MADRID 2014 ESMO congress

Selinexor (KPT-330), an Oral, Selective Inhibitor of Nuclear Export (SINE) Shows Anti-Prostate Cancer (PrCa) Activity Preclinically & Disease Control in Patients (pts) with Chemotherapy Refractory, Castrate-Resistant Prostate Cancer (CRPC)

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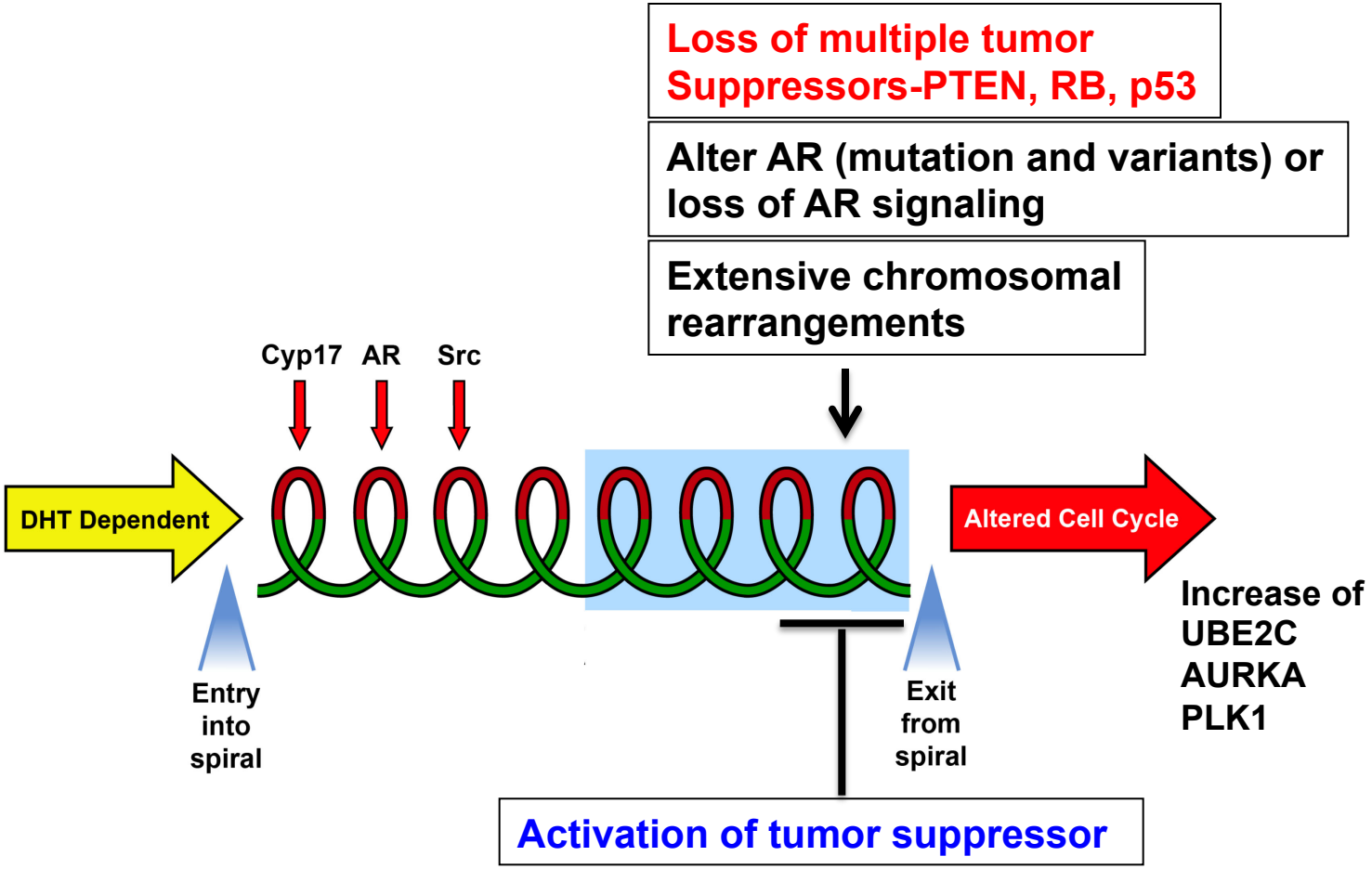
Presenter Disclosures

