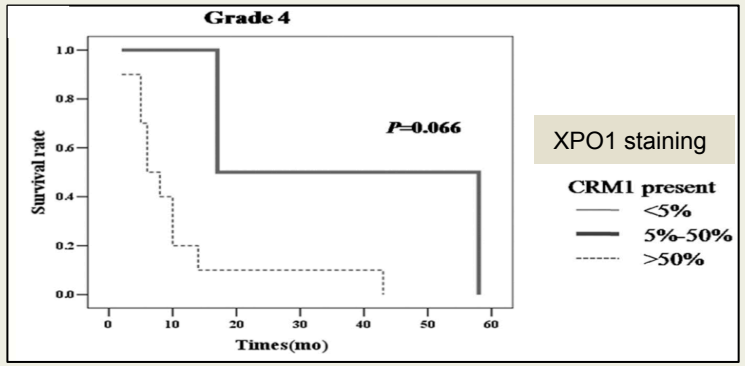
XPO1 Is Overexpressed in Cancer and is Correlated with Disease Stage or Poor Prognosis



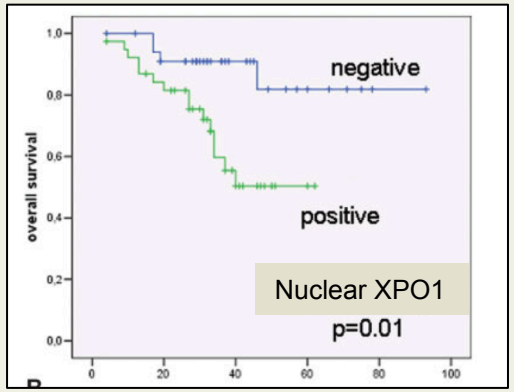




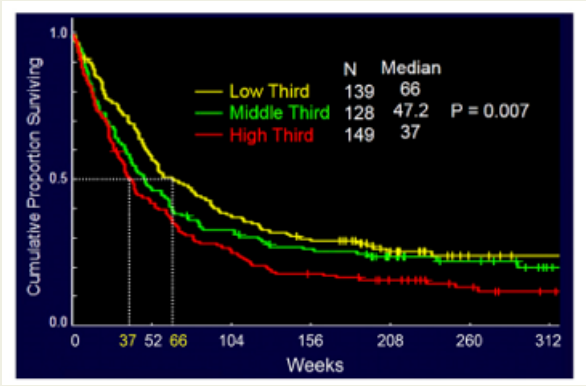
Multiple myeloma (**Tai et al 2013**)



Glioblastoma
(**Shen 2009**)



Ovarian
(**Noske 2008**)

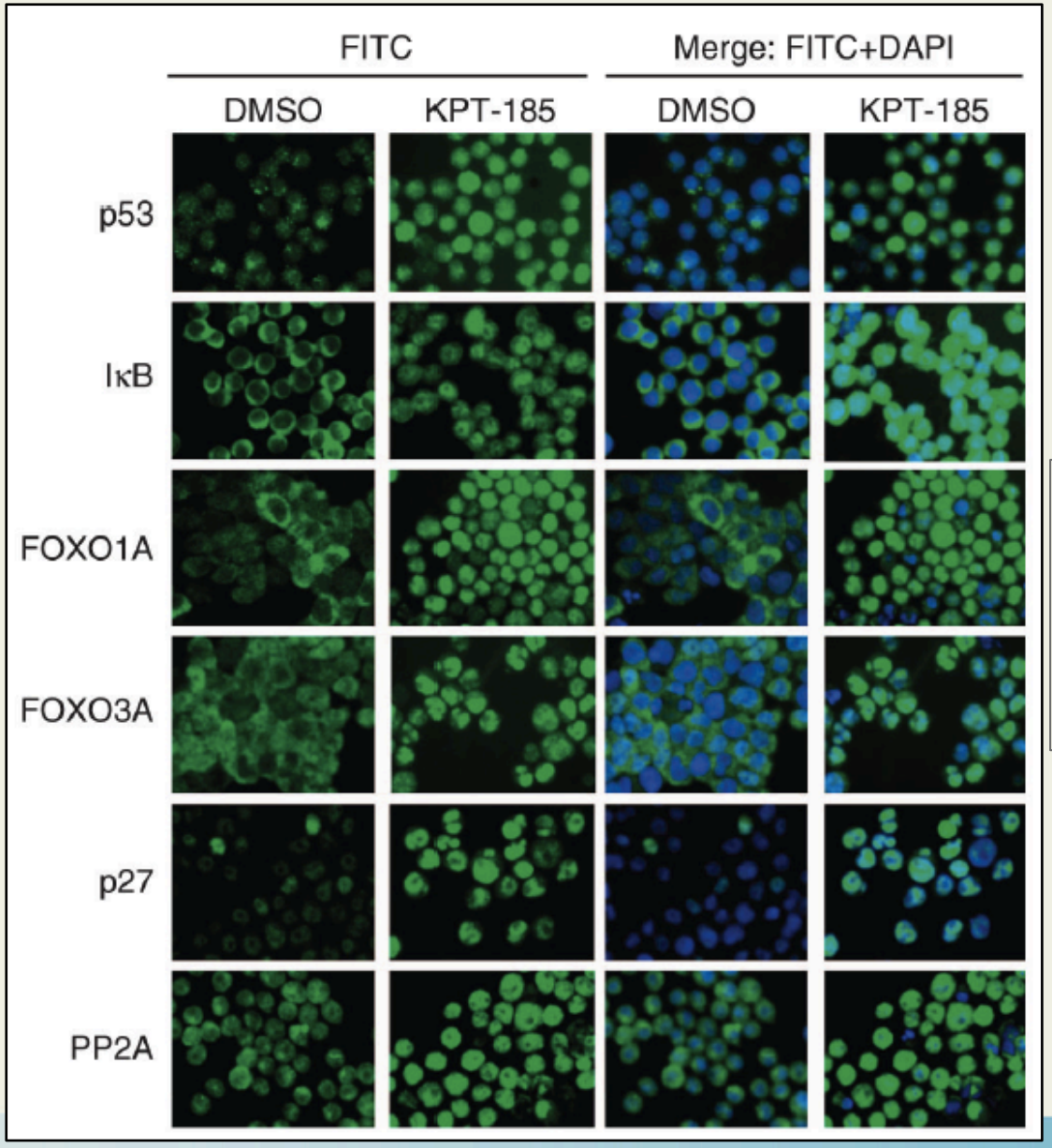


AML
(**Kojima 2013**)

Selinexor Rapidly Inhibits Nuclear Export

Time-Lapse FOXO1α-GFP in U-2 OS Cells

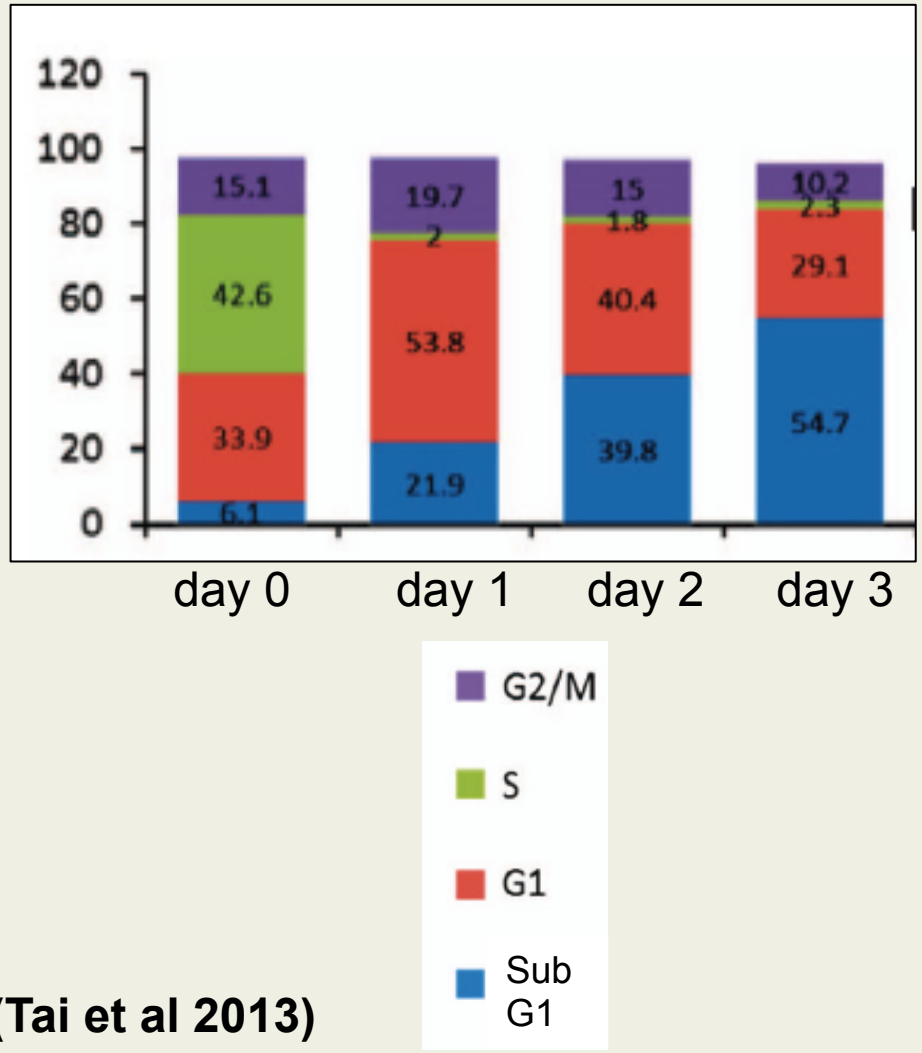
SINE Compounds Force Nuclear Retention of TSPs in MM Cells