No Disclosures

Changes In Prostate Cancer: Cellular Program Drives Androgen Therapy Resistance



Logothetis et al. Cancer Discovery, 2013

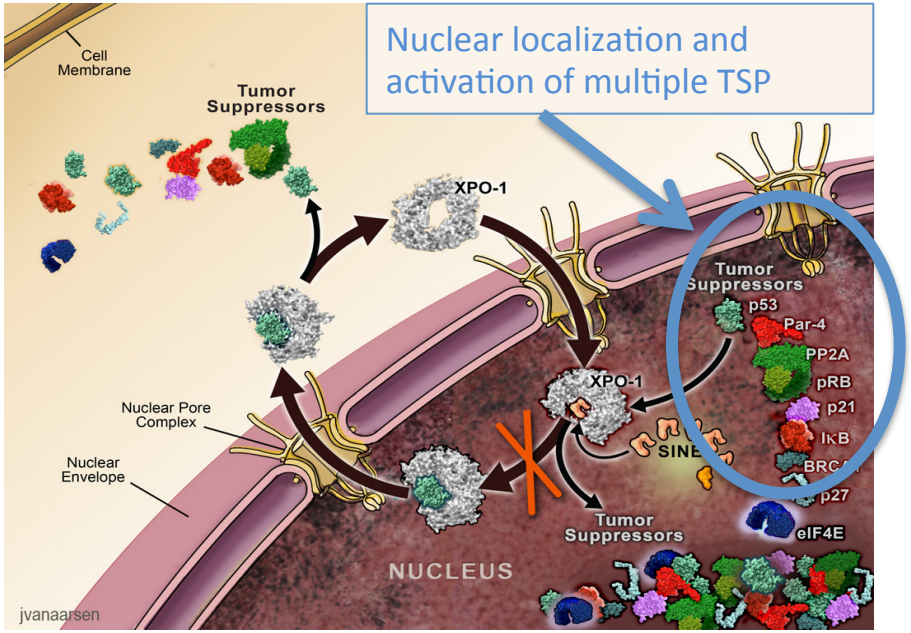
Loss of Tumor Suppressors

→ **Genetic Mutation/Deletion of PTEN, RB1, TP53 genes**

→ **Degradation of Wild Type Tumor Suppressor Proteins By Nuclear Export Mechanism**

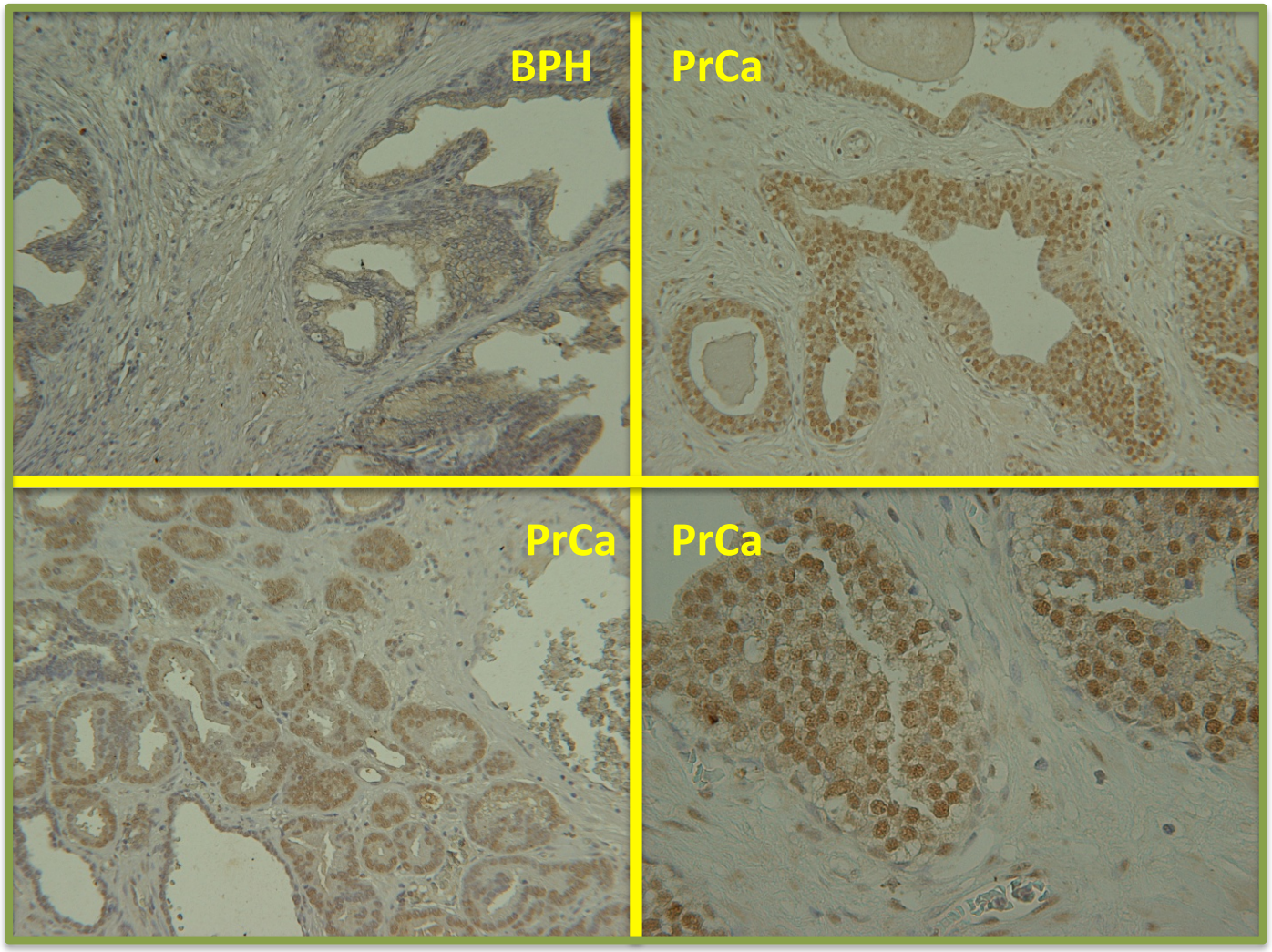
Selective Inhibitor of Nuclear Export (SINE™)

- Cancer cells can inactivate their Tumor Suppressor Proteins (TSPs) via nuclear export
- Exportin 1 (XPO1, CRM1) is the *only* nuclear exporter of most TSPs
- Selinexor (KPT-330) is a covalent, slowly reversible, oral selective inhibitor of nuclear export (SINE™) that inhibits XPO1
- Selinexor forces nuclear retention and activation of *multiple* TSPs, including p53, RB, and Foxo transcription factors (*Turner 2012*)



- In castrated mice, selinexor induced regression of patient-derived metastatic prostate tumor xenografts and forced nuclear retention of AR, p53, FOXOA3 and p27 (*Maity 2014*)