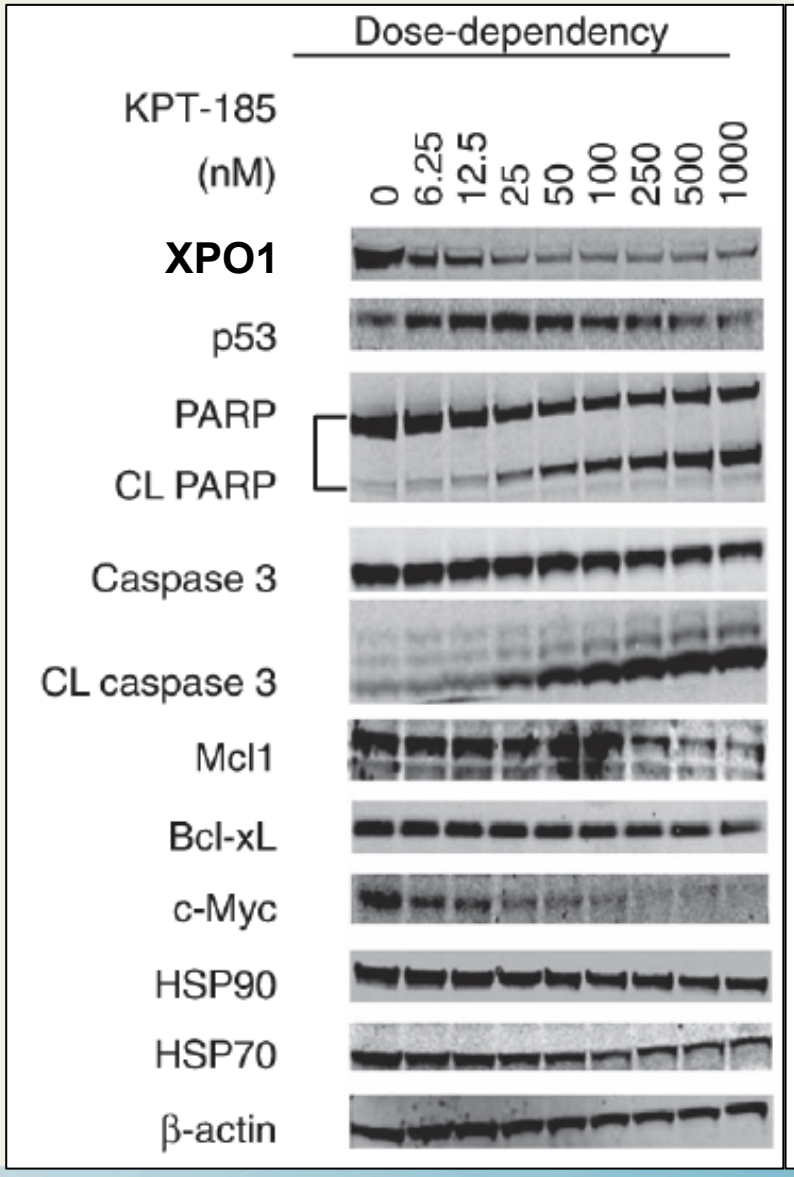
MM1.S cells treated with SINE compound KPT-185 show nuclear retention and increased levels of multiple TSPs

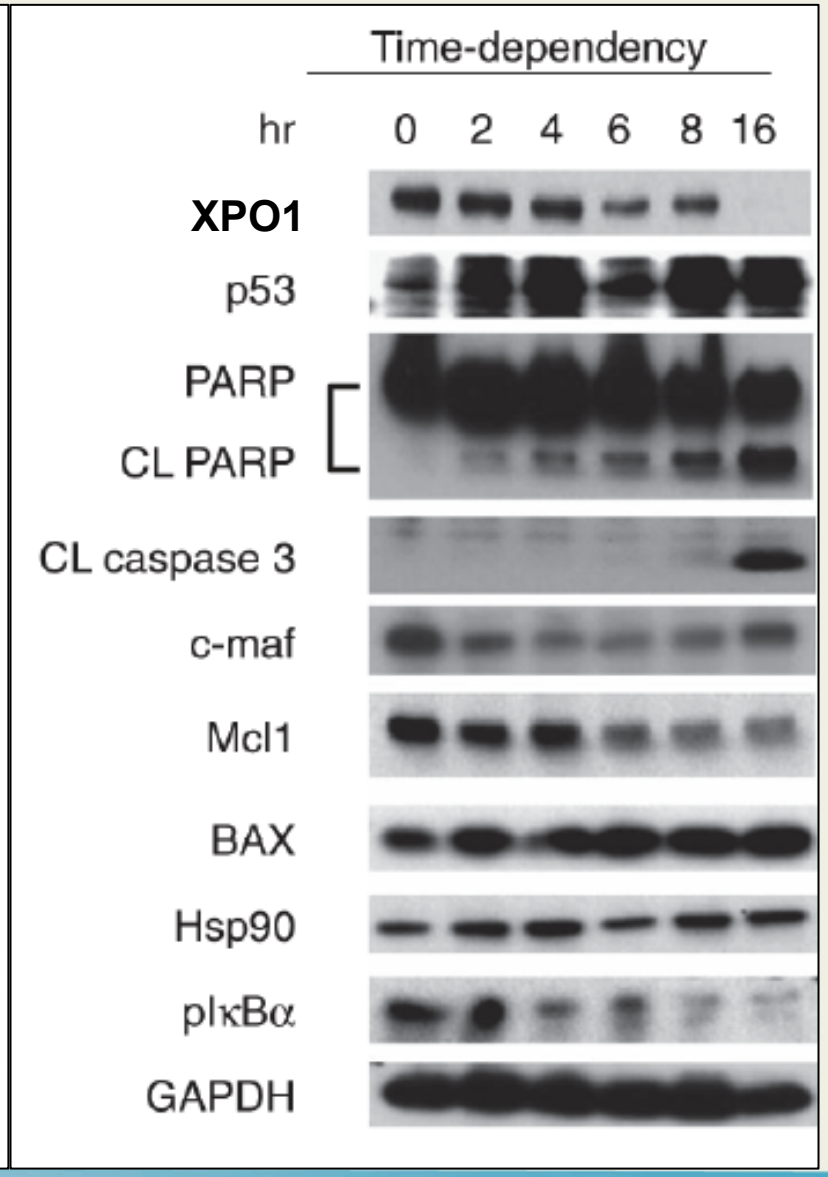
(**Tai et al 2013**)

Selinexor Blocks Cell Division and Induces Apoptosis in MM



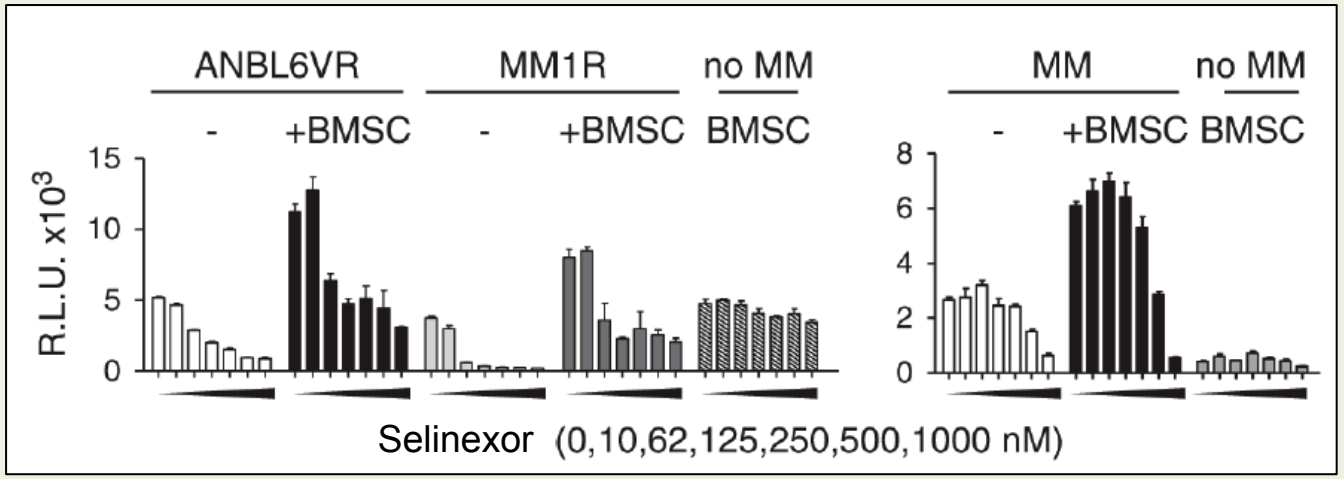
(Tai et al 2013)



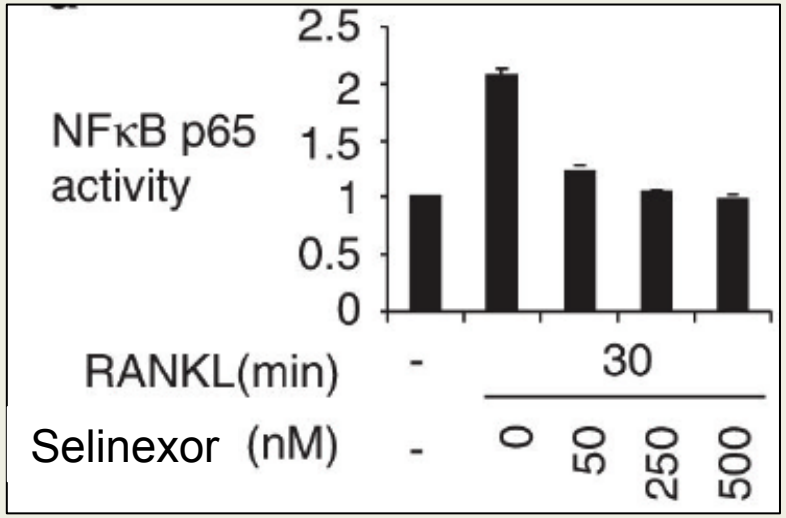


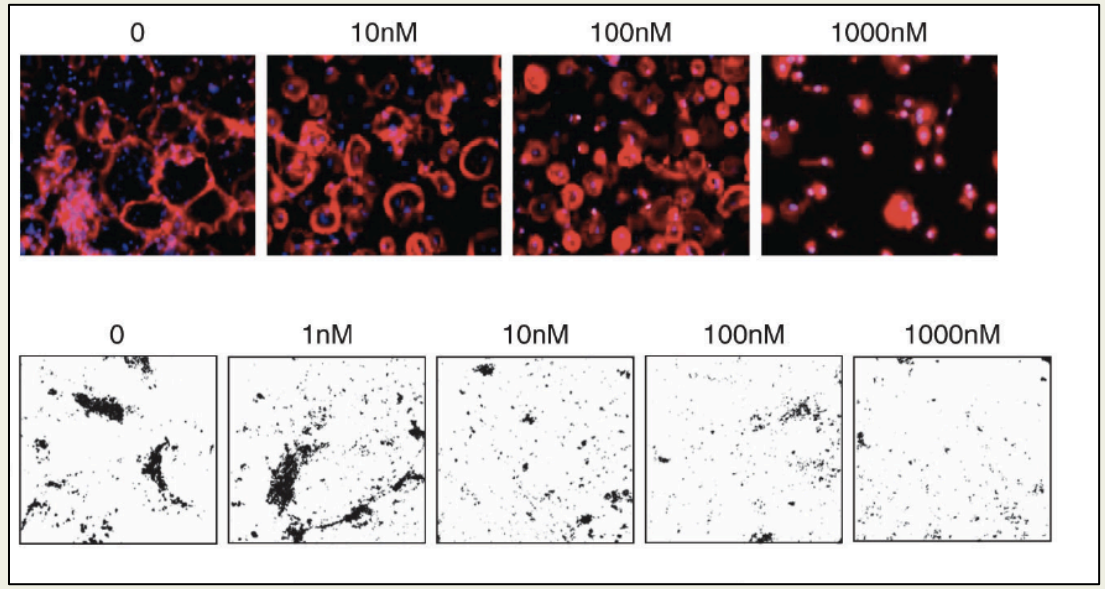
Selinexor Inhibits Tumor Protective Effects by Bone Marrow Stromal Cells, Osteoclastogenesis and Bone Resorption

Inhibition of Bone Marrow Stromal Cell Protection



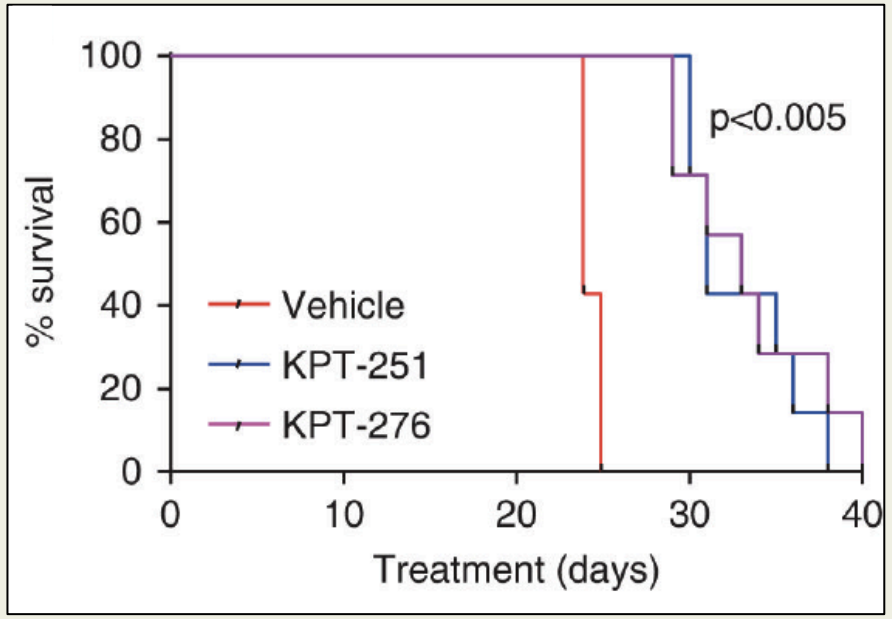
Inhibition of Osteoclastogenesis



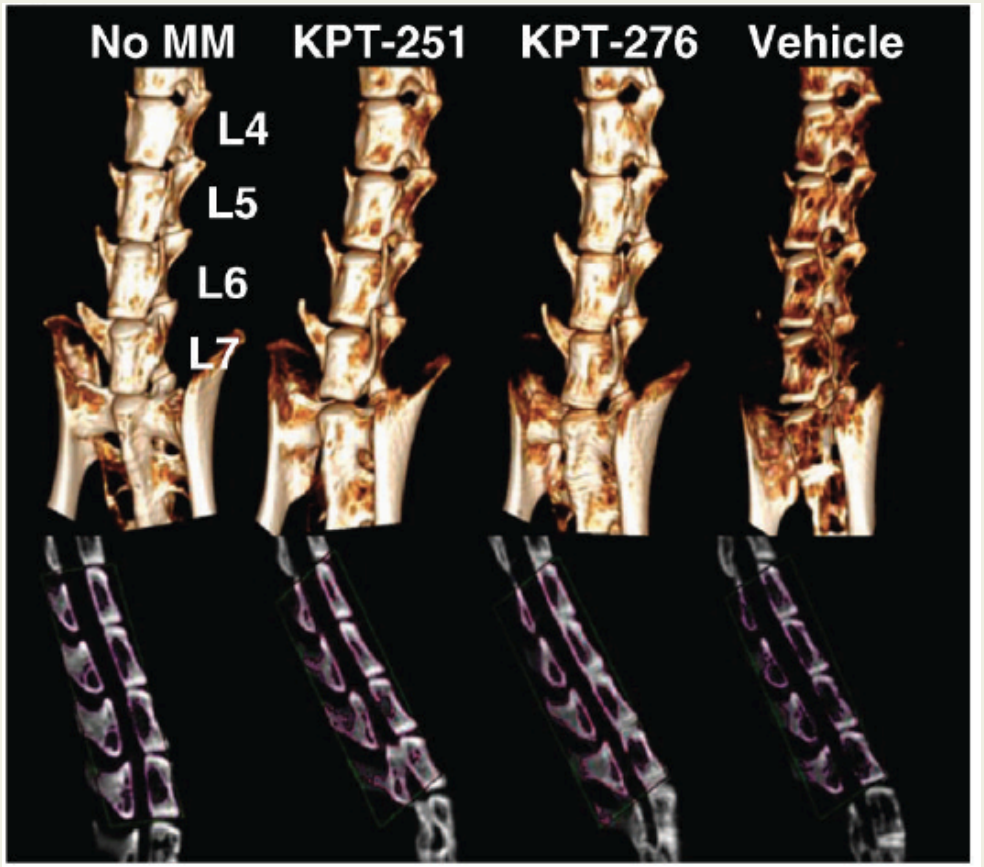


(Tai et al 2013)