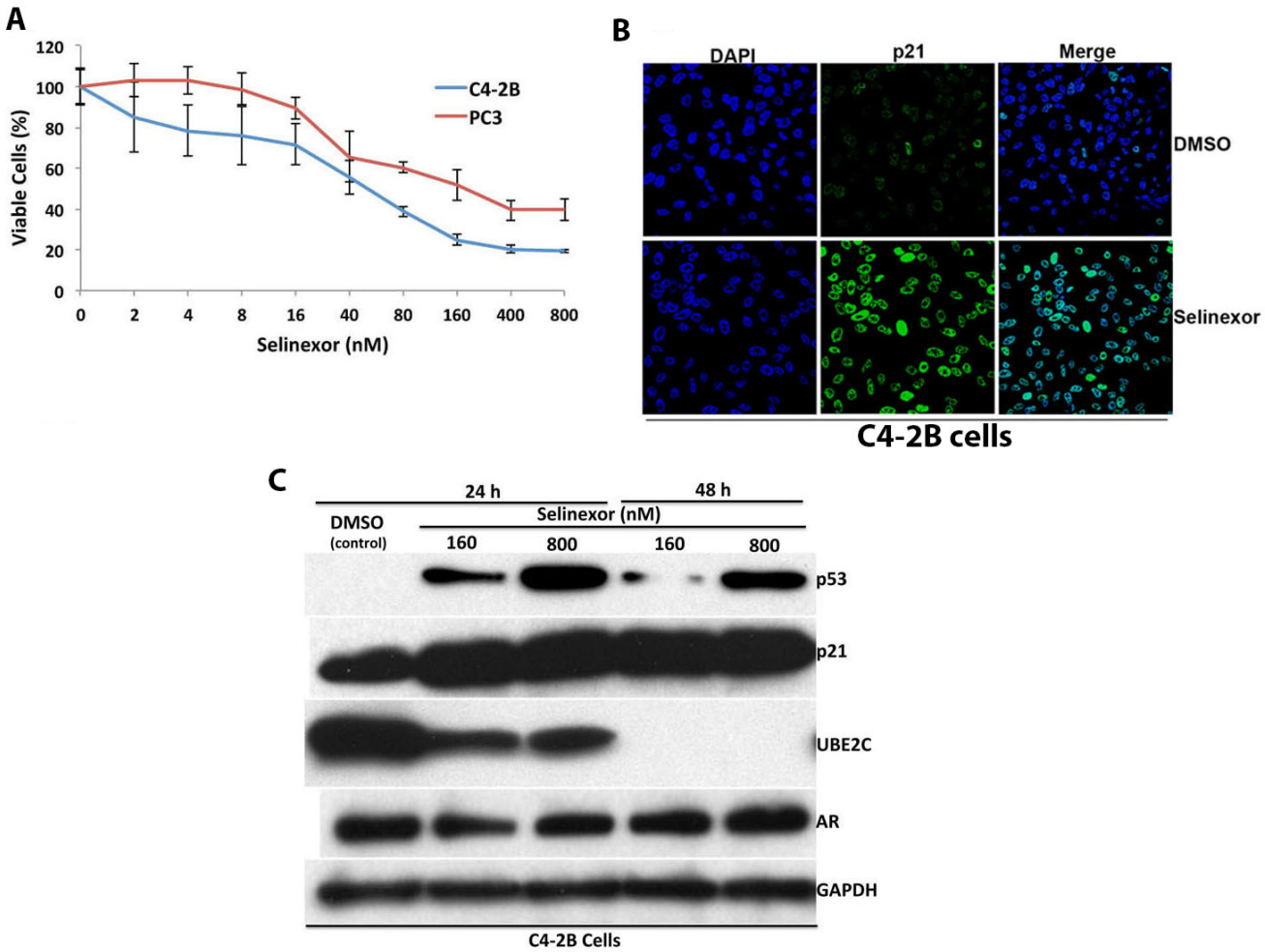
Exportin 1 (XPO1) is Overexpressed in Prostate Specimens