SINE Compounds in Mouse MM Models and Bone Effects

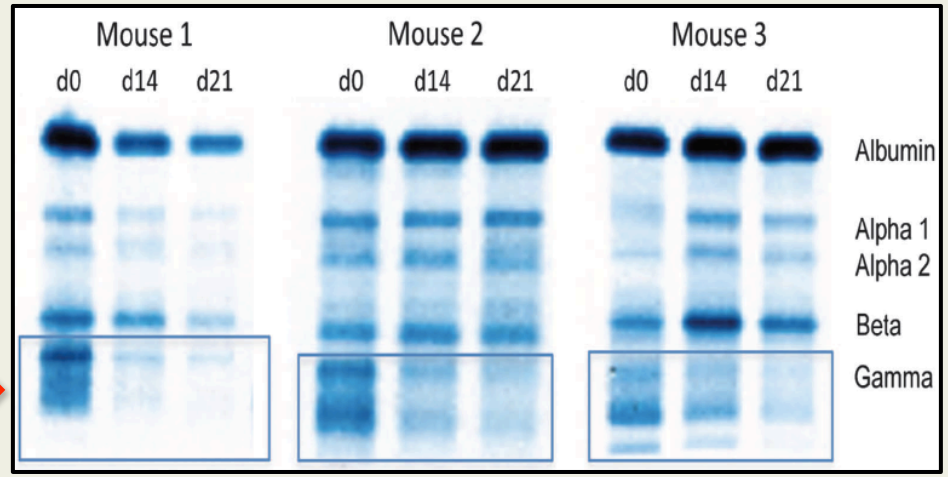


(Tai et al 2013)



No MM	MM	MM	MM
Untreated 58% / 657	KPT-251 55% / 651	KPT-276 54% / 651	Vehicle 47% / 521

M-spike



(Schmidt et al 2013)

Selinexor in Combination with Backbone Therapies is Currently being Tested in Various Multiple Myeloma Clinical Trials (Presented in ASH 2016 Conference)

1. **Selinexor** shows synergy **in combination treatment with Pomalidomide and low dose Dexamethasone** in Patients with relapsed / refractory multiple myeloma - Results from the Phase I STOMP clinical trial (Chen et al 2016)

2. Encouraging activity of **Selinexor in combination with Bortezomib and low dose Dexamethasone** in patients with heavily pretreated (≥4 lines of therapy) multiple myeloma, including those with proteasome inhibitor (PI) –Results from the Phase I STOMP clinical trial (Bahlis et al 2016)

3. Encouraging activity of **Selinexor in combination with Carfilzomib, and Dexamethasone** in relapsed / refractory multiple myeloma - Final Results of Phase 1 clinical trial (Jakubowiak et al 2016)

4. Encouraging activity of **Selinexor in combination with low dose Dexamethasone** in patients with quad and penta refractory multiple myeloma – Results from the STORM Phase II clinical trial (Vogl et al 2016)

5. Karyopharm is initiated the BOSTON phase 3 clinical trial: **Selinexor in combination with Bortezomib, and Dexamethasone** versus Bortezomib and Dexamethasone in patients with Relapsed / Refractory disease who have received 1 to 3 prior anti-multiple myeloma regimens

Combination of Selinexor with Immune Checkpoint Inhibitors in Melanoma and Colon Cancer

Syngeneic Melanoma Mouse Model

B116F10 Melanoma

TREATMENT

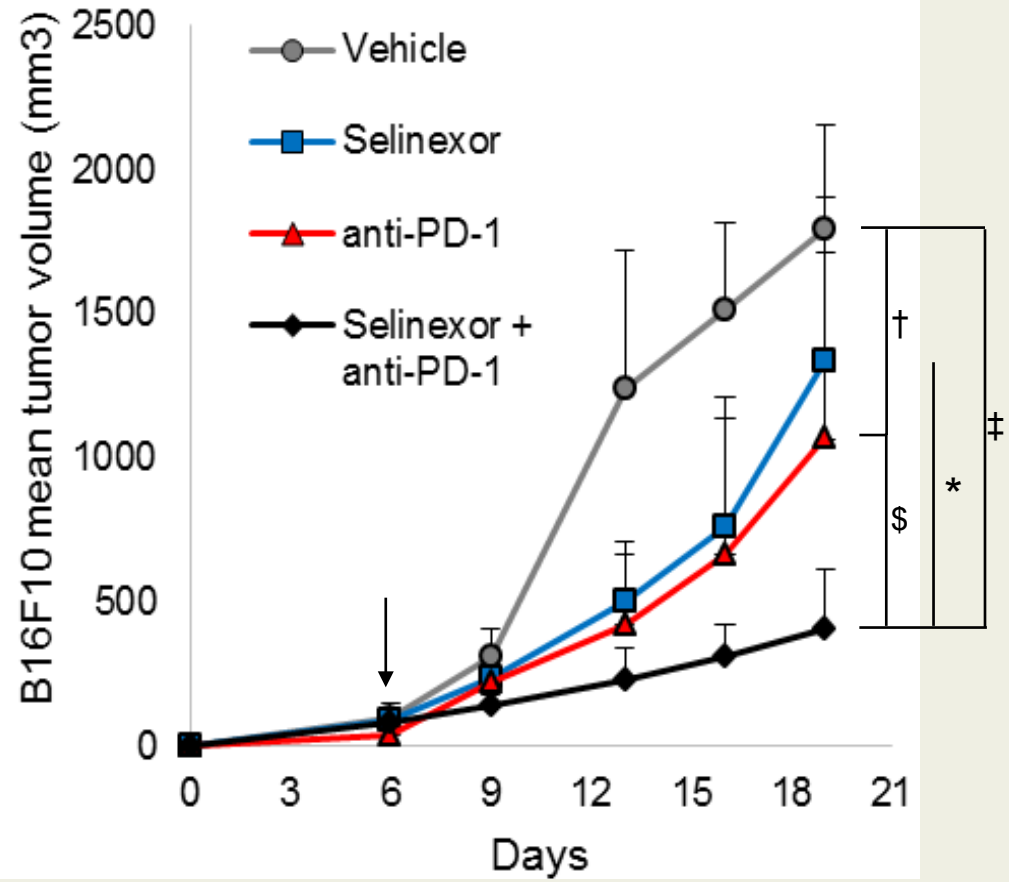
Selinexor (oral)- 15mg/kg Monday, Thursday

Antibody (IP) – 100µg or 200µg Monday, Thursday

Necropsy & Immune Assays

(Farren et al 2017)

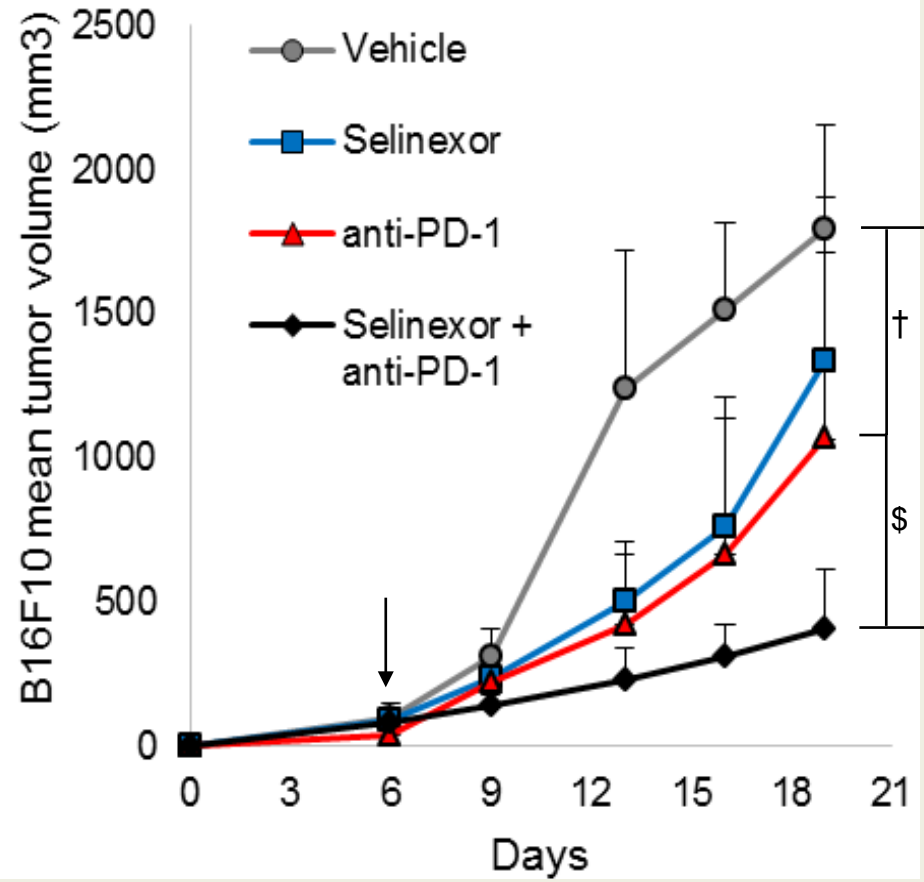
Selinexor Exerts Superior Anti-Tumor Activity When Combined with Immune Checkpoint Inhibitors



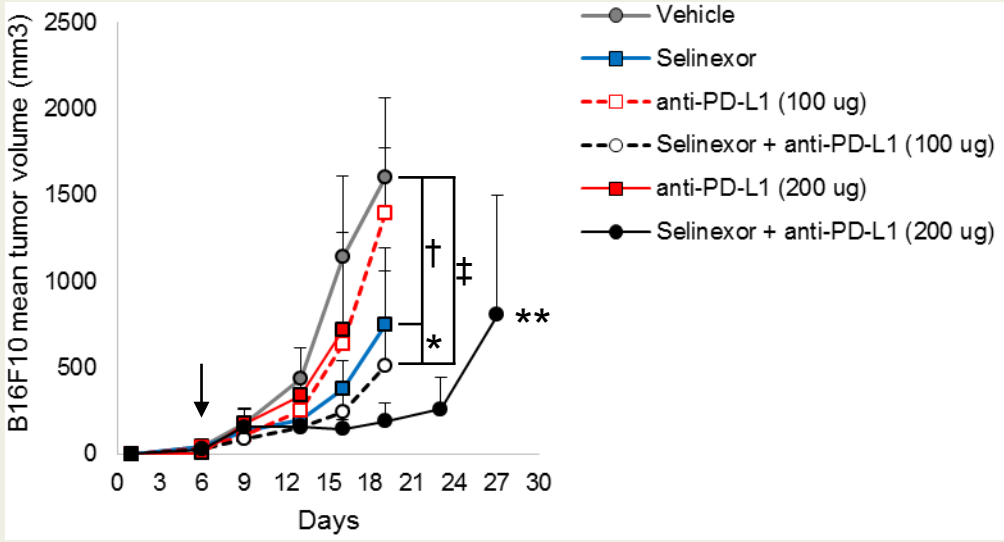
Selinexor + anti-PD-1

(Farren et al 2017)

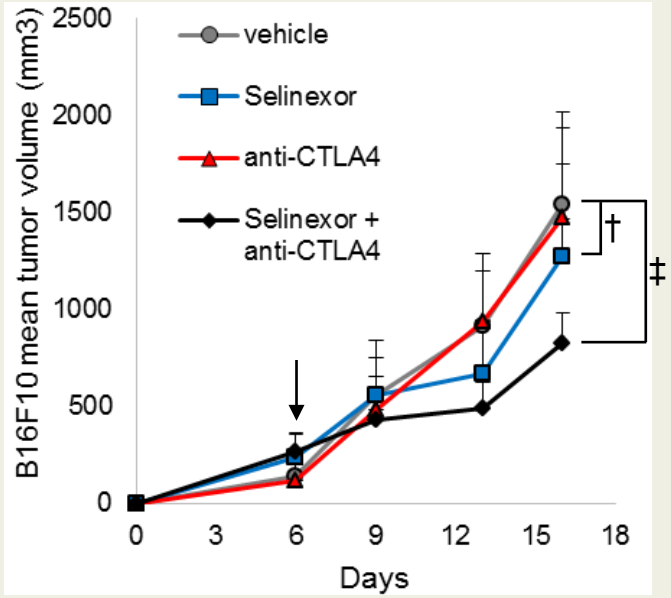
Selinexor Exerts Superior Anti-Tumor Activity When Combined with Immune Checkpoint Inhibitors



Selinexor + anti-PD-1



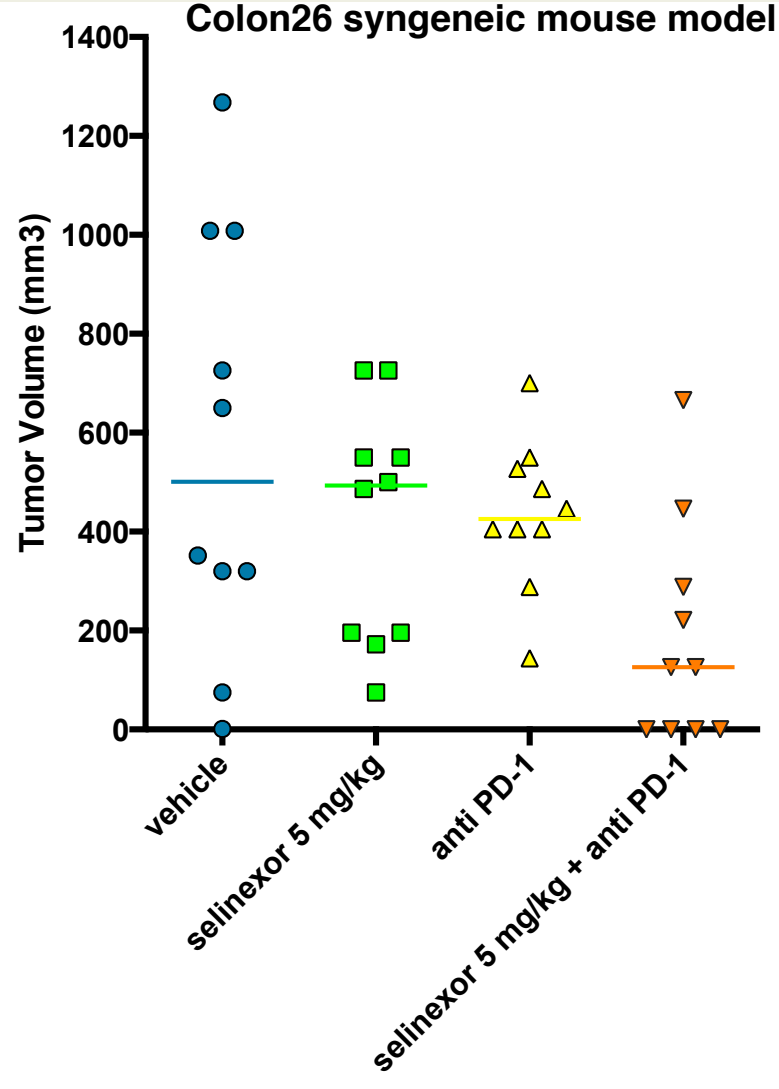
Selinexor + anti-PDL-1



Selinexor + anti-CTLA4

(Farren et al 2017)

Selinexor Shows Synergistic Anti-tumor Activity When Combined with PD-1 Blockade in a Mouse Model of Colon Cancer

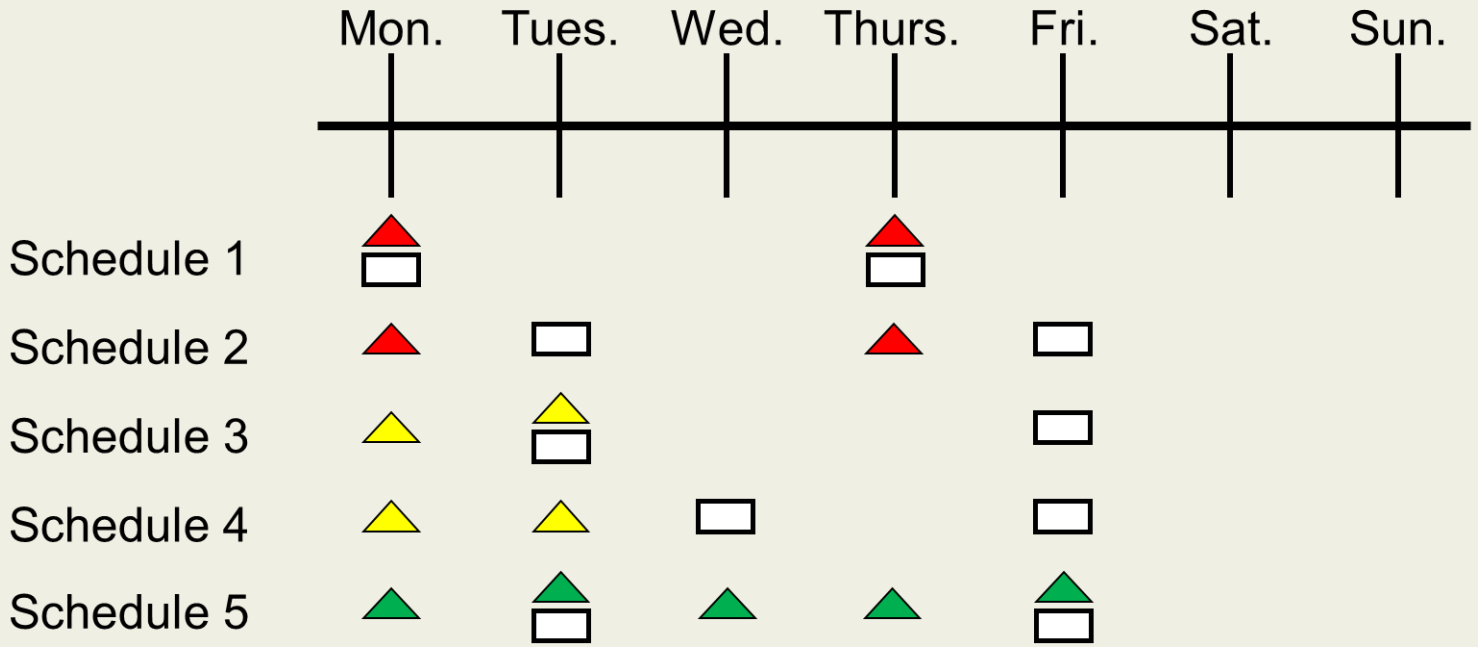


Treatment	% TGI (day 22)
Selinexor	27
Anti PD-1	24
Selinexor + anti PD-1	67

- 4/10 mice (female BALB/c) in the combination group did not have detectable tumors at day 22. These mice were also tumor free at the end of the study (day 45).
- No weight loss or signs of toxicity were evident.