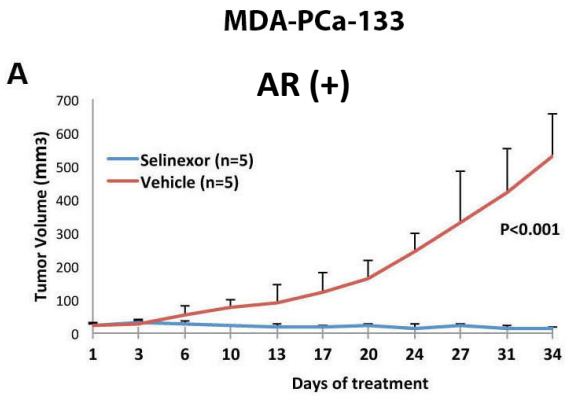
- Benign Prostatic Hyperplasia (BPH) and Prostate Cancer (PrCa) tissues were stained with antibodies to exportin 1.
- PrCa specimens consistently showed more exportin 1 expression in tumor cells compared with benign tissue

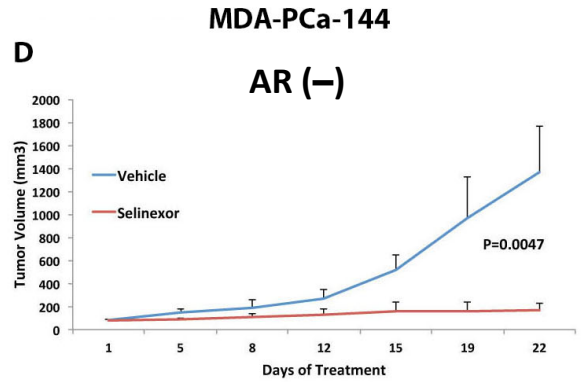
* *Gravina et al. AACR 2012*

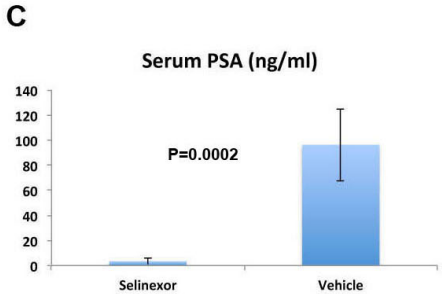
Selinexor Stabilizes p53, & Activates p53 Signature Genes (p21/CDKN1A, PUMA), and Inhibits Cell Cycle Genes (UBE2C, Aurora Kinase A)



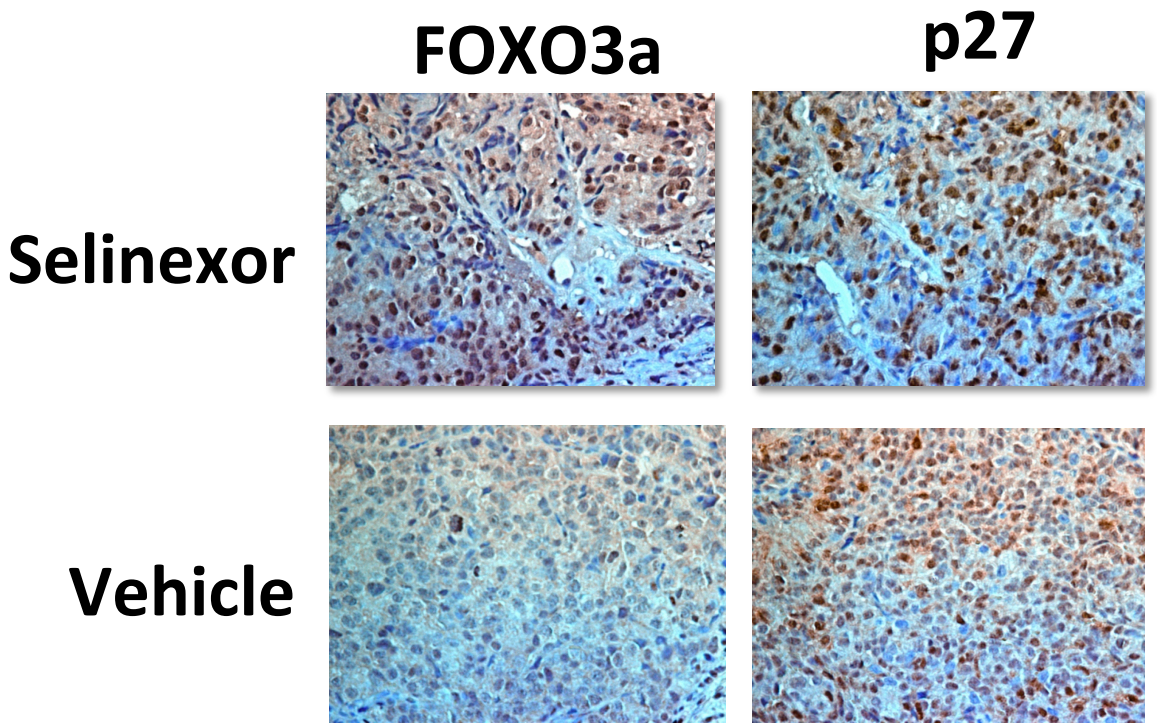
Selinexor Strongly Inhibits Tumor Growth of Patient Derived Xenografts in Castrate Mice