(Elloul et al AACR 2016)

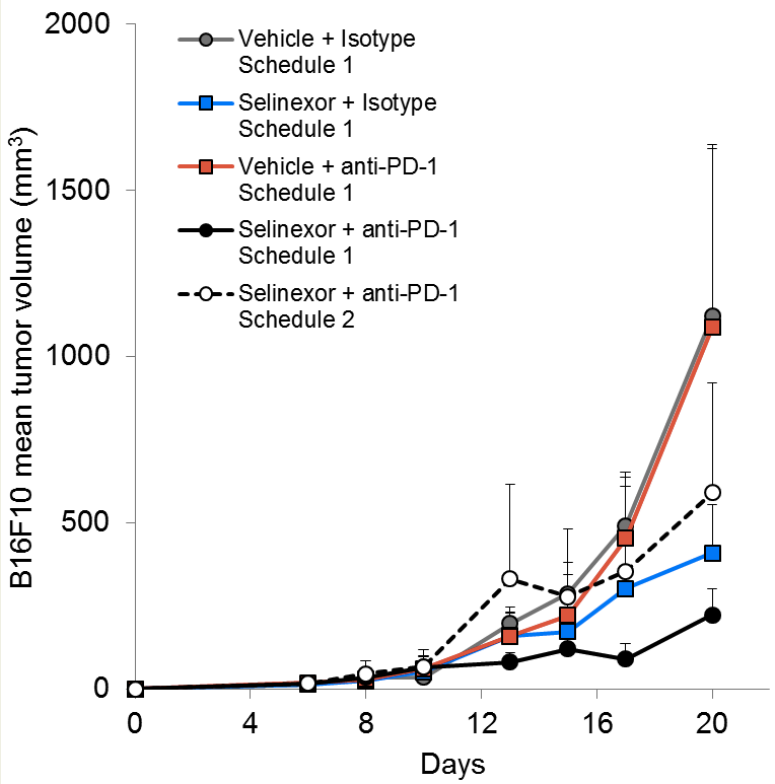
Optimization of Dosing Schedule for Selinexor in Combination with anti-PD1 Immunotherapy



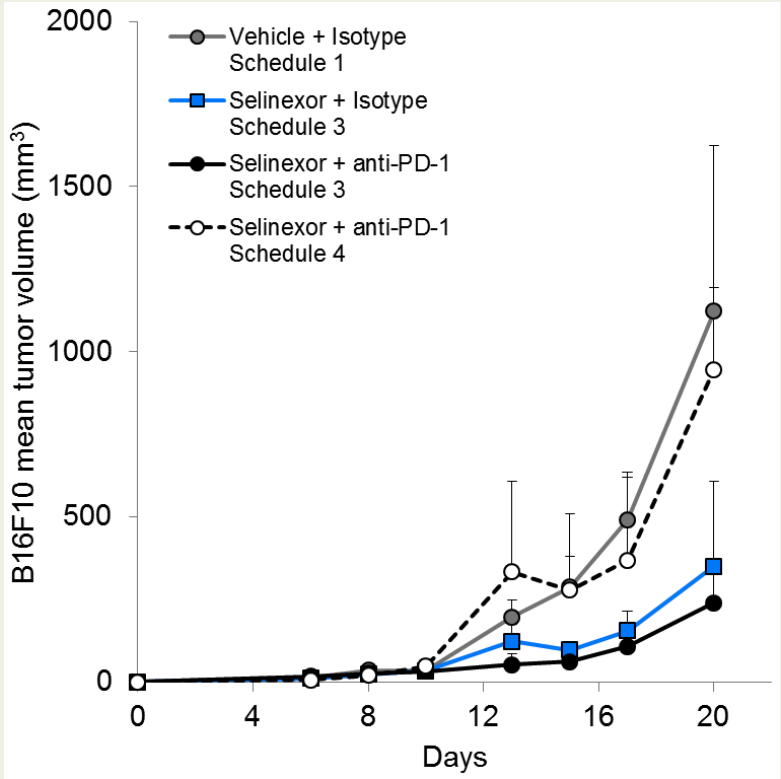
(Farren et al 2017)

Dosing Optimization of Selinexor Combination with anti-PD1

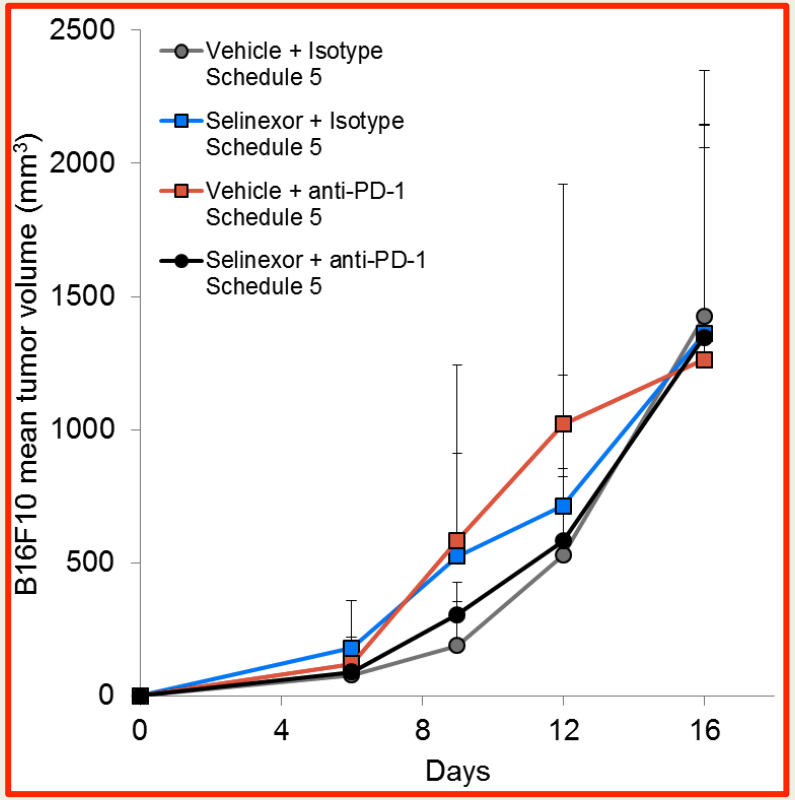
Schedule 1 and 2



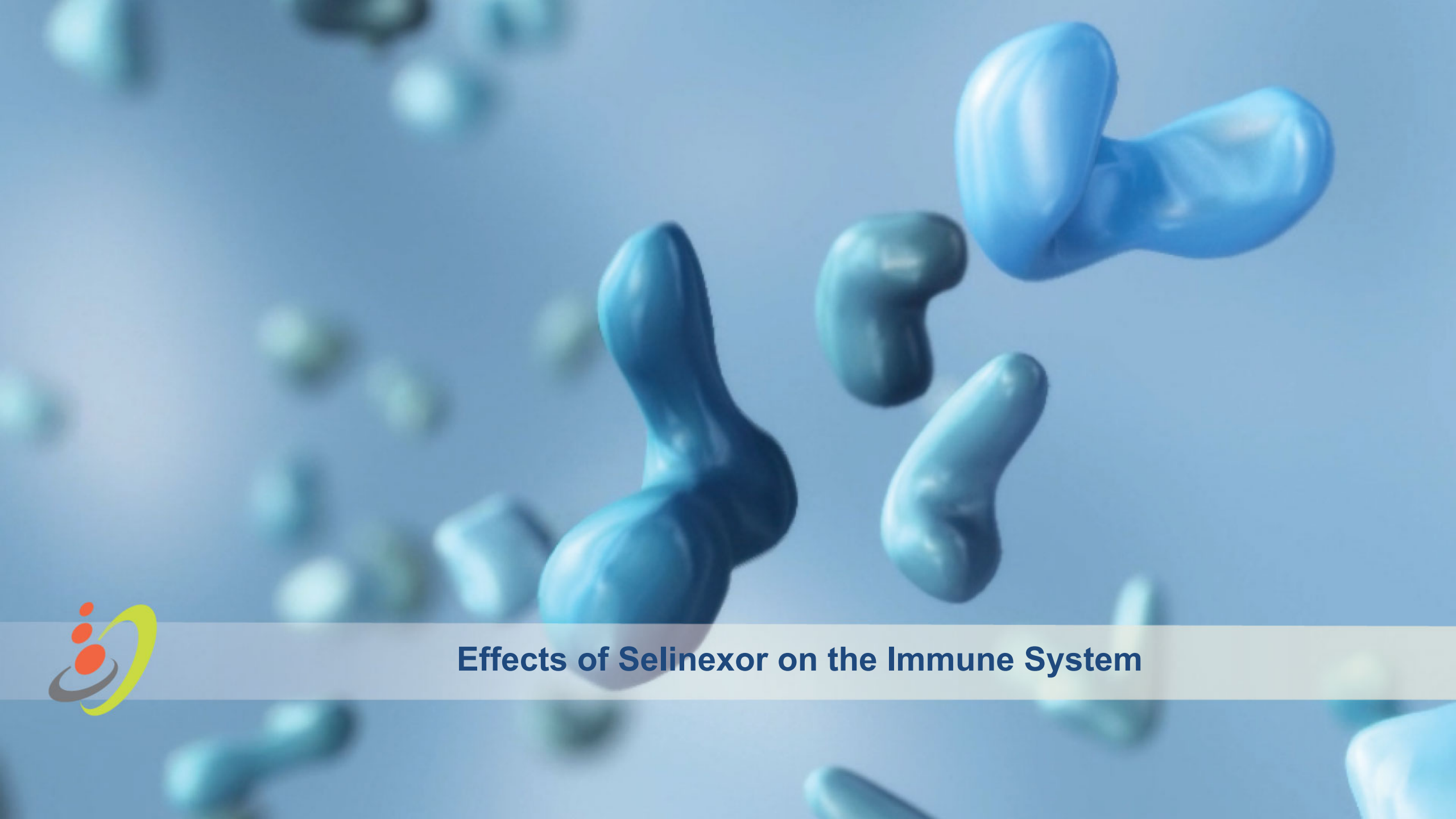
Schedule 3 and 4



Schedule 5:
Daily selinexor - inhibitory

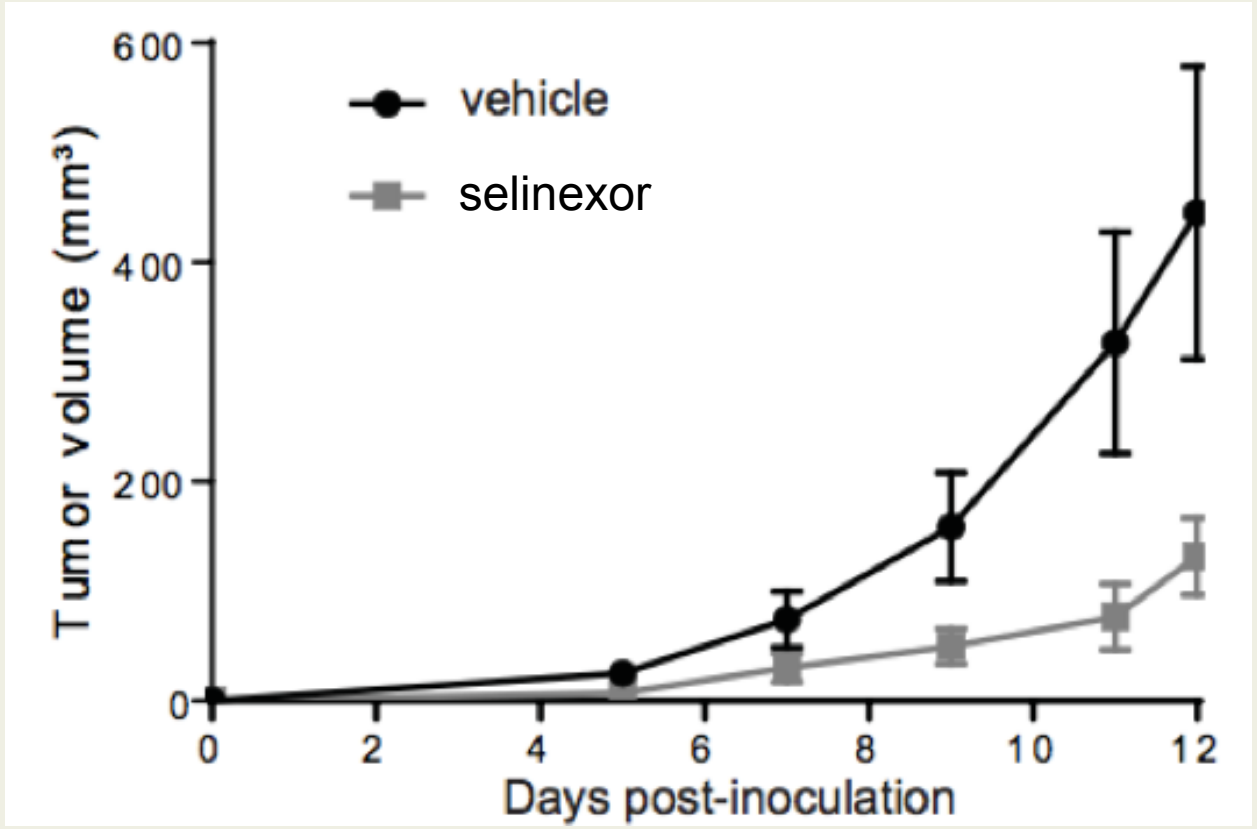


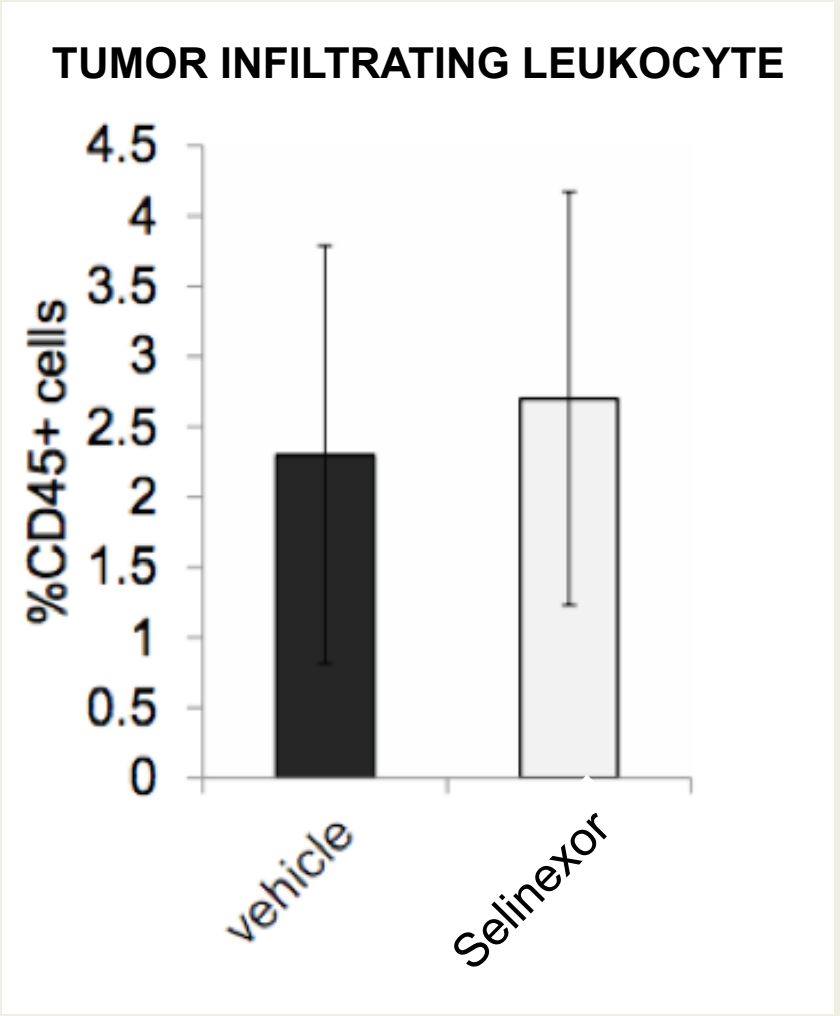
(**Farren et al 2017**)



Effects of Selinexor on the Immune System

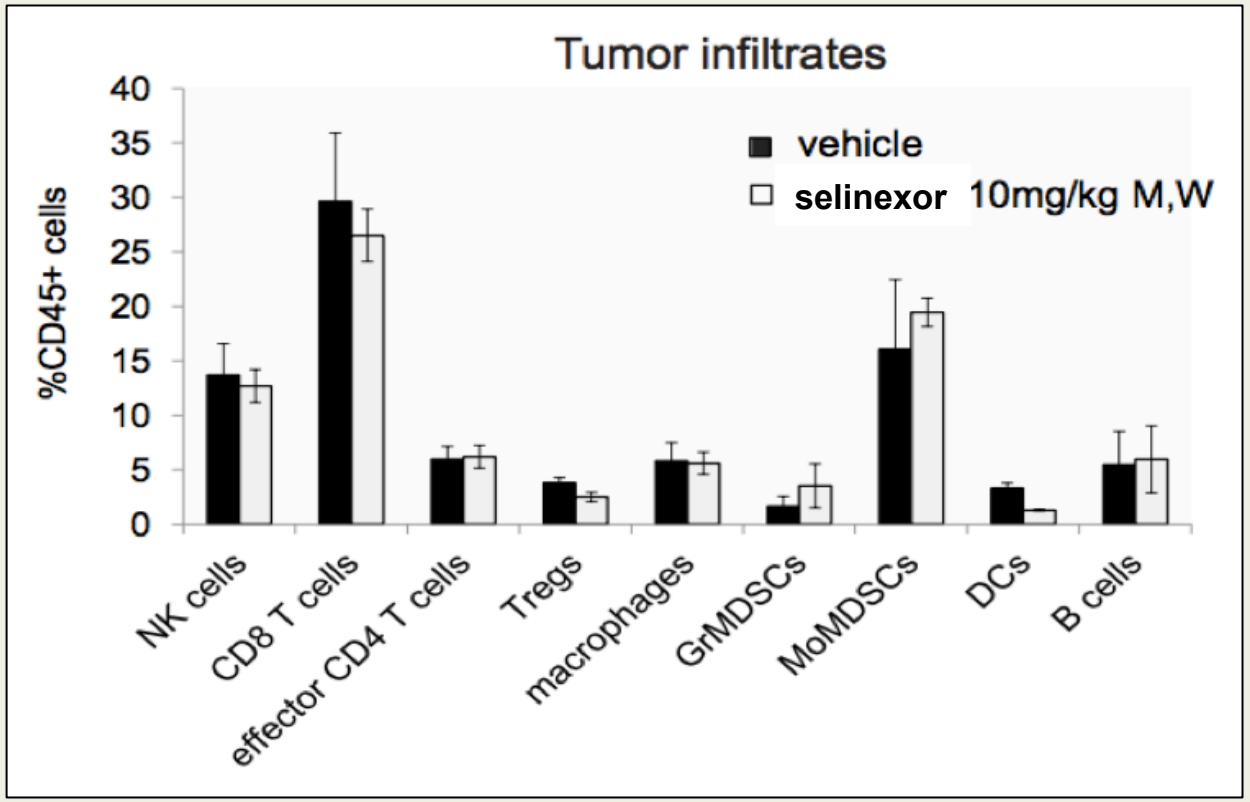
Selinexor Recommended Phase 2 Dosing Regimen Maintains Normal Immune Homeostasis and T cell Effector Function in Mice