Selinexor Induces Nuclear Accumulation of FOXO3a and p27/ CDKN1B in MDA-PCa-133 (AR +)



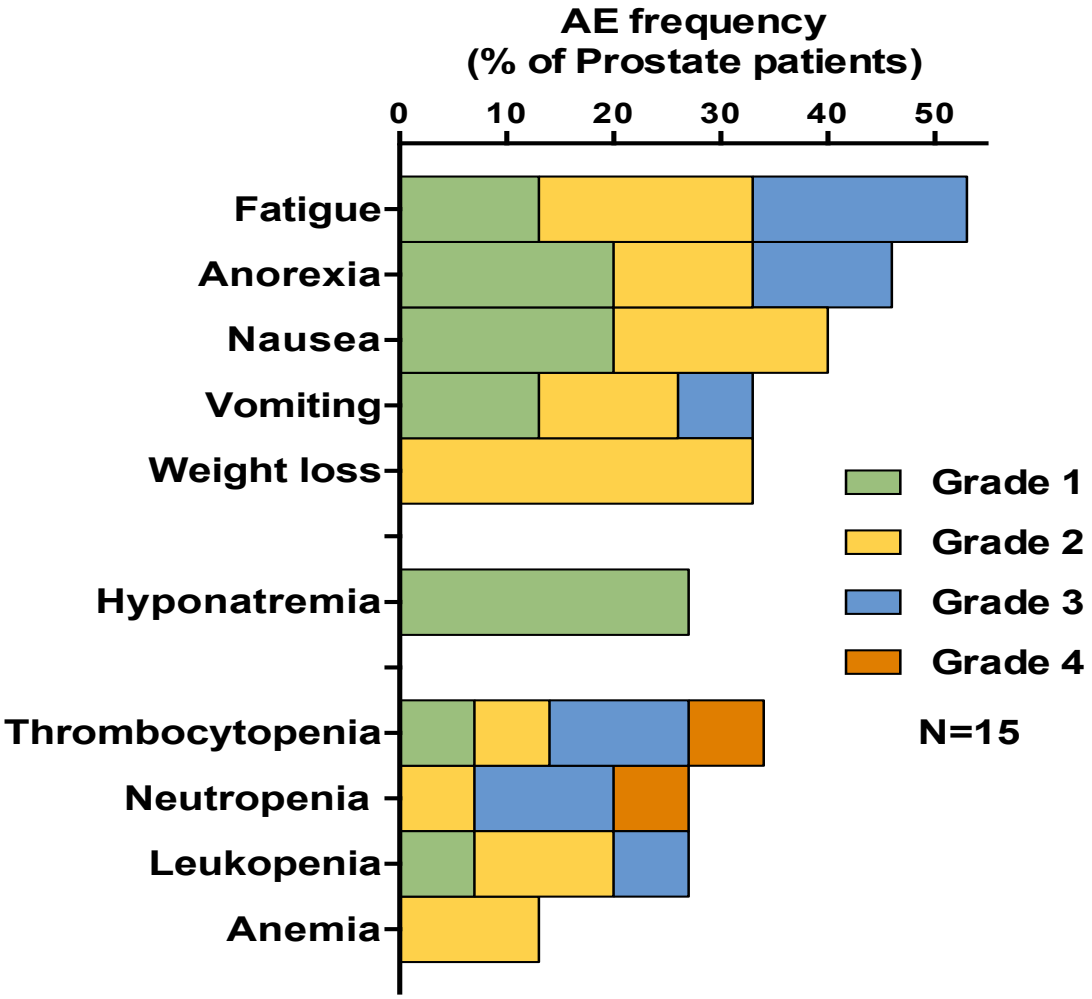
Selinexor Phase 1 Study Design

- Objectives (modified 3+3 design)
  - Primary: Safety, tolerability and Recommended Phase 2 Dose (RP2D) of selinexor
  - Secondary: Pharmacokinetics, pharmacodynamics, anti-tumor response, confirmation of RP2D of selinexor
- Selinexor oral dosing
  - Schedule: Three doses weekly, twice weekly or once weekly
  - Doses: 3 mg/m^2 – 85 mg/m^2
- Major eligibility criteria:
  - Patients (ECOG ≤2) with relapsed/refractory solid tumors with no available standard treatments
  - Documented progression at study entry

Selinexor Phase 1 Study: Prostate Patient Characteristics

Characteristics	N=15
Median Age (Range)	65 years (53 – 84)
ECOG Performance Status (0:1)	4 : 11
Median Prior Treatment Regimens (Range)	4 (2 – 10)
Previously Treated With Abiraterone (%)	8 (53%)
Previously Treated With Enzalutamide (%)	8 (53%)
Previously Treated With Taxanes (%)	15 (100%)

Selinexor Phase 1: AEs ≥ 2 pts Drug Related Adverse Events



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Selinexor Phase 1: Efficacy & PSA Assessment*

Best Response in Prostate Patients as 10-Sept-2014				
Prostate	N	SD (%)	PD (%)	NE (%)
Total	15	9 (60%)	2 (13%)	4 (27%)

Patient No.	Dose (mg/m^2)	Days on Study	Max PSA Reduction	Best Response	Last Therapy Prior to Selinexor	Time to Progression (Days)