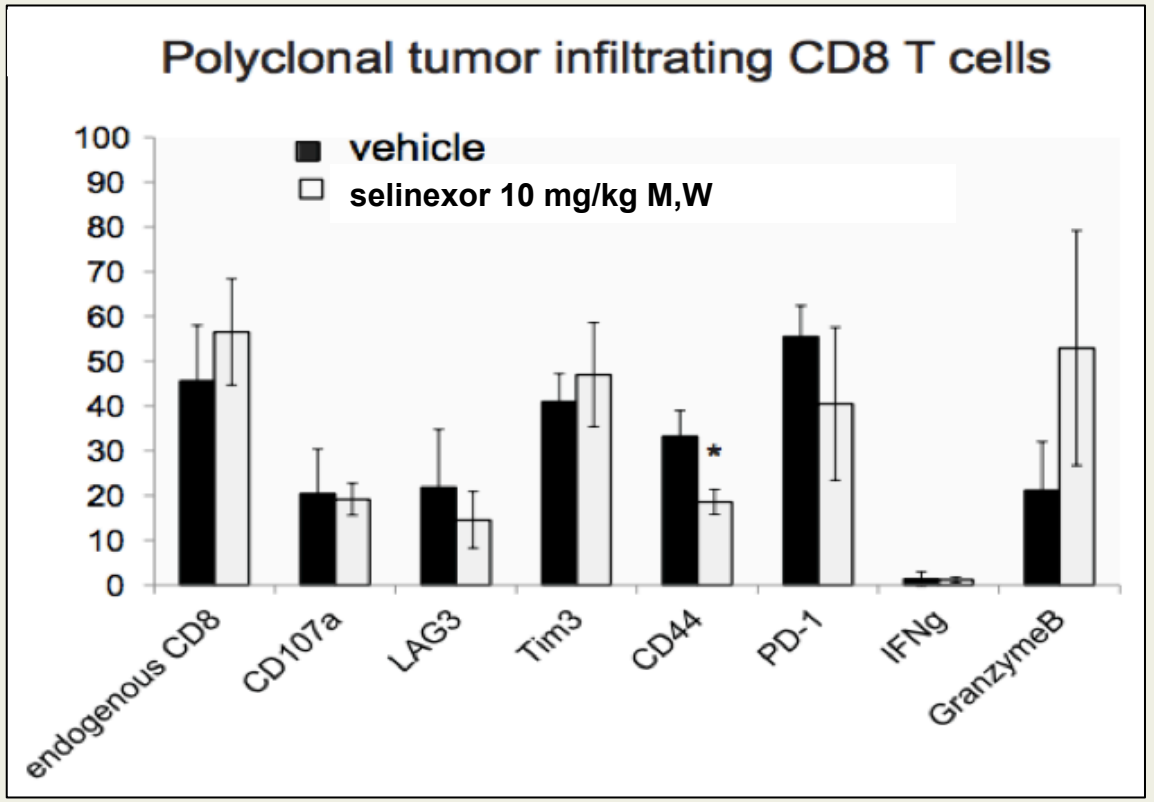




(Tyler et al 2017)

Selinexor Recommended Phase 2 Dosing Regimen Maintains Normal Immune Homeostasis and T cell Effector Function in Mice

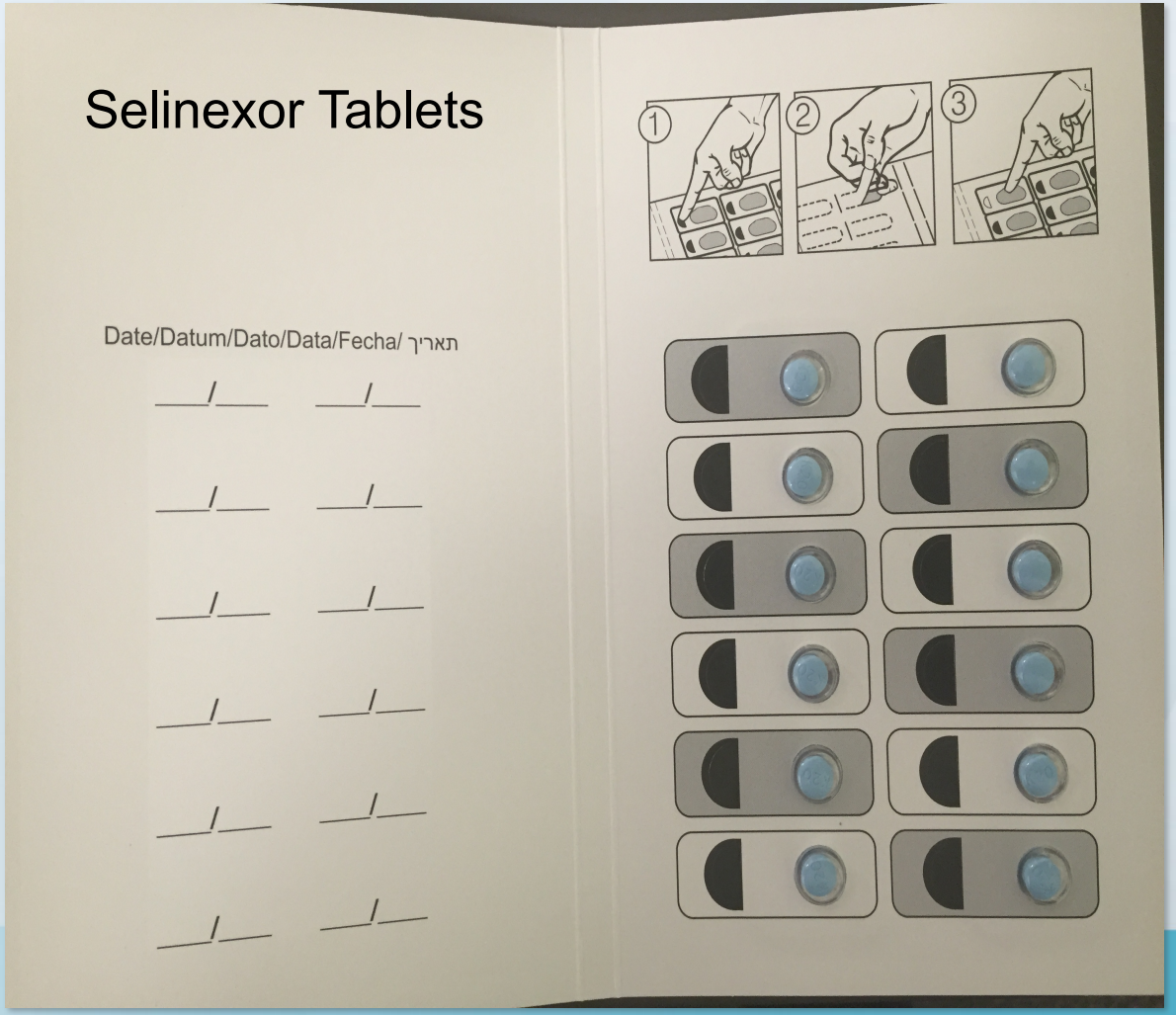




(Tyler et al 2017)

SUMMARY

- Selinexor and other SINE compounds inhibit XPO1 and have demonstrated anti-tumor activity across a spectrum of cancer types, including multiple myeloma
- Ongoing clinical trials are testing selinexor in combination with multiple myeloma backbone therapies.
- Preclinical studies demonstrated enhanced activity of selinexor when combined with immune checkpoints in melanoma as well as in colorectal cancer.
- We are currently testing combinations of selinexor with anti-PD1 antibodies mouse models of multiple myeloma to define clinical dosing conditions.
- Preclinical studies confirmed that the recommended phase 2 dosing schedule of selinexor maintains normal immune homeostasis and T cell effector function in mice.
- Clinical study of **selinexor** + **pembrolizumab** in patients with **melanoma** and **NSCLC** is currently on-going (ClinicalTrials.gov Identifier: NCT02419495)



Thank you for your attention!