043-043	35	430 +	– 50%	SD	Taxotere	502
043-034	35	325	– 34%	SD	Immune Therapy + Taxotere	112
043-033	35	280	– 28%	SD	Taxotere	83
043-064	35	114	– 60%	SD	PSMA ADC	31
043-067	35	290 +	--	SD	Abiraterone + Pred	182
043-078	35	114	No decrease	SD	PI3Kβ Inhibitor	123
043-080	58	69	– 27%	SD	Cabazitaxel	96
043-308	65	65	– 33%	SD	Enzalutamide	59
043-083	65	56	No decrease	PD	Taxotere	330
043-303	65	52	No decrease	PD	Enzalutamide	191
043-317	65	55 +	– 51%	SD	Abiraterone + Pred	55

** Excludes 4 non-evaluable patients*

Conclusions

- XPO1 is overexpressed in prostate cancer. The inhibition of XPO1-mediated nuclear export by selinexor in prostate cancer cells resulted in nuclear retention of tumor suppressor proteins including p53, FOXO3a, and p27
- Strong inhibition of castrate resistant PDX tumor growth by selinexor indicates XPO1-nuclear export can be a targeted therapy in CRPC
- Preclinical data suggests selinexor overcomes castrate resistance, AR alterations
- Phase 1 clinical data reveals selinexor to be tolerated with manageable side effects of fatigue, anorexia, nausea, thrombocytopenia and neutropenia as common side effects
- Early data in prostate cancer patients reveals PSA decreases, in a heavily treated population
- Selinexor provides a novel mechanism to overcome the castration and/or chemotherapy resistance in both preclinical and clinical